Marlies E. Alvarenga
Don Byrne
Editors

Handbook of Psychocardiology

Springer Reference

Handbook of Psychocardiology

Marlies E. Alvarenga • Don Byrne
Editors

Handbook of Psychocardiology

With 95 Figures and 36 Tables

Springer Reference

Editors
Marlies E. Alvarenga
MonashHEART, Monash Cardiovascular Research Centre
Monash Health and Department of Medicine (SCS at Monash)
Monash University
Melbourne, VIC, Australia

Don Byrne
ANU Medical School
College of Medicine Biology and Environment, Australia National University
Canberra, ACT, Australia

ISBN 978-981-287-205-0 ISBN 978-981-287-206-7 (eBook)
ISBN 978-981-287-207-4 (print and electronic bundle)
DOI 10.1007/978-981-287-206-7

Library of Congress Control Number: 2016936690

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer Science+Business Media Singapore Pte Ltd.

Foreword

The phrase "hearts and minds" rolls off the tongue with ease and a conviction that the two are faithfully linked. Risk factors for heart, stroke, and vascular disease have deeply rooted social and behavioral determinants. People with depression or other major psychiatric illness are more likely to develop cardiovascular disease either de novo or as a consequence of the treatment they receive. People with acute cardiac disease are faced with the possibility of mortality or future disability and it is no surprise this carries a significant psychological burden. This is a complex two-way relationship.

Our knowledge of psychocardiology is increasing rapidly as new tools become available and the new biology including imaging, omics, and other techniques are applied to help unravel the links between brain function, the autonomic nervous system, and the circulation. This book is very timely in addressing a fast moving field where there are significant challenges for the future.

The burden of cardiovascular disease is increasing worldwide associated with development, the stresses associated with globalization, and the socioeconomic gradients that occur. Obesity is on the rise and its metabolic consequences including diabetes are closely related to behavior and to future cardiac and vascular diseases. In developed economies, increasing longevity is giving rise to concerns about the future burden of dementia. About half of dementia is vascular in origin and the risk factors for the other half overlap closely with the classical cardiovascular risk factors.

These and many other subjects are dealt with in this book. Professor Byrne and Dr. Alvarenga have made significant contributions to the field themselves and they have assembled an impressive list of authors to produce a comprehensive resource for all those interested in the field.

The book provides a firm basis for the development of the science of cardiac psychology in the opening section, providing a historical perspective, an outline of the causes, pathophysiology, and role of tobacco smoking, alcohol, and other lifestyle aspects. This is followed by an account of the psychopathology associated with cardiovascular disease, including depression, anxiety, and stress as well as psychoses and more specific and contemporary issues such as posttraumatic stress, occupational stress, and the stress associated with cardiac disease itself and its various remedies, particularly surgery. Special populations are particularly

susceptible to both cardiovascular disease and depression, and there are chapters on indigenous populations, refugees, the poor, and the homeless. These well-known social determinants of cardiovascular disease are most likely linked by stress, depression, and associated factors. Controversies on personality and propensity to develop heart disease are the subject of other chapters of the book. Finally, there is an ambitious attempt to explain these associations through the neurobiology of psychology and of cardiovascular disease.

This is a comprehensive examination of a complex but important issue, and the editors have not shirked any of the innate, social, psychological, or biomedical factors involved. It will no doubt find a place as a valuable resource for all those interested in the field, crossing disciplinary boundaries and stimulating new work in the area.

Garry Jennings
Melbourne, Australia

Preface

In September 2008, the inaugural *Heart and Mind: Psychogenic Cardiovascular Disease Conference* was held in the beautiful town of Prato in central Italy. The conference was held under the auspices of the (then) Baker Heart Research Institute (now the Baker IDI Heart and Diabetes Institute) in Melbourne, Australia, and was the product of a fruitful collaboration between an eminent cardiologist (Professor Murray Esler) and a clinical psychologist (Dr. Marlies E. Alvarenga). The conference brought together a truly international participation of around 150 active scientists and clinicians from diverse disciplinary backgrounds to consider the evidence linking psychological factors with cardiovascular disease (CVD), and the proceedings were published in a Special Issue of the journal *Stress and Health* (Volume 24, Issue 3) under the editorship of Professor Graham Burrows, a psychiatrist. Two further meetings of what had by then become simply and fondly known as the Prato Conference were held in 2010 and 2012, and extended this collegial sharing of knowledge and wisdom to define in clear terms the new and exciting field of psychocardiology. The two editors of this current volume had the significant privilege (and the great pleasure) of taking part in both the inaugural and subsequent Prato Conferences, and from those meetings – and many other discussions we had between 2008 and 2010 – the idea that this knowledge and wisdom should be tapped, documented, and put between hard covers was born.

The *Handbook of Psychocardiology* then is to our knowledge the only currently available compendium of evidence and practice which has both systematically and comprehensively addressed the role of psychological and behavioral factors, broadly defined, in the genesis, clinical course, and management of CVD. In bringing this about, the *Handbook* has striven to address four areas in the overall domain of CVD – epidemiology, stress and psychopathology, psychobiological mechanisms, and patient management – which, on the face of it, may appear to be quite separate, but which (we believe) are intricately interrelated to one another. And in brining this material together, we have held as our dominant objective the establishment of psychocardiology as an emerging *force majeure* in the field of CVD. To achieve this, it has been our aim from the very beginning – and one in which we believe we have well succeeded – to seek chapters from scientists and clinicians of preeminent international distinction in each of the fields of the basic biomedical sciences, cardiology and cardiovascular biology (of course), psychiatry and psychology, and

epidemiology. We have sought to question the rigidity of the boundaries between these disciplinary areas and to suggest, instead, that those boundaries are in fact surprisingly porous. We (as the *Handbook*'s editors) see the field of psychocardiology as a truly constructive intermingling of these seemingly separate areas of investigation and discourse – a new field in which the Gestalt principle is beautifully illustrated, that the whole is indeed greater than the sum of the parts. But naturally, the success of this objective will be for the reader to judge.

In our respective careers in psychocardiology, we have each, at various times, been so fortunate to have been in the company of some real giants in the area. One of us (MA) has had the benefit of working closely with Professor Murray Esler, and his quite pioneering research on bringing cardiology together with psychology has been inspirational. And for the other of us (DB), the opportunity some time ago to have researched and published with one of the true (perhaps grand) parents of cardiac psychology, the late Dr. Ray Rosenman, was an undeserved but deeply appreciated privilege, and a formative experience never to be forgotten.

A number of colleagues generously reviewed chapter content for us, and we are grateful in particular to Professor Murray Esler (Prof. Murray D. Esler, Senior Director, BakerIDI Heart and Diabetes Research Institute, Melbourne, Australia) and Dr. Miguel A. Fernandez Rubio (Dr. Miguel A. Fernandez Rubio, Unit Head, Youth ELMHS, and Consultant Psychiatrist, RAPP Team, Monash Health, Melbourne, Australia) for clear reviews of chapters where the formal content exceeded our levels of expertise. At a more informal level, very useful comments on some chapters were given to us by a number of friends and colleagues in the area, and we are also grateful to each for their valuable input.

We also consider it a matter of great fortune to have been accepted by a publisher as prominent in the field as Springer. The *Handbook* was commissioned by Dr. Mokshika Gaur and we are grateful indeed that she first saw merit in the work and then placed her faith in us to bring it to a successful conclusion. The Springer editorial team (Ms. Keerthi Sudevan, Ms. Nivedita Baroi, and Ms. Indu MG) have been an outstanding support to us throughout the publication process – and we could not have been blessed with a more consummately professional group. Their organizational skills, editorial acumen, attention to details which had escaped us, and so importantly their exceptional patience when progress did not seem to be happening at our end of the enterprise was so often able to allay our own frequent anxiety that the work would never quite come together. And so we thank you – each of you – so much!

A work such as this *Handbook* would not, however, have come together at all had it not been for the scholarly efforts of our authors. As one might expect from a work of this magnitude, there are so many of them to thank. As working scientists and clinicians ourselves, we well know the pressures that face eminent and productive people in universities and health care facilities across the world. There are always often dauntingly large numbers of students to teach and supervise, grant applications to write, data to collect and papers to publish, patients to treat with great skill and care, and seemingly endless administrative tasks to complete. Yet in the face of this workload, our authors generously shared with us their scholarship, their experience,

and their own particular visions for psychocardiology. And from our own experience, where scholarly writing has often taken precedence over relaxation, we confidently predict that their contributions to the *Handbook* were so often done "out of hours." We are sincerely grateful to them for this – and it is on such willingly shared wisdom that the *Handbook*'s value to cardiac psychology will ultimately stand.

September 2015

Don Byrne
Canberra
Marlies E. Alvarenga
Melbourne

Contents

Volume 1

About the Editors

Marlies E. Alvarenga
Monash Cardiovascular Research Centre
Monash Health and Department of Medicine
(SCS at Monash)
Monash University
Melbourne, VIC, Australia

Marlies E. Alvarenga is a Clinical Psychologist, a Senior Lecturer with the School of Public Health, Monash University, and consultant cardiac psychologist at the Monash Cardiovascular Centre and MonashHEART within Monash Health and the Department of Medicine. She is the former Director of the Monash Clinical Psychology Centre at Monash University and current Director of the Medipsych Clinical Psychology Clinic in Melbourne, Australia. Dr. Alvarenga holds a Doctorate in Clinical Psychology, a Masters in Public Health as well as undergraduate and postgraduate degrees in Science and Education. She is a member of the Australian Psychological Society and the College of Clinical Psychology. Her main area of interest is in cardiac neurosciences and psychosomatic research. Dr. Alvarenga has published on national and international journals focusing on the link between stress, mental illness, and increased risk of cardiovascular disease. She also lectures and supervises in the area of cardiac psychology, both within the School of Medicine and Psychology at various universities in Australia. She is also a past co-convener of the BakerIDI's Heart and Mind International Conference on psychogenic heart disease. Dr. Alvarenga is also an active practicing clinician.

Don Byrne
ANU Medical School
Australian National University
Canberra, ACT, Australia

Don Byrne is a Clinical Psychologist, and is now an Emeritus Professor of the Australian National University in Canberra and a Visiting Fellow in the ANU Medical School. Prior to his retirement in July 2014, he was Foundation Director of the Research School of Psychology at the ANU, and over the past two decades he has held a number of senior positions in academic administration in the University, including Head of the School of Psychology, Director of the School of Health and Psychological Sciences, and Interim Dean of the Faculty of Science. Professor Byrne holds doctorates from both the University of Adelaide (Ph.D.) and the Norwegian University of Science and Technology (Doctor Honoris Causa). He is an elected Fellow of both the Australian Psychological Society and the Academy of the Social Sciences in Australia, and he has authored, coauthored, or coedited 13 books (the *Handbook of Psychocardiology* makes the 14th) and around 150 commissioned book chapters or peer-reviewed papers in scholarly journals both in psychology and medicine. Professor Byrne's research has focused largely on the interface between psychology and physical illness, much of this related to identifying and treating psychological risk for cardiovascular disease. He continues to be active in research and currently sits on the Advisory Board of the Centre for Research in Health Promotion at the Norwegian University of Science and Technology in Trondheim, where he is also an Honorary Professor.

List of Contributors

Walter Abhayaratna ANU Medical School, College of Medicine, Biology and Environment, Australian National University, Garran, Canberra, ACT, Australia

Academic Unit of Internal Medicine, Canberra Hospital, Garran, Canberra, ACT, Australia

Marra G. Ackerman New York–Presbyterian Hospital, New York University Langone Medical Center, New York, NY, USA

Marcel Adriaanse Department of Health Sciences and the EMGO+ Institute for Health and Care Research, VU University Amsterdam, Amsterdam, The Netherlands

Marlies E. Alvarenga MonashHEART, Monash Cardiovascular Research Centre, Monash Health and Department of Medicine (SCS at Monash), Monash University, Melbourne, VIC, Australia

Shalini Arunogiri Turning Point, Fitzroy, VIC, Australia

Eastern Health Clinical School, Monash University, Box Hill, VIC, Australia

Shaira Baptista Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia

David Anthony Barton Human Neurotransmitters Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Faculty of Medicine, Nursing Health Sciences, Monash University, Melbourne, VIC, Australia

Roger Bartrop Discipline of Psychiatry, Sydney Medical School–Northern, St Leonards, University of Sydney, Sydney, NSW, Australia

Department of Mental Health, Blacktown–Mt Druitt Clinical School, School of Medicine, Western Sydney University, Sydney, NSW, Australia

Bernhard T. Baune Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, SA, Australia

Richard Bayles Laboratory for Vascular Translational Science, Inserm UMR-S1148, Paris, France

Scott R. Beach Department of Psychiatry, Massachusetts General Hospital/Warren 605, Boston, MA, USA

Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

George D. Bishop Division of Social Science, Yale–NUS College, Singapore, Singapore

Department of Psychology, National University of Singapore, Singapore, Singapore

James A. Blumenthal Department of Psychiatry and Behavioral Medicine, Duke University School of Medicine, Durham, NC, USA

Peter Bosanac St Vincent's Hospital, Melbourne, VIC, Australia

University of Melbourne, Melbourne, VIC, Australia

J. Douglas Bremner Emory University School of Medicine, Atlanta, GA, USA

Mental Health Research, Atlanta VAMC, Decatur, GA, USA

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

Kathryn M. Bruce Department of Surgery, Monash University, Monash Medical Centre, Clayton, VIC, Australia

Thomas Buckley Sydney Nursing School, University of Sydney, Sydney, NSW, Australia

Department of Cardiology, Royal North Shore Hospital, Sydney Medical School, University of Sydney, Sydney, NSW, Australia

Don Byrne ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia

ANU Medical School, Research School of Psychology, Australian National University, Acton, Canberra, ACT, Australia

John Cahill Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Greenville, NC, USA

Edward Callus Pediatric and Adult Congenital Heart Disease Centre, IRCCS Policlinico San Donato University Hospital, San Donato Milanese, Lombardy, Italy

James Cameron MonashHeart, Monash Medical Centre, Monash Health, Clayton, VIC, Australia

Monash Cardiovascular Research Centre, Southern Clinical School, Monash University, Melbourne, VIC, Australia

Luca Carnevali Department of Neuroscience, University of Parma, Parma, Italy

Melissa F. Casey Department of Psychological Medicine, Monash University, Monash Health, Clayton, VIC, Australia

David Castle St Vincent's Hospital, Melbourne, VIC, Australia

University of Melbourne, Melbourne, VIC, Australia

Christopher M. Celano Department of Psychiatry, Massachusetts General Hospital/Warren 605, Boston, MA, USA

Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

Mihail G. Chelu Department of Medicine, University of Utah, Salt Lake City, UT, USA

Massimo Chessa Pediatric and Adult Congenital Heart Centre, IRCCS-Policlinico San Donato-University Hospital, San Donato Milanese (Milan), Lombardy, Italy

David M. Clarke Department of Psychological Medicine, Monash University, Monash Health, Clayton, VIC, Australia

Fiona Cocker Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia

Sarah Cohen-Woods Matthew Flinders Fellow, School of Psychology, Flinders University, Adelaide, SA, Australia

Arup Kumar Dhar Human Neurotransmitters Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Faculty of Medicine, Nursing Health Sciences, Monash University, Melbourne, VIC, Australia

Assam El-Osta Epigenetics in Human Health and Disease Laboratory, Epigenomics Profiling Facility, The Alfred Medical Research and Education Precinct, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Department of Pathology, The University of Melbourne, Parkville, VIC, Australia

Central Clinical School, Department of Medicine, Monash University, Melbourne, VIC, Australia

Linda Ernstsen Faculty of Health and Social Sciences, Department of Nursing Sciences, Norwegian University of Science and Technology, Trondheim, Norway

Murray Esler Human Neurotransmitters Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Geir Arild Espnes Center for Health Promotion Research, Department of Social Work and Health Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Australian National University, Canberra, ACT, Australia

Ephrem Fernandez Department of Psychology, University of Texas, San Antonio, TX, USA

Jessica H. Ford Department of Psychology, East Carolina University, Greenville, NC, USA

Yariv Gerber School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Robert Gooley MonashHeart, Monash Medical Centre, Monash Health, Clayton, VIC, Australia

Monash Cardiovascular Research Centre, Southern Clinical School, Monash University, Melbourne, VIC, Australia

Robert A. M. Gregson Research School of Psychology, Australian National University, Canberra, ACT, Australia

Angela J. Grippo Department of Psychology, Northern Illinois University, De Kalb, IL, USA

Kaitlin Nicole Harkess School of Psychology, University of Adelaide, Adelaide, SA, Australia

Geoffrey A. Head Neuropharmacology Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Rosemary O. Higgins Heart Research Centre, Melbourne, VIC, Australia

Department of Physiotherapy, University of Melbourne, Melbourne, VIC, Australia

Jostein Holmen Department of Public Health and General Practice, HUNT Research Centre, Norwegian University of Science and Technology, Levanger, Norway

Jeff C. Huffman Department of Psychiatry, Massachusetts General Hospital/ Warren 605, Boston, MA, USA

Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

Alun C. Jackson Heart Research Centre, North Melbourne, VIC, Australia

Centre on Behavioral Health, University of Hong Kong, Pokfulam, Hong Kong

Richard Keegan Research Institute for Sport and Exercise, Faculty of Health, University of Canberra, Canberra, ACT, Australia

Steinar Krokstad Department of Public Health and General Practice, HUNT Research Centre, Norwegian University of Science and Technology, Levanger, Norway

Gavin William Lambert Human Neurotransmitters Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Faculty of Medicine, Nursing Health Sciences, Monash University, Melbourne, VIC, Australia

Magdalena Anna Lazarewicz Department of Medical Psychology, Medical University of Warsaw, Warsaw, Poland

Dan Lubman Turning Point, Fitzroy, VIC, Australia

Eastern Health Clinical School, Monash University, Box Hill, VIC, Australia

Jason Mazanov School of Business, UNSW-Canberra, Canberra, ACT, Australia

Graham Meadows Department of Psychiatry, Monash University, Clayton, VIC, Australia

School of Global and Population Health, The University of Melbourne, Clayton, VIC, Australia

Ian Meredith MonashHeart, Monash Medical Centre, Clayton, VIC, Australia

Southern Clinical School, Monash Cardiovascular Research Centre, Monash University, Melbourne, VIC, Australia

Harry Minas Global and Cultural Mental Health Unit, Melbourne Refugee Studies Program, School of Population and Global Health, The University of Melbourne, Parkville, VIC, Australia

Unni Karin Moksnes Center for Health Promotion Research, Norwegian University of Science and Technology, Trondheim, Norway

Roger Mulder Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

Barbara M. Murphy Heart Research Centre, Melbourne, VIC, Australia

Department of Psychology, University of Melbourne, Melbourne, VIC, Australia

Faculty of Health, University of Newcastle, NSW, Australia

Vicki Myers School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Eugene Nalivaiko School of Biomedical Sciences Flinders Medical Centre, University of Newcastle, Callaghan, NSW, Australia

School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, NSW, Australia

Matthew T. Naughton Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Monash University, Melbourne, VIC, Australia

Nenad Naumovski School of Public Health and Nutrition, Faculty of Health, University of Canberra, Canberra, ACT, Australia

Raj Nekkanti Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Greenville, NC, USA

Camilla Nguyen Center for Health Promotion Research, Department of Social Work and Health Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Brian Oldenburg Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia

Lisa Olive Research School of Psychology, The Australian National University, Canberra, ACT, Australia

Adrienne O'Neil Melbourne School of Population and Global Health, The University of Melbourne, Parkville, VIC, USA

School of Public Health and Preventive Medicine, Monash University, Clayton, VIC, USA

IMPACT Strategic Research Centre, Deakin University, Geelong, VIC, USA

Kristina Orth-Gomér Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Alice Owen School of Public Health and Preventive Medicine, CCRE Therapeutics, Monash University, Melbourne, VIC, Australia

Dinali N. Perera Department of Psychological Medicine, Monash University, Monash Health, Clayton, VIC, Australia

Anna C. Phillips Health Psychologist and Reader in Behavioural Medicine, School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK

Frans Pouwer Department of Medical and Clinical Psychology, Center of Research on Psychology in Somatic diseases (CoRPS), Tilburg University, Tilburg, The Netherlands

Emilia Quadri Pediatric and Adult Congenital Heart Disease Centre, IRCCS Policlinico San Donato University Hospital, San Donato Milanese, Lombardy, Italy

Christopher Reid School of Public Health and Preventive Medicine, CCRE Therapeutics, Monash University, Melbourne, VIC, Australia

Elizabeth Rieger Research School of Psychology, ANU College of Medicine, Biology and Environment, Australian National University, Acton, Canberra ACT, Australia

Stephen R. Robinson School of Health Sciences, RMIT University, Bundoora, VIC, Australia

Lindsey Rosman Department of Psychology, East Carolina University, Greenville, NC, USA

Rosemary Schwarz Baker IDI Heart and Diabetes Institute, Fitzroy, VIC, Australia

Samuel F. Sears Department of Psychology, East Carolina University, Greenville, NC, USA

Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Greenville, NC, USA

Andrea Sgoifo Department of Neuroscience, University of Parma, Parma, Italy

Peter A. Shapiro Department of Psychiatry, Columbia University Medical Center, Columbia University, New York, NY, USA

Frances Shawyer Department of Psychiatry, Monash University, Clayton, VIC, Australia

Chantal F. Ski Centre for the Heart and Mind, Australian Catholic University, Melbourne, VIC, Australia

Julian A. Smith Department of Surgery, Monash University, Monash Medical Centre, Clayton, VIC, Australia

Timothy W. Smith Department of Psychology, University of Utah, Salt Lake City, UT, USA

Aanchal Sood Voice Psychologists and Allied Professionals, Melbourne, VIC, Australia

Theodore A. Stern Department of Psychiatry, Massachusetts General Hospital/ Warren 605, Boston, MA, USA

Michael Stokes MonashHeart, Monash Medical Centre, Clayton, VIC, Australia

Erik R. Sund Department of Public Health and General Practice, HUNT Research Centre, Norwegian University of Science and Technology, Levanger, Norway

Yrsa Bergmann Sverrisdóttir Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK

Nuffield Department of Surgical Sciences, Department of Functional Neurosurgery, John Radcliffe Hospital, University of Oxford, Oxford, UK

Fatma Aboalsoud Taha Faculty of Medicine, Tanta University, Tanta, Egypt

Richard Telford Research Institute of Sport and Exercise, University of Canberra, Bruce, Canberra, ACT, Australia

Rohan Telford Centre for Research and Action in Public Health, University of Canberra, Bruce, ACT, Australia

David R. Thompson Centre for the Heart and Mind, Australian Catholic University, Melbourne, VIC, Australia

Geoffrey H. Tofler Department of Cardiology, Royal North Shore Hospital, Sydney Medical School, University of Sydney, Sydney, NSW, Australia

Alyna Turner IMPACT SRC, School of Medicine, Deakin University, Geelong, VIC, Australia

School of Medicine and Public Health, The University of Newcastle, Callaghan, NSW, Australia

Department of Psychiatry, University of Melbourne, Parkville, VIC, Australia

Viola Vaccarino Department of Epidemiology, Rollins School of Public Health, Department of Medicine, School of Medicine, Emory University, Atlanta, GA, USA

Gautam Vaddadi Department of Cardiology, The Alfred Hospital, Melbourne, VIC, Australia

Amanda Whited Department of Psychology, East Carolina University, Greenville, NC, USA

Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Greenville, NC, USA

Ilan S. Wittstein Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Dorota Wlodarczyk Department of Medical Psychology, Medical University of Warsaw, Warsaw, Poland

Marian Una Worcester School of Public Health, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia

Bo Xu MonashHeart, Monash Medical Centre, Clayton, VIC, Australia

Gregory W. Yelland School of Health Sciences, RMIT University, Bundoora, VIC, Australia

Julie Zarifeh Consultation-Liaison Service, Christchurch Public Hospital, Christchurch, New Zealand

Part I

Foundations of Cardiac Psychology

Psychogenesis and Heart Disease Now: The Thinking Heart in Action

Don Byrne and Marlies E. Alvarenga

Contents

Abstract

The term Psychocardiology has achieved prominence quite recently to describe both a field of research and an approach to clinical practice, though the evidence upon which this is based is not at all new. Systematic research linking the heart and the mind has a far longer history – its origins in medical science can be found more than a century ago in, for example, the work of the psychoanalytic movement. And from a more cardiologic space, the speculations of the eminent physician Sir William Osler clearly foreshadowed moves to link personality with diseases of the heart when he said of the person at risk of angina, that . . . *It is not the delicate neurotic person who is prone to angina, but the robust, the vigorous in mind and body, the keen and ambitious man, the indicator of whose engines is always at full speed*

D. Byrne (✉)
ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia

ANU Medical School, Research School of Psychology, Australian National University, Acton, Canberra, ACT, Australia
e-mail: Don.Byrne@anu.edu.au

M.E. Alvarenga
MonashHEART, Monash Cardiovascular Research Centre, Monash Health and Department of Medicine (SCS at Monash), Monash University, Melbourne, VIC, Australia
e-mail: marlies.alvarenga@monash.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_2

ahead. This chapter traces the origins of thought linking the heart and mind, commencing with the place of the heart in literature and religion, and ending with a hypothesis that subjective perceptions of cardiovascular activation arising from sympathetic arousal account for the compelling belief among person-kind that diseases of the heart are inextricably linked to afflictions of the mind.

Keywords
Heart disease • Psychogenic heart disease • Aetiology of heart disease • Psychocardiology • Mental illness • Cardiovascular disease

Introduction

The heart can quite accurately be called the driving organ of the human body. Its regular cycle of systole and diastole pumps life-sustaining blood through the arterial circulation to the rest of the body and then picks up waste materials through the venous circulation as blood returns to the heart, taking advantage of the cleansing capacity of the kidneys along its way. We have some conscious perception of this fundamental and continuous biological process through such physical sensations as the heartbeat – a regular pulsation felt in the left thoracic region of the body, clearly evident at rest on palpation or auscultation, and even more clearly apparent to us during such activities as strong physical exercise, when neither finger tips nor stethoscope is necessary to alert us to the constant action of the heart. The same conscious perception, of course, accompanies the myriad forms of psychological arousal – but more of that later. And while we can feel this action, we do not – and need not – consciously will it to happen. This is well taken care of – in the healthy individual at least – by the close interface between the cardiovascular system and both the central and peripheral nervous systems. The force of life is provided for us through a well-understood set of biological activities, deeply intricate in their individual functions but, at the same time, relatively clear-cut in mechanistic overview.

Of course that understanding of the functions of the cardiovascular system was not always so. Fleming's (1996) *A Short History of Cardiology* nicely explains the development of knowledge on the functions and actions of the heart from around 1700 to the mid-twentieth century, and Granger's (1998) paper on advances in cardiovascular physiology during the last century tracks the major biomedical milestones in this essential piece of medical history. The focus of these excellent works – and others as well – has however been clearly on biomedicine. And if we venture back further – or indeed if we just look in parallel with these major biomedical landmarks, at how person-kind has viewed the human heart throughout history – we see a somewhat more elaborate, divergent, and quintessentially poetic view of this organ so central to our existence.

We say this because in works of poetry, religion, and philosophy, or simply in folk wisdom, the heart has been identified unambiguously as the seat of human consciousness – the origin of our motives and emotions, indeed of our moral characters, whether good or bad. And references to the heart in this role abound in countless works of (nontechnical) literature.

Poets, Philosophers, and Other Wise People

In 1819 the romantic poet John Keats wrote, in his *Ode to a Nightingale*:

> My heart aches, and a drowsy numbness pains
> My sense, as though of hemlock I had drunk . . .

Keats spoke here of the bittersweet emotion he felt on hearing the beauty of the nightingale's song but reminded in doing so of the frailty and insignificance of human life – whether his own or of person-kind in general, we do not know. But it was his heart in which he located the felt and identifiable emotion and not his rational thinking self – no mention was made of the role of his cognitive persona.

Much will be made in this *Handbook* of the nexus between the heart and three of the most prominent of the more psychopathological emotions – anxiety, depression, and anger. This is not surprising since there is now unequivocal evidence from many sound and instructive scientific studies – epidemiological, clinical, and psychobiological alike – to causally link the continued experience of one or other of these emotions with the genesis of cardiovascular pathology and ultimately of cardiovascular disease (CVD). Even so, this now widely accepted scientific evidence is predated by a more poetic recognition that the heart is the true locus of the experienced emotion. Anxiety is said not just to reside in the heart but also to have deleterious consequences (*An anxious heart weighs a man down* – Proverbs, 12:25), and the angry heart too does not escape note (*Be not quick in your spirit to become angry for anger lodges in the heart of fools* – Ecclesiastes 7:9). But it is probably the sad and anguished heart that has attracted most attention from poets and those of like mind. Keats again, in 1820, highlights the heart in its anguish:

> Sudden a thought came like a full-blown rose,
> Flushing his brow, and in his pained heart
> Made purple riot. (From The Eve of St Agnes)

On the other hand, Emily Brontë (perhaps 20 years later but undated) spoke in a brief poem of the *sad and weary heart* (from *What Use is it to Slumber Here*). And of course William Shakespeare's archetypal depressive, Hamlet Prince of Denmark, in what must be one of the most recited and quoted reflections on the sad – and possibly suicidal – heart, said:

> To die, to sleep—
> No more—and by a sleep to say we end
> The heartache and the thousand natural shocks
> That flesh is heir to (Hamlet, Act 1, Scene 3).

But a plethora of other emotions and motives have also been linked to the heart through the pens of both well-known and lesser known commentators. The heart has been said to drive courage (*The brave*, *impetuous heart* . . . Matthew Arnold, from *Empedocles on Etna*, 1852) and moral purity (*Blessed are the pure in heart* . . .

Matthew 5:8) but also to be the seat of evil (*The heart is deceitful above all things, and desperately wicked* . . .Jeremiah 17:9). Both joy (*A laugh, to be joyous, must flow from a joyous heart* . . . Thomas Carlyle, 1795–1881) and anguish (*I groan in anguish of heart* . . . Psalm 38:8) have been attributed to the heart, as have both love (*Keep love in your heart* . . . Oscar Wilde, 1854–1900) and hope (*Walk on, walk on with hope in your heart* . . . from Rodgers and Hammerstein's 1945 musical *Carousel*). Kindness (*The larger heart, the kindlier hand* . . . from Alfred Lord Tennyson's *Ring Out Wild Bells*, 1850) and generosity (*If you haven't got any charity in your heart, you have the worst kind of heart trouble* . . . Bob Hope, 1903–2003) have both also been ascribed to the heart.

A commonly used Internet thesaurus provides many synonyms for the term *lightheartedness* (http://www.thesaurus.com/browse/lightheartedness), all of them equating to a state of care-free happiness. And to be lighthearted appears to be advantageous – an old Irish proverb is reported to promise that . . .*A light heart lives long*, a saying repeated in Shakespeare's *Loves Labours Lost*. Some among us are said (we hope) to be *big hearted* (generous, benevolent, or charitable), but others regrettably show the antithetical quality of being *mean hearted*. To be *coldhearted* implies a lack of empathy or feeling, while being *hard-hearted* is to be unkind, merciless, or pitiless. And in passing here, it is worth noting here that one of the really seminal scientific papers linking emotional experience to cardiovascular mortality, published by C Murray Parkes and his colleagues in 1969, was titled *Broken Heart*: *A Statistical Study of Increased Mortality Among Widowers*, the term *brokenhearted* being commonly used to describe the anguish of bereavement.

Thus, the question central to the introduction to this *Handbook* is why should the heart have been linked so consistently to emotions and motives in times before the emergence of persuasive scientific evidence on the biological operation of the cardiovascular system? Does the heart really *think*, does it *feel*, and does it drive our observable behaviors in ways which characterize our unique identities as individuals?

Stress, Distress, and the Cardiovascular System

In the light of empirical evidence accumulating over the past half century or more, the answer is now rather more straightforward – evidence emerging from the interface of psychology, neuroscience, and cardiovascular physiology makes it abundantly clear that the emotional lives of person-kind and the psychological forces which drive us and form our motivations have their origins in and are largely regulated by the central nervous system.

The issue of the psychobiological mechanisms linking the heart with the mind therefore presents itself to us for consideration. Much of the evidence documenting these mechanisms will be presented in considerable detail in many of the substantive chapters making up this *Handbook* and we do not intend to foreshadow or predetermine the substance of those chapters – they will speak for themselves with good authority. The nature of these mechanisms does, however, also have a strong

history of theoretical speculation and scientific investigation, and when added to a significant corpus of contemporary empirical evidence, an interesting and useful story may be told of why the heart has assumed a focus of such importance in the emotional and motivational lives of all of us as members of the human species.

The *Flight/Fight Mechanism* – that fundamental biological mechanism developed so early in the phylogenetic history of all mammalian (and many nonmammalian) organisms – was first (and so cogently) described by the pioneering psychologist William James in his landmark *Textbook of Psychology* as far back as 1892. This quite essential mechanism, and one which endows significant survival advantage to all organisms possessing it, has the simple function of biologically preparing individual organisms, as far apart in sophistication as humans and reptiles, for flight or fight in the face of threat or challenge. The manifestations of the mechanism are widespread across the body's basic biological systems, but the cardiovascular system figures prominently in its actions. Under threat or challenge, cardiac output is increased via an elevation in heart rate to deliver an increased volume of oxygen-rich blood and essential nutrients to those parts of the body which will need them in a state of focused exertion. At the same time, respiration rate (though not strictly a cardiovascular action) goes up to maintain an adequate level of gas exchange in the pulmonary circulation. One overall consequence of increased cardiac output important to any consideration of psychocardiology is the measurable, if not necessarily perceptible, increase in blood pressure – and particularly in systolic pressure – while the threat or challenge continues to exist. The entire process is intricately stage managed by a complex set of neurochemical responses to the presence of stimuli external to the organism and perceived by that organism to constitute a threat or challenge to its existence (broadly defined). But the fundamental character of the flight/fight mechanism is now very widely understood, and the contemporary evidence explaining its operation, and the consequences of its actions, may be found in Caltabiano et al. (2008).

There is a truly abundant collection of published evidence, both historically (see, e.g., Schneiderman et al. 1989) and right through to the present (see, e.g., Liao and Carey 2015), documenting clear associations between laboratory-imposed stressors of many kinds – typically though not always involving cognitive challenge – and cardiovascular arousal measured in a multitude of both simple and sophisticated ways. This general association is not in serious dispute. There is also published evidence documenting associations between psychosocial stress of a more chronic character, and cardiovascular arousal (Dienstbier 1989; Esch et al. 2002; Larsen and Christenfeld 2009), though the evidence here is both less voluminous and less clear-cut. And again, much of the contemporary evidence in both these domains of investigation will be reviewed in other chapters of this *Handbook*.

Of course the extent to which such measurable and well-documented cardiovascular changes – transient though they often are – can be subjectively perceived and then reported on by us as sentient beings is central to this story, as are the individual interpretations and meanings that we each (as individuals) place on those perceptions of altered cardiovascular activity which accompany the experience of external psychosocial events.

A useful – though somewhat less unified and consistent – corpus of laboratory-based evidence also tells us that a variety of widely different emotions, experienced, subjectively self-identified, and then reported on, are all, though in complex and often individually unique ways, characterized by measurable patterns of transiently altered cardiovascular activity. On the negative side of the domain of emotional experience, that of anger under stress or provocation has been associated with heightened cardiovascular reactivity (Siegman et al. 1992), particularly among those with high scores on measures of trait hostility (Suarez and Williams 1989). This finding is, however, probably further influenced by individual predispositions toward the capacity for emotional expression or suppression (Kline et al. 2008), and so the finding is not absolutely clear-cut.

Both anxiety and depression of clinical intensity have been associated with decreased levels of heart rate variability (HRV), a phenomenon which may be most apparent following an acute clinical episode of myocardial infarction (Gorman and Sloan 2000), possibly resulting in an increased vulnerability to further acute – and perhaps life-threatening – cardiovascular events. Why and Johnston (2008) found that the (self-reported) experience of cynicism was positively related to elevated blood pressure reactivity in normal participants undertaking a challenging computer task, but that this association was mediated by a simultaneous measure of state anger – and when state anger was low, the relationship between cynicism and blood pressure reactivity became negative. And in an examination of the infrequently investigated negative emotion of disgust, Rohrmann and Hopp (2008) found that decreased heart rate was related to the disgust associated with viewing a video clip of a challenging surgical procedure (an amputation). This result is both interesting and enlightening when considering the literature on disgust and trauma (Engelharda et al. 2011) and on trauma and heart disease (Coughlin 2011; Dennis et al. 2014).

And when we turn to the positive side of the domain of emotional experience, interruptions to compassion-oriented meditation sessions were shown to be related to an increase in heart rate, especially among those skilled in this meditation (Lutz et al. 2009), suggesting that the experience of compassion may exert a calming cardiovascular effect. It should be noted, however, that since some participants in this study were experienced meditators, the broadly calming influence of that cognitive state might, in large part, be responsible for the finding. The experience of happiness, however, exerted the opposite effect on cardiovascular arousal. Ambulant recordings of heart rate were quite strongly and positively correlated with self-reported happiness in a small sample of Japanese baseball fans watching a game in real time (Yoshino et al. 2011). In a similar manner, the self-reported experience of amusement during the viewing of humorous films was associated with elevated sympathetic arousal evident in the cardiovascular system (Lackner et al. 2014), though the authors caution lest an implication be taken from this, that in order to achieve enhanced cardiovascular health, we should strive to maintain a constant state of amusement. And of love, that emotion which some might consider the most positive of all? There has been a good deal of speculation, and some

cogent attempts to fit the experience of love into a clear neurobiological framework of autonomic arousal (Porges 1998, 2003), but little in the way of systematic and persuasive psychophysiological evidence has been provided to document this. And so perhaps, just for the time being, we must leave love to the poets.

In a recent and comprehensive review of the relevant literature, Appelhans and Luecken (2006) cogently argued that HRV might lay at the foundation of emotional regulation and, by extension, might provide a cogent biological mechanism through which subjective perceptions of cardiovascular activity may be causally linked to the experience of recognized and identifiable emotions. However, a broad perusal of the literature on the nature and functions of emotional regulation suggests that the area is typically defined and investigated as a global construct (Krohne et al. 2002; Mauss et al. 2007). And the psychobiological evidence to date does not provide a sustainable foundation for claims of any simple direction of causality – either that the experience of any particular emotion leads to a consistent and recognizable pattern of cardiovascular activation, or that identifiable and differentiable profiles of cardiac activity are interpreted to be uniquely linked to the subjective experience of specific emotional states.

The absence of causal evidence linking emotional experience and cardiovascular activity, one way or the other, presents an obvious barrier to a more complete understanding either of the feeling heart or of the thinking heart – but not a fatal one. Models driving further investigations in the area must – and almost certainly will – incorporate elements of cognition and the individual interpretation of perceived cardiovascular activity, along with the more traditional and objective measures of stimulus (events arising in the psychosocial environment) and response (cardiovascular activity itself). And though this will require complex and sophisticated research designs, and perhaps novel and creative approaches to measurement, it will in our view have the potential to advance the field of understanding significantly.

So where has this story lead us thus far? The functions of the heart and of the central and peripheral nervous systems – the mind, in more purely psychological terms – are intricately and inextricably linked. The evidence is abundantly clear on this point. But the heart does not – in and of itself – think or feel or cause us to act in one way or another. Rather, it reflects these cognitions and emotions and motives more or less faithfully, and in ways which are open to the subjective perceptions of the individual – and to the unique meanings which these perceptions give rise to in any among us. The heart can therefore be claimed to be a relatively accurate barometer of the nature and intensity of those psychological events – cognitions, emotions, and motivations – which in past times were believed to emanate directly from that organ itself. The linking psychobiological mechanisms remain to be fully clarified in the laboratory, though the rate and volume of the emergent published evidence are conspicuously apparent in progressive reviews of the literature – and much of this evidence will be expertly presented and reviewed in the remaining chapters of this *Handbook*. And of course the translation of evidence to clinical practice will not be forgotten.

Psychocardiology Now

While the heart/mind nexus has been acknowledged for many decades now (Koch 2013) and seriously investigated employing a multitude of research paradigms and methodologies, from those focusing largely on the psychosocial correlates of cardiovascular events through to those more concerned with these events themselves – and including diagnosed pathological events as well as those within the more normal domain of cardiovascular physiology – the origins of the term *psychocardiology* are obscure and its provenance is not easily attributed. In quite recent times, however, the use of the term has been seen more and more frequently in the scientific literature. A very systematic consideration of the evidence supporting the heart/mind nexus, and using the term psychocardiology in the title of the resulting publication, appeared less than a decade ago (Jordan et al. 2007). At around the same time, the inaugural *Heart and Mind*: *Psychogenic Cardiovascular Disease Conference* was convened by Australia's Baker IDI Heart and Diabetes Institute in 2008, and psychocardiology became an identifying catchphrase for this continuing series of meetings. And in a slightly more clinically oriented context, the term was proposed independently both by Koch (2013) and Halaris (2013) to delineate an emerging clinical field where the interface between cardiology, psychiatry, and psychology assumed a unique and integrated importance in addressing the effective management of the alarmingly large number of people in so many populations worldwide either with conspicuous CVD or at risk of manifesting this in the near future. A clearer recognition over time of the importance of the role played by depression in the genesis and course of CVD was certainly one driver of this movement (Halaris 2013), but it is equally apparent from a now overwhelming body of published evidence spanning a hundred years or more that psychocardiology delineates a far broader field of knowledge and clinical practice.

Conclusion

The *Handbook of Psychocardiology* has therefore taken as its mission, the presentation of this evidence, coupled with critical and expert commentary evaluating its worth and significance, in objectively establishing the nature of the heart/mind nexus as we now know it. It has undertaken this task fully recognizing the theoretical and empirical breadth of that evidence – from the psychosocial to the molecular biological, from the findings of the cardiovascular laboratory to those of population epidemiology, from studies of psychobiological causality to those from the realm of clinical management, and from the individual disciplinary perspectives of cardiology to those of psychology and psychiatry. And moreover – and probably most importantly – the *Handbook* takes as axiomatic the view that psychocardiology reflects above all the need for blurred and porous disciplinary boundaries and for disciplinary integration rather than jealously guarded territories in fully addressing the challenges of cardiovascular disease in the twenty-first century.

The *Handbook* aims to present as complete and authoritative as possible a contemporary picture of the field of psychocardiology. But just as it will answer many questions for research scientists and clinical practitioners alike, it will raise many more questions for research and practice into the future. To that extent, the *Handbook of Psychocardiology* presents a learning journey for a multitude of scientists and clinicians from so many individual areas, but all working to the common goal of better understanding and treating cardiovascular disease. It is a journey which we – as the *Handbook's* editors – have been truly pleased and excited to set in motion. And it is a journey on which we hope that you – the *Handbook's* readers – will share the excitement of taking forward.

References

Appelhans, B. M., & Luecken, L. J. (2006). Heart rate variability as an index of regulated emotional responding. *Review of General Psychology, 10*, 229–240.

Caltabiano, M. L., Byrne, D. G., & Sarafino, E. P. (2008). *Health psychology: Biopsychosocial interactions. Second Australasian edition*. Milton: Wiley.

Coughlin, S. S. (2011). Posttraumatic stress disorder and cardiovascular disease. *Open Cardiovascular Medical Journal, 5*, 164–170.

Dennis, P. A., Watkins, L. L., Calhoun, P. S., Oddone, A., Sherwood, A., Dennis, M. F., Risslingg, M. B., & Beckham, J. C. (2014). Posttraumatic stress, heart rate variability and the medicating role of behavioural health risks. *Psychosomatic Medicine, 76*(8), 629–637.

Dienstbier, R. A. (1989). Arousal and physiological toughness: Implications for mental and physical health. *Psychological Review, 96*, 84–100.

Engelharda, I. M., Olatunji, B. M., & de Jong, P. J. (2011). Disgust and the development of posttraumatic stress among soldiers deployed to Afghanistan. *Journal of Anxiety Disorders, 25*, 58–63.

Esch, T., Stefano, G. B., Fricchione, G. L., & Benson, H. (2002). Stress in cardiovascular diseases. *Medical Science Monitor, 8*, 93–101.

Fleming, P. (1996). *A short history of cardiology*. Atlanta: Editions Rodopi B. V. Amsterdam.

Gorman, J. M., & Sloan, R. P. (2000). Heart rate variability in depressive and anxiety disorders. *American Heart Journal, 140*(4 Suppl), 77–83.

Granger, H. J. (1998). Cardiovascular physiology in the twentieth century: Great strides and missed opportunities. *American Journal of Physiology, 275*, 1925–1936.

Halaris, A. (2013). Psychocardiology: Moving towards a new subspecialty. *Future Cardiology, 9*, 635–640.

James, W. (1892). *Textbook of psychology*. London: McMillan and Co.

Jordan, J., Bardé, B., & Zeiher, A. M. (Eds.). (2007). *Contributions toward evidence-based psychocardiology: A systematic review of the literature*. Washington, DC: American Psychological Association.

Kline, K. A., Fekete, E. M., & Sears, C. M. (2008). Hostility, emotional expression, and hemodynamic responses to laboratory stressors: Reactivity attenuating effects of a tendency to express emotion interpersonally. *International Journal of Psychophysiology, 68*, 177–185.

Koch, H. J. (2013). Psychocardiology: The spectrum of stress in the genesis of heart disease: A point of view. *Research Reports in Clinical Cardiology, 4*, 153–159.

Krohne, H. W., Manuela Pieper, M., Knoll, N., & Breimer, N. (2002). The cognitive regulation of emotions: The role of success versus failure experience and coping dispositions. *Cognition and Emotion, 16*(2), 217–243.

Lackner, H. K., Weiss, E. M., Hinghofer-Szalkay, H., & Papousek, I. (2014). Cardiovascular effects of acute positive emotional arousal. *Applied Psychophysiology and Biofeedback, 39*(1), 9–18.

Larsen, B. A., & Christenfeld, N. J. S. (2009). Cardiovascular disease and psychiatric comorbidity: The potential role of perseverative cognition. *Cardiovascular Psychiatry and Neurology*, *2009*. doi:10.1155/2009/791017. Article ID 791017, 8 p.

Liao, L.-M., & Carey, M. G. (2015). Laboratory-induced mental stress, cardiovascular response, and psychological characteristics. *Review of Cardiovascular Medicine, 16*(1), 28–35.

Lutz, A., Greischar, L. L., Perlman, D., & Davidson, R. J. (2009). BOLD signal in insula is differentially related to cardiac function during compassion meditation in experts vs. novices. *NeuroImage, 47*(3), 1038–1046.

Mauss, I. B., Bunge, S. A., & Gross, J. J. (2007). Automatic emotion regulation. *Social and Personality Psychology Compass, 1*, 146–167.

Parkes, C. M., Benjamin, B., & Fitzgerald, R. G. (1969). Broken heart: A statistical study of increased mortality among widowers. *British Medical Journal, 1*(5646), 740–743.

Porges, S. W. (1998). Love: An emergent property of the mammalian autonomic nervous system. *Psychoneuroendorinology, 23*(8), 837–861.

Porges, S. W. (2003). The polyvagal theory: Phylogenetic contributions to social behavior. *Physiology and Behavior, 79*, 503–513.

Rohrmann, S., & Hopp, H. (2008). Cardiovascular indicators of disgust. *International Journal of Psychophysiology, 68*, 201–208.

Schneiderman, N., Weiss, S. M., & Kaufmann, P. G. (Eds.). (1989). *Handbook of research methods in cardiovascular behavioral medicine*. New York: Plenum Press.

Siegman, A. W., Anderson, R., Herbst, J., Boyle, S., & Wilkinson, J. (1992). Dimensions of anger-hostility and cardiovascular reactivity in provoked and angered men. *Journal of Behavioral Medicine, 15*(3), 257–272.

Suarez, E. C., & Williams, R. B., Jr. (1989). Situational determinants of cardiovascular and emotional reactivity in high and low hostile men. *Psychosomatic Medicine, 51*(4), 404–418.

Why, Y. P., & Johnston, D. W. (2008). Cynicism, anger and cardiovascular reactivity during anger recall and human–computer interaction. *International Journal of Psychophysiology, 68*, 219–227.

Yoshino, K., Matsumoto, S., Someya, E., & Kitajima, M. (2011). Happiness and heart rate response: A case of fan services at Japanese professional baseball games. *Natural Science, 3*, 255–258.

Cardiac Psychology: Ancient and Modern History

Murray Esler and Rosemary Schwarz

Contents

Abstract

Ideas linking the heart to the brain exist in ancient and of course modern texts. In antiquity, the brain was not given its due! The London physician and neuroanatomist Thomas Willis changed this, correctly attributing the source of emotions to the brain. Contemporary research does establish the existence, and autonomic nervous system mechanisms, of cardiac responses to emotion. Further, it documents the phenomenon of "triggered" heart disease, when the autonomic nervous control of the heart goes awry, producing heart disease of sudden onset, precipitated by acute emotional upheaval.

M. Esler (✉)
Human Neurotransmitter Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia
e-mail: murray.esler@bakeridi.edu.au

R. Schwarz
Baker IDI Heart and Diabetes Institute, Fitzroy, VIC, Australia
e-mail: schwarzr@bigpond.net.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_1

Keywords
Mental stress • Autonomic nervous system • Psychosomatic heart disease • Depressive illness • Panic disorder • "Triggered" heart attacks

Introduction

Ideas linking the heart to the brain and emotions exist in ancient and of course modern texts. For Aristotle (Hamilton and Richards 1982; Zimmer 2004), the eyes and ears were connected not to the brain but to blood vessels, which carried perceptions to the heart. In his dialogues, *Timaeus* (Hamilton and Richards 1982; Zimmer 2004), Plato located the "vital soul" in the heart. *The heart was a distributor of the vital spirit and seat of the soul*. In the heart, Herophilus and Erasistratus described the blood turning red as it was imbued with vital spirit (Hamilton and Richards 1982; Zimmer 2004). Vital spirit was distributed through arteries to the body, including to the brain where, acting as a pump, the brain distributed it as a liquor through the nerves. The vital soul was "endowed with courage and passion and loves contention," Plato wrote (Hamilton and Richards 1982; Zimmer 2004). Along with the blood, the vital soul's passions flowed out of the heart, exciting the body into action. The superior soul, in his spiritual anatomy, had the brain at its apex; the lower souls were the liver and heart. Plato ascribed no physical site to the immortal soul, but early Christian Church fathers did. Although having no physical dimension, its faculties resided in the ventricles of the brain (Zimmer 2004).

The Heart as Both a Prime Mover and a Mirror of the Emotions

For Aristotle (Hamilton and Richards 1982; Zimmer 2004), the heart had centrality, governing all sensations, movements, and emotions, through heat generation and distribution through blood vessels; the brain was secondary, in that it "tempers the heat and seething of the heart." An explicit ancient "psychocardiology" reference was attributed to Philistion of Locri, in Plato's dialogue, *Timaeus* (Hamilton and Richards 1982): "As a means of relief from the leaping heart when the passion is excited . . . from the action of fire they (the engendered sons of God) contrived and implanted the form of the lung – soft and bloodless . . ." (Hamilton and Richards 1982).

The Heart Upstaged by the Brain: Mind and Soul Made Flesh in the Brain

The London physician and neuroanatomist, Thomas Willis introduced the "Neurocentric Age," which has dominated thinking until the present day, as a central tenet of contemporary Western thought (Zimmer 2004). From his study of

the anatomy of the healthy brain, of the "brain of brutes" (sufferers of insanity or mental defect), and by his clinical observations on those of his patients whom on their death came to anatomical dissection, he banished the soul, and the source of emotions, from the heart to the brain (Zimmer 2004). The biography of Willis and his pivotal contributions are recounted in the book of Carl Zimmer, *Soul Made Flesh* (Zimmer 2004).

Autonomic Innervation of the Heart

The studies of the anatomist, Vesalius, and the physician and experimenter, Harvey (Hamilton and Richards 1982), established that, above all, the heart is a pump, although a responsive pump, responding to physical needs and to emotion. The extrinsic regulation of the heart is primarily via the autonomic nervous system, by way of its vagal and sympathetic nervous system innervation, supplemented by adrenal medullary secretion of adrenaline. Heart rate and cardiac output reflexly increase with exercise, to distribute the oxygen needed to sustain the physical work of muscles, and additionally both are augmented by emotions in the fight or flight response, to facilitate engagement or escape at times of threat. Reflex heart rate slowing driven by the cardiac vagus occurs in "vasovagal" hypotension and syncope, triggered by prolonged standing, pain, or anxiety (Vaddadi et al. 2010).

Autonomic control of the heart in humans can be studied through the use of pharmacological autonomic blockade, of the vagus nerve with atropine (Julius et al. 1971), and of the cardiac sympathetic nerves, with beta-adrenergic blockade (Julius and Esler 1975; Esler et al. 1977), allowing investigation of the influence of the autonomic nervous system on heart rate, cardiac output, and left ventricular contractility. The release of the neurotransmitter, noradrenaline, from the sympathetic nerves of the human heart has been measured with isotope dilution methodology (Esler et al. 1984), to quantify cardiac sympathetic nervous activity at rest, during exercise (Hasking et al. 1988), and during laboratory mental stress responses (Esler et al. 1989, 1995) and in patients with anxiety and depression (Alvarenga et al. 2006; Barton et al. 2007).

Heart Rate in Psychological Measurement

Increase in heart rate is so central to alerting responses and to acutely experienced anxiety that heart rate measurements have been used as a surrogate measure of stress and anxiety. This was formalized in the lie-detector polygraph test, where measurements of change in heart rate, blood pressure, respiration, and galvanic skin response (increased electrical conductance from stimulated sweating) with structured questioning were used to detect criminal deception. Non-specificity in the test limited its validity and judicial acceptance. The common use of increases in heart rate to quantify cardiac sympathetic nerve stimulation is actually not valid, due to the confounding contribution of cardiac vagal withdrawal to the tachycardia.

"Heart on Your Sleeve": The Heart in Language

English language of the present day (Collins Dictionary 2001) captures both the ancient concepts of the heart as the center of vitality and passions and contemporary ideas encompassed in the various constructs of psychocardiology. Common parlance considers the heart as the seat of life, emotions, love, courage, tenderness, and pity. Your heart can be "on your sleeve," "in your mouth," or "in your boots." You may "lose your heart" (by being in love) or be "heartbroken" (with grief or despair). Doing something "heart and soul" (i.e., absolutely) is an expression which would have conveyed meaning for the ancients.

Psychosomatic Heart Disease

There has been a recent strong resurgence of support for the idea, often in the past banished to the realm of medical folklore, that mental stress and psychological illness is a cause of cardiovascular disease (Table 1). This acceptance, however, has been in the face of a high level of skepticism, very explicitly illustrated in the deliberations of a panel charged with reviewing the topic for an Australian national health body on which one of us served. The opening address of the chair included the opinion, "there is no evidence that stress causes heart disease, nor will there ever be." The authors, who are a cardiologist and a psychiatrist, here aim to correct the chairman's error.

War has been a fertile field for the development of psychosomatic heart disease, with identification and nomenclature being dependent on the era and the level of sophistication in the psychiatric formulation. *Soldiers heart*, *irritable heart*, *shell shock*, *and combat exhaustion* are wartime disorders which have morphed post-DSM III into the rubric of post-traumatic stress disorder. In civilian life, the contemporary evidence supporting the existence of psychosomatic (psychogenic) cardiovascular disease (Table 1) is perhaps strongest for the acute precipitation ("triggering") of the cardiac events (Rozanski et al. 1999) of myocardial infarction,

Table 1 Psychosomatic cardiovascular disease

Acute mental stress as a cardiac "trigger"
Myocardial infarction, sudden death
Takotsubo cardiomyopathy
Depressive illness
Post-traumatic stress disorder
Panic disorder
Chronic mental stress
Causally linked to coronary heart disease and essential hypertension
Schizophrenia
Manic-depressive disorder
Psychotropic drugs

sudden death, and takotsubo cardiomyopathy (stress cardiomyopathy) (Tsuchihashi et al. 2001) by acute mental stress. Triggered cardiac end points, and their mechanism, are presented in the next section.

There is strong evidence that patients with *major depressive disorder* are at increased risk of developing coronary heart disease (Frasure-Smith et al. 1993; Musselman et al. 1998; Bunker et al. 2003). This elevated risk is independent of classical risk factors such as smoking, obesity, hypercholesterolemia, diabetes and hypertension.

While the mechanism of increased cardiac risk attributable to depressive illness is uncertain, the research of several groups indicates the probable importance of the existing high level of chronic sympathetic nervous system activation in depressive illness in the generation of cardiac risk (Esler et al. 1982; Gold et al. 2005; Barton et al. 2007). In a range of other clinical contexts, most notably heart failure (Kaye et al. 1995), ongoing stimulation of the cardiac sympathetic outflow has been demonstrated to contribute to mortality.

Panic disorder sufferers often fear that they have heart disease, because of the nature of their symptoms, but in the past were reassured that this is not the case. Epidemiological studies, however, indicate that there is an increased risk of myocardial infarction and sudden death in patients with panic disorder (Kawachi et al. 1994a, b). In his own extensive clinical experience with the management of panic disorder sufferers, the cardiologist author has encountered case material which indicates the range of cardiac complications which can occur during panic attacks, variously triggered cardiac arrhythmias, recurrent emergency room attendances with angina and ECG changes of ischemia, coronary artery spasm documented in panic attacks occurring during coronary angiography, and myocardial infarction associated with coronary spasm and thrombosis (Mansour et al. 1998). Activation of the sympathetic nervous system during panic attacks is a mediating mechanism (Alvarenga et al. 2006; Wilkinson et al. 1998). With subcutaneous multifiber sympathetic nerve recording, stimulation of the sympathetic nervous system during panic attacks has been documented, accompanied by surges of adrenaline secretion from the adrenal medulla (Wilkinson et al. 1998).

The causal importance of chronic mental stress in the genesis of *coronary heart disease* and *essential hypertension* and cardiac risk in schizophrenia is presented elsewhere in the handbook.

"Triggered" Heart Disease

It has always seemed plausible that short-term mental stress can act as an immediate precipitant ("trigger") for the development of abnormal heart rhythm and sudden death in patients with existing heart disease. For many years this claimed relation of acute mental stress to heart attacks was largely based on individual anecdotes, such as the celebrated case of the famous eighteenth-century English surgeon, John Hunter, who wrote that he was at the mercy of any scoundrel who aggravated him and then proved the point by dying suddenly in the middle of a stormy meeting

of the board of his hospital. Some people are predisposed through genetic flaws to heart risk at times of mental stress, such as those with inherited variants of the long QT interval syndrome, in whom abnormal ion transport in cardiac myocytes causes electrical instability of the heart muscle (Zipes 1991).

In recent years systematic evidence has been gathered at times of disasters, including war, missile attacks on civilians, and earthquakes, which also strongly supports the proposition of a mental stress-heart attack link. Research linking mental stress to sudden death is often disputed because of disagreement over what constitutes a stress and whether stress can be accurately measured. Evidence that rates of sudden, non-traumatic death are markedly increased during earthquakes, the 1994 Los Angeles earthquake providing a very telling example (Leor et al. 1996), is free of this criticism, as here no finessing is needed in the psychological measurement of stress. During an earthquake, no doubt everyone is terrified. Are heart attacks during community disasters a special case only or of more general relevance? In individual personal life, "emotional earthquakes" do occur. In his clinical practice, the cardiologist author has seen heart attacks in his patients triggered by armed robbery, assaults, and even a racehorse winning by a "nose." Additionally, cardiac events during panic attacks are an explicit instance of triggering (Mansour et al. 1998).

The biological mechanisms by which acute mental stress triggers heart attacks are clear (Rozanski et al. 1999) (Fig. 1). First, this occurs almost exclusively in those with existing atherosclerotic coronary artery narrowing, although this may have been clinically silent and unrecognized. In the presence of coronary artery stenosis and myocardial ischemia, the preferential activation of the sympathetic nervous outflow to the heart with acute mental stress (Esler et al. 1989) can cause

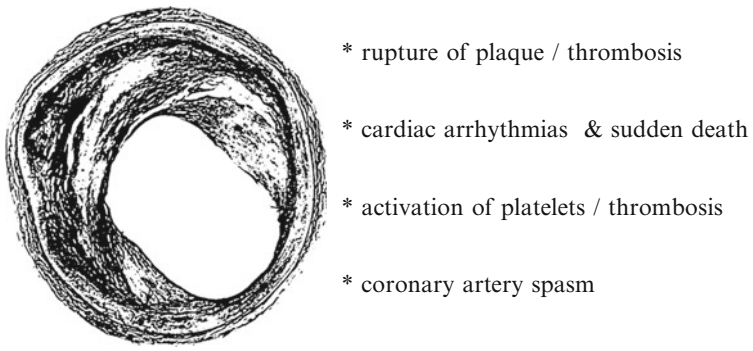


Fig. 1 "Triggering" of myocardial infarction and sudden death. Sympathetic nervous activation with acute mental stress (accompanied by vagal withdrawal) can act as a "trigger" for clinical presentation of previously silent coronary artery disease. The blood pressure surge with mental stress can lead to fissuring or rupturing of an atherosclerotic plaque, coronary artery thrombosis, myocardial infarction, and sudden death. In the presence of coronary artery stenosis, sympathetic activation and vagal withdrawal can induce lethal ventricular arrhythmias. Catecholamine activation of platelets is thrombogenic. High levels of activation of the cardiac sympathetic nerves can cause coronary artery spasm, perhaps via neuropeptide Y release

ventricular arrhythmias. Increased adrenaline secretion by the adrenal medulla activates platelets, predisposing to thrombosis. The blood pressure surge accompanying acute mental stress can fissure coronary artery plaques, providing a focus for thrombosis, leading to myocardial infarction. Neural mechanisms, perhaps the release of neuropeptide Y at high rates of sympathetic nerve firing (Esler et al. 2004), can cause coronary artery spasm.

Conclusion

Sudden cardiac death is the most significant and challenging problem in contemporary cardiology. So often coronary atherosclerosis is clinically silent and undetected, to become catastrophically evident when an unstable atherosclerotic plaque fissures or ruptures, leading to coronary thrombosis, myocardial infarction, and a lethal ventricular arrhythmia. An acute physical stressor, commonly extreme exercise, or acute mental stress is the usual trigger. To counter the sudden cardiac death nemesis, recent coronary artery imaging research aims to detect subcritical but clinically silent coronary artery stenosis and unstable coronary atherosclerotic plaques. Delineating the biological mediators of heart risk in an acute mental stress would provide a potential target for prevention, to inhibit platelet activation and block excessive cardiovascular stimulation by the sympathetic nervous system and adrenaline.

References

Alvarenga, M. E., Richards, J. C., Lambert, G., & Esler, M. D. (2006). Psychophysiological mechanisms in panic disorder: A correlative analysis of noradrenaline spillover, neuronal noradrenaline reuptake, power spectral analysis of heart rate variability and psychological variables. *Psychosomatic Medicine, 68*, 8–12.

Barton, D. A., Dawood, T., Lambert, E. A., Esler, M. D., Haikerwal, D., Hotchkin, E., et al. (2007). Sympathetic activity in major depressive disorder: Identifying those at increased cardiac risk? *Journal of Hypertension, 25*, 2117–2124.

Bunker, S. J., Colquhoun, D. M., Esler, M. D., Hickie, I. B., Hunt, D., Jelinek, V. M., et al. (2003). "Stress" and coronary heart disease: Psychosocial risk factors. National Heart Foundation of Australia position statement update. *Medical Journal of Australia, 178*, 272–276.

Esler, M., Julius, S., Zweifler, A., Randall, O., Harburg, E., Gardiner, H., et al. (1977). Mild high-renin essential hypertension: A neurogenic human hypertension? *New England Journal of Medicine, 296*, 405–411.

Esler, M., Turbott, J., Schwarz, R., Leonard, P., Bobik, A., Skews, H., et al. (1982). The peripheral kinetics of norepinephrine in depressive illness. *Archives of General Psychiatry, 9*, 295–300.

Esler, M., Jennings, G., Korner, P., Blombery, P., Sacharias, N., & Leonard, P. (1984). Measurement of total and organ-specific norepinephrine kinetics in humans. *American Journal of Physiology, 247*(Endocrinol Metab 10), E21–E28.

Esler, M., Jennings, G., & Lambert, G. (1989). Measurement of overall and cardiac norepinephrine release into plasma during cognitive challenge. *Psychoneuroendocrinology, 14*, 477–481.

Esler, M. D., Thompson, J. M., Kaye, D. M., Turner, A. G., Jennings, G. L., Cox, H. S., et al. (1995). Effects of aging on the responsiveness of the human cardiac sympathetic nerves to stressors. *Circulation, 91*, 351–358.

Esler, M., Alvarenga, M., Lambert, G., Kaye, D., Hastings, J., Jennings, G., et al. (2004). Cardiac sympathetic nerve biology and brain monoamine turnover in panic disorder. *Annals of the New York Academy of Science, 1018*, 505–514.

Frasure-Smith, N., Lesperance, F., & Talajiic, M. (1993). Depression following myocardial infarction: Impact on 6-month survival. *JAMA, 270*, 1819–1861.

Gold, P. W., Wong, M.-L., Goldstein, D. S., Gold, H. K., Ronsaville, D. S., Esler, M., et al. (2005). Cardiac implications of increased arterial entry and reversible 24-h central and peripheral norepinephrine levels in melancholia. *PNAS, 102*, 8303–8308.

Hamilton, W. F., & Richards, D. W. (1982). Output of the heart. In A. P. Fishman & D. W. Richards (Eds.), *Circulation of the blood, men and ideas*. Bethesda: American Physiological Society.

Hasking, G. J., Esler, M. D., Jennings, G. L., Dewar, E., & Lambert, G. (1988). Norepinephrine spillover to plasma during steady-state supine bicycle exercise: Comparison of patients with congestive heart failure and normal subjects. *Circulation, 78*, 516–521.

Julius, S., & Esler, M. D. (1975). Autonomic cardiovascular regulation in borderline hypertension. *American Journal of Cardiology, 36*, 685–696.

Julius, S., Pascual, A., & London, R. (1971). Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. *Circulation, 44*, 413–418.

Kawachi, I., Colditz, G. A., Ascherio, A., Rimm, E. B., Giovannucci, E., Stampfer, M. J., et al. (1994a). Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation, 89*, 1992–1997.

Kawachi, I., Sparrow, D., Vokanas, P. S., & Weiss, S. T. (1994b). Symptoms of anxiety and coronary heart disease. The normative aging study. *Circulation, 90*, 2225–2229.

Kaye, D. M., Lefkovits, J., Jennings, G. L., Bergin, P., Broughton, A., & Esler, M. D. (1995). Adverse consequences of high sympathetic nervous activity in the failing human heart. *Journal of the American College of Cardiology, 26*, 1257–1263.

Leor, J., Poole, W. K., & Kloner, R. A. (1996). Sudden cardiac death triggered by an earthquake. *New England Journal of Medicine, 334*, 413–419.

Mansour, V. M., Wilkinson, D. J. C., Jennings, G. L., Schwarz, R. G., Thompson, J. M., & Esler, M. D. (1998). Panic disorder: Coronary spasm as a basis for cardiac risk? *Medical Journal of Australia, 168*, 390–392.

Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The relationship of depression to cardiovascular disease. *Archives of General Psychiatry, 55*, 580–592.

Rozanski, A., Blumenthal, J. A., & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation, 99*, 2192–2217.

Tsuchihashi, K., Ueshima, K., Uchida, T., Oh-mura, N., Kimura, K., Owa, M., et al. (2001). Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. Angina pectoris-myocardial infarction investigations in Japan. *Journal of the American College of Cardiology, 38*, 11–18.

Vaddadi, G., Esler, M. D., Dawood, T., & Lambert, E. (2010). Persistence of muscle sympathetic nerve activity during vasovagal syncope. *European Heart Journal, 31*, 2027–2033.

Wilkes, G. A. (Ed.). (2001). *Collins dictionary of the English language* (Australian edition, 2nd ed.). Sydney: William Collins Publishers.

Wilkinson, D. J. C., Thompson, J. M., Lambert, G. W., Jennings, G. L., Schwarz, R. G., Jefferys, D., et al. (1998). Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress and during panic attacks. *Archives of General Psychiatry, 55*, 511–520.

Zimmer, K. (2004). *Soul made flesh*. London: The Random House (Arrow Books).

Zipes, D. P. (1991). The long QT interval syndrome. A Rosetta stone for sympathetic related ventricular tachyarrhythmias. *Circulation, 84*, 1414–1419.

Fundamentals of Cardiology for the Non-Cardiologist

Bo Xu, Michael Stokes, and Ian Meredith

Contents

Abstract

Awareness of the fundamentals of cardiac anatomy, physiology and various disease states is essential to clinicians managing a patient with cardiac pathology. This chapter summarizes the key aspects of cardiac structure and function, as well as providing an overview of the broad range of cardiac pathology.

B. Xu (✉) • M. Stokes
MonashHeart, Monash Medical Centre, Clayton, VIC, Australia
e-mail: greatbear2237@hotmail.com; mbstokes83@gmail.com

I. Meredith
MonashHeart, Monash Medical Centre, Clayton, VIC, Australia

Southern Clinical School, Monash Cardiovascular Research Centre, Monash University, Melbourne, VIC, Australia
e-mail: ian.meredith@monash.edu; ian.meredith@myheart.id.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_3

The chapter discusses the various presentations of cardiac disease and the clinical assessment that is performed. Diseases discussed include those of cardiac rhythm, vessels, valves, and muscle as well as congenital heart disease. The various modalities of investigation and basic principles of management are also reviewed.

Keywords

Atrial fibrillation (AF) • Bradyarrhythmias • Bundle of His • Cardiology • Basic anatomy of • Basic embryology of • Cardiac cycle • Cardiovascular disorders. *see* Cardiovascular disorders • Heart rate regulation • Normal electrical conduction system • Cardiovascular disorders • Arrhythmias • Cardiomyopathy and heart failure • Congenital heart disease • Ischemic heart disease • Valvular heart disease • Congenital heart disease • Contractility • Coronary artery disease (CAD) • Diastole • Endocardium • Epicardium • Heart block • Heart failure with preserved ejection fraction (HF-PEF) • Heart failure with reduced ejection fraction (HF-REF) • Left atrial appendage • Myocardium • Non-ST-elevation myocardial infarction (NSTEMI) • Patent foramen ovale (PFO) • Percutaneous coronary intervention (PCI) • Permanent pacemaker (PPM) • Primary foramen • Secondary foramen • Secondary septum • ST-elevation myocardial infarction (STEMI) • Systole • Tachyarrhythmias • Torsades de pointes • Transcatheter aortic valve replacement (TAVR) • Unstable angina (UA) • Valvular heart disease

Cardiology is the branch of medicine which deals with the comprehensive assessment, diagnosis, and management of patients with diseases and disorders of the heart. Within the specialty of cardiology, adult cardiologists deal with patients with cardiovascular disorders in the adult age group, including elderly patients, while pediatric cardiologists treat patients with cardiovascular disorders in the pediatric age group, including newborns. There are further subspecialty areas of practice within cardiology, broadly divided into interventional cardiology, noninvasive cardiology, and electrophysiology. Firstly, interventional cardiologists use percutaneous techniques to diagnose and manage patients with coronary artery disease and other structural heart problems. Percutaneous coronary intervention refers to a number of techniques that are used to treat significant atherosclerotic lesions in coronary arteries. Congenital heart defects such as patent foramen ovale and atrial septal defect can also be closed percutaneously. Recent advances in percutaneous transcatheter aortic valve replacement (TAVR) have revolutionized the treatment of patients with severe symptomatic aortic stenosis, who were previously deemed inoperable. Secondly, noninvasive cardiologists specialize in the diagnosis and assessment of patients with cardiac problems by employing multimodality cardiac imaging techniques, including echocardiography, multi-detector computed tomography (MDCT), and cardiac magnetic resonance imaging (CMR). These cardiac imaging techniques help guide diagnosis and the selection and delivery of appropriate interventional treatment options for the appropriate patients. Thirdly, cardiac

electrophysiologists deal with rhythm disorders of the heart. They specialize in the implantation of cardiac devices, such as permanent pacemakers (PPMs) to treat bradyarrhythmias, implantable cardioverter defibrillators (ICDs) to prevent ventricular fibrillation and sustain ventricular tachycardia, and cardiac resynchronization therapy (CRT) in appropriate patients with severe symptomatic congestive cardiac failure. Electrophysiologists also employ complex techniques to diagnose and treat rhythm disorders of the heart.

The purpose of this chapter is to provide readers with a general overview of cardiology. It will begin with an overview of the anatomy, embryology, and physiology of the human heart, followed by a focused and clinically relevant discussion of common cardiovascular disorders.

Basic Anatomy of the Human Heart

The heart is located in the thoracic cavity. It works as an efficient muscular pump as a result of the coordinated function of the four cardiac chambers. The atria (the left and right atria) are smaller and superiorly located. The ventricles (the left and right ventricles) are larger and inferiorly located (Fig. 1). The heart is slightly rotated toward the left in the thoracic cavity, such that the right ventricle is the most anterior cardiac chamber. The left ventricular wall thickness is approximately twice that of the right ventricle. This is because the left ventricle is required to pump blood through the entire body in the systemic circulation. In comparison, the right ventricle pumps blood through the lungs in the pulmonary circulation. Under

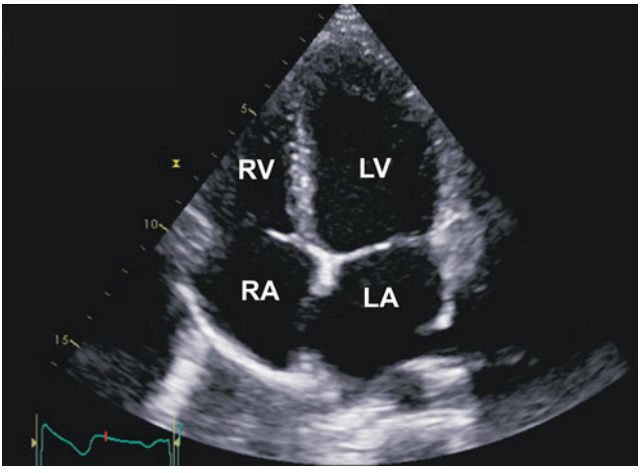


Fig. 1 Normal structure of the heart showing the four cardiac chambers (apical four-chamber view on transthoracic echocardiography). *Abbreviations*: *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

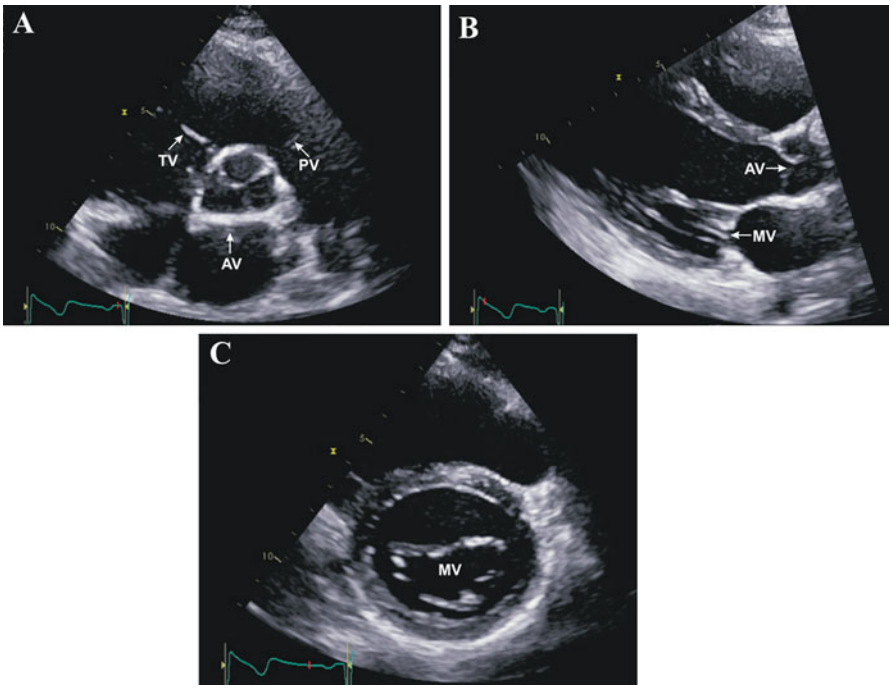


Fig. 2 Transthoracic echocardiography depicting the four cardiac valves, in parasternal short-axis (**a**), parasternal long-axis (**b**), and parasternal short-axis (mitral valve level) (**c**) views. During diastole, mitral valve opening gives rise to a characteristic "fish-mouth" appearance (**c**). *Abbreviations*: *TV* tricuspid valve, *AV* aortic valve, *PV* pulmonary valve, *MV* mitral valve

normal conditions, the pulmonary circulation is a low-pressure system compared to the systemic circulation.

Disorders of cardiac muscle are broadly known as cardiomyopathy. These disorders result in a common clinical syndrome termed congestive cardiac failure.

The heart contains four valves: two atrioventricular valves and two outflow tract valves. The tricuspid valve is situated between the right atrium and the right ventricle (Fig. 2a). The pulmonary valve is located in the right ventricular outflow tract (Fig. 2a). The mitral valve is situated between the left atrium and the left ventricle (Fig. 2b, c). The aortic valve is located in the left ventricular outflow tract (Fig. 2a, b). Cardiac valves can be affected by various disease processes and become pathologically narrowed (stenosis) or leaky (regurgitant). Disorders of the cardiac valves are broadly known as valvular heart disease.

The heart muscle is supplied with blood by the coronary arteries. The coronary arteries arise from the sinuses of Valsalva at the level of the aortic root. Coronary arteries are unique in that they accommodate blood flow predominantly during diastole, the relaxation phase of the cardiac cycle. The coronary arteries are divided into a left anterior descending artery, a left circumflex artery, and a right coronary

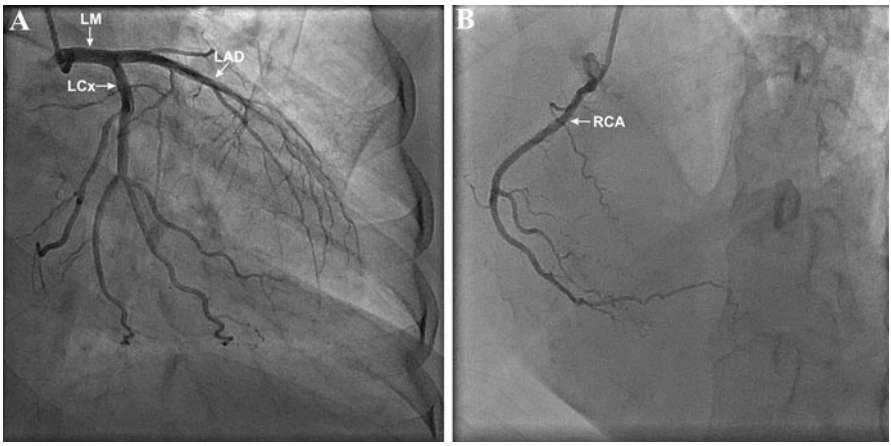


Fig. 3 Coronary angiogram demonstrating the left coronary system in the right anterior oblique caudal projection (**a**) and the right coronary artery in the left anterior oblique cranial projection (**b**). *Abbreviations*: *LM* left main trunk, *LAD* left anterior descending artery, *LCx* left circumflex artery, *RCA* right coronary artery

artery (Fig. 3). The dominance of the coronary arterial circulation is determined by which artery (either the left circumflex artery or the right coronary artery) that gives rise to the posterior descending artery branch which resides in the posterior interventricular groove. Disorders of the coronary arteries are broadly known as coronary artery disease. The commonest cause of coronary artery disease is atherosclerosis.

Basic Embryology of the Heart

By the eighth week of gestation, the major morphological developments of the human heart have been completed (Watanabe and Wikenheiser 2015). The primitive heart is derived from the lateral plate mesoderm, consisting of symmetric mesoderm regions on each side of the primitive streak (Oostra and Moorman 2009). A tube is then formed from these tissues, consisting of an inner layer, called the endocardium, a layer of extracellular matrix, and an outer layer, called the myocardium (Oostra and Moorman 2009). The outermost layer is called the epicardium, arising from the tissue dorsal to the heart at the level of the atrioventricular junction (Oostra and Moorman 2009). The epicardium spreads over the outer surface of the myocardium. Rhythmic contraction of this simple tube follows, resulting in areas of dilatation, which ultimately will form the cardiac chambers, and areas of constriction, which ultimately will form the interatrial and interventricular septa (Oostra and Moorman 2009). Subsequently, the outflow tract and the sinus venosus are appended to the distal ends of the simple tube (Oostra and Moorman 2009; Preeta et al. 2012).

The primitive common atrial chamber arises from the expansion of the caudal region of the simple tube (Oostra and Moorman 2009). It subsequently divides into the two atrial chambers by the formation of a crescentic ridge (primary septum) (Oostra and Moorman 2009; Preeta et al. 2012). The area between the leading edge of the developing primary septum and the endocardial cushions is known as the primary foramen (Oostra and Moorman 2009). The primary foramen becomes progressively smaller in size, as the primary septum grows toward the endocardial cushions. Eventually, the primary foramen closes as a result of fusion of the primary septum with the endocardial cushions (Oostra and Moorman 2009). Subsequently, multiple small fenestrations develop at the superior aspect of the primary septum to form the secondary communication between the developing atria known as the secondary foramen (ostium secundum) (Oostra and Moorman 2009; Preeta et al. 2012). Next, an infolding of the atrial roof grows down along the right atrial side of the primary septum. This infolding of the atrial roof is known as the secondary septum (Oostra and Moorman 2009; Preeta et al. 2012). The secondary septum develops to lie over the secondary foramen, except for a small area inferiorly. The area of the primary septum which is exposed on the right atrial side, not covered by the secondary septum, is the fossa ovalis (Oostra and Moorman 2009; Preeta et al. 2012). A flap-like valve called the foramen ovale is created between the two atria (Oostra and Moorman 2009; Preeta et al. 2012). The foramen ovale functions as a one-way valve to allow only right-to-left blood flow between the two atria in utero. Shortly after birth, this defect is permanently fused in most people. Persistence of this communication between the atria is known as a patent foramen ovale (PFO). PFO is a common congenital heart lesion occurring in 30 % of the general population. It is commonly an incidental finding of no major clinical significance. However, for certain patients, it can be associated with ischemic stroke by facilitating the passage of paradoxical embolus from the right-sided cardiac chambers to the systemic circulation. In these situations, the PFO required could be closed percutaneously by interventional cardiologists. PFO closure has also been advocated by some as an effective treatment for migraine. However, this claim has not been supported by results from recent randomized trial data (Ailani 2014).

Ventricular septation continues after the primary atrial septum is formed. It results from the complex process of growth and remodeling of trabecular sheets, expansion of the ventricular chambers, and the fusion of several tissues to form the membranous and the muscular interventricular septum (Watanabe and Wikenheiser 2015; Oostra and Moorman 2009; Preeta et al. 2012).

Basic Physiology of the Heart

Cardiac Cycle

In a standard cardiac cycle, there are two phases that allow blood to transition through the heart's four chambers. Systole refers to the phase of contraction, while diastole refers to the phase of relaxation (Guyton and Hall 2000). The two atria and

the two ventricles alternatively contract and relax, providing the environment to force blood from areas of higher pressure to areas of lower pressure. When blood is flowing from the atria to the ventricles, the tricuspid and mitral valves are open to allow this movement. Similarly, during ventricular systole, when blood is flowing from the right ventricle to the lungs and from the left ventricle to the systemic circulation, the pulmonary and aortic valves, respectively, open.

Cardiac output refers to the volume of blood which is ejected from the left ventricle into the aorta each minute (Guyton and Hall 2000). It equals the stroke volume (the volume of blood ejected by the left ventricle with each contraction) multiplied by the heart rate (the number of heartbeats per minute) (Guyton and Hall 2000). In a healthy heart, stroke volume is regulated by the following three factors:

1. Preload – the degree of stretch in the heart before it contracts. The effect of volume on myocardial stretch is explained by the Frank-Starling mechanism. The Frank-Starling law dictates that the volume of blood ejected by the ventricles during systole is dependent upon the volume of blood present in the ventricles at the end of diastole. With increased myocardial fiber length at the end of diastole (with higher volume), the strength of cardiac contraction and consequently stroke volume and cardiac output will be higher. This principle applies for the healthy human heart but not in hearts with disorders of contraction.
2. Contractility – this refers to the strength of myocardial contraction at any given preload. With stimulation of the sympathetic division of the autonomic nervous system and the presence of the hormones adrenaline and noradrenaline, cardiac muscle fiber contraction is more forceful which will increase stroke volume. Drugs which increase ventricular contractility are classified as inotropes.
3. Afterload – this refers to the resistance that needs to be overcome for the ventricles to eject their volume of blood. In disease states where there is increased resistance to be overcome (e.g., hypertension or valve stenosis), left ventricular wall stress is increased, which, if significant, may reduce stroke volume and cardiac output.

Normal Electrical Conduction System

The heart has its own intrinsic electrical conduction system. In the normal physiological state, the dominant electrical impulse is generated from the sinoatrial node (SA node) within the right atrium. This electrical signal, traveling through the atrium, corresponds to the P wave on ECG. Before reaching the ventricles, the electrical impulse has to pass through the atrioventricular node (AV node). At the AV node, the electrical impulse is delayed. This corresponds to the PR interval on ECG. From the AV node, the electrical impulse is conducted through specialized conduction tissue known as the bundle of His, which is composed of the left and right bundle branches. Subsequently, the electrical signal reaches the distal ventricles directly via the Purkinje fibers. This process of ventricular muscle

depolarization corresponds to the QRS complex on ECG. Electrical repolarization of the ventricular muscle then takes place, corresponding to the T wave on ECG. The PR interval is measured from the onset of the P wave to the onset of the QRS complex. The QT interval is measured from the onset of the QRS complex to where the downstroke of the T wave meets the electrical baseline on the ECG. Disorders of the cardiac conduction system often manifest as deranged timing or shape of the ECG complexes.

Heart Rate Regulation

Variations in heart rate can affect the cardiac output. This can occur in various physiologic states. The most important regulation of heart rate occurs via the autonomic nervous system and its eventual modulation of the SA node (Guyton and Hall 2000). The hormones adrenaline and noradrenaline which are released from the adrenal medullae also affect heart rate regulation and, consequently, cardiac output. A cardiovascular regulation center is located in the medulla oblongata of the brain stem (Guyton and Hall 2000). Sensory impulses monitoring movements, blood chemistry, and blood pressure feed into this center. Other brain centers also provide input, including the limbic system. This cardiovascular center modulates output by increasing or decreasing the nerve impulse activity via the sympathetic and parasympathetic components of the autonomic nervous system.

Sympathetic fibers extend from the medulla oblongata to the spinal cord and leave the spinal cord at the thoracic level (Guyton and Hall 2000). These fibers then innervate the SA node, the AV node, and the myocardium via efferent cardiac accelerator nerves. Sympathetic effect on heart rate is mediated at the muscle level by the neurohormone, noradrenaline. Parasympathetic nerve impulses reach the heart via the right and left vagus nerves (Guyton and Hall 2000). These fibers then innervate the SA node, the AV node, and the atrial myocardium. The parasympathetic nerve fibers release acetylcholine at these sites, resulting in reduction in heart rate.

Cardiovascular Disorders

Disorders of the Coronary Arteries: Ischemic Heart Disease

Coronary artery disease (CAD) due to obstructive atherosclerotic lesions is the overwhelmingly predominant cause of ischemic heart disease. Patients with coronary artery disease commonly present with chest pain. It is important to differentiate chest pain as a result of myocardial ischemia from other causes of chest pain (Fig. 4). There is a wide clinical spectrum of ischemic heart disease, depending on the acuity of the presentation, and electrocardiographic (ECG) and cardiac biomarker changes. Patients with underlying CAD, who have stable nonprogressive angina symptoms on exertion, are classified as having chronic stable ischemic heart

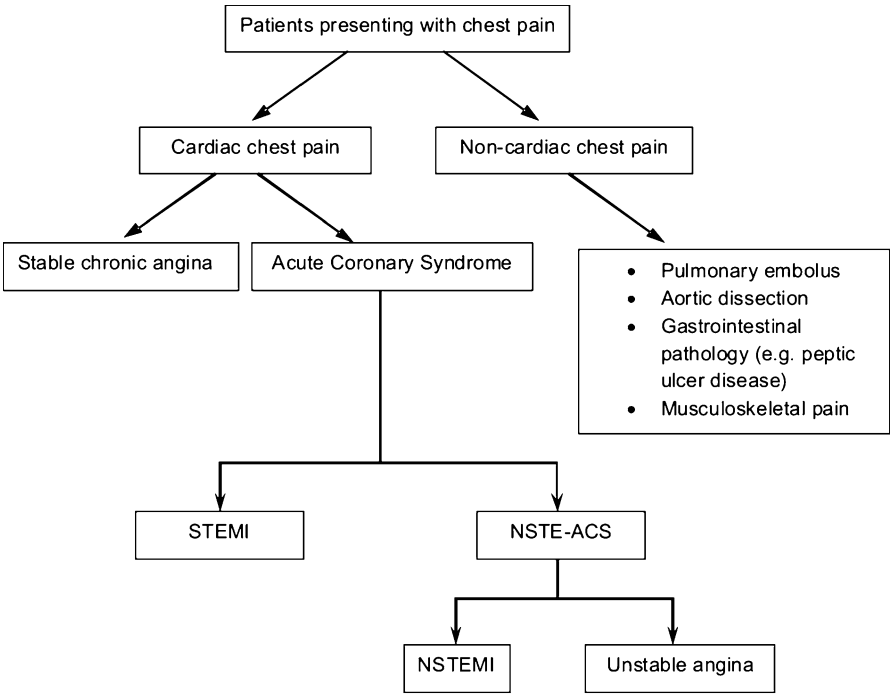


Fig. 4 A clinical classification of patients presenting with chest pain. Refer to the text for details. *Abbreviations*: *STEMI* ST-elevation myocardial infarction, *NSTE-ACS* non-ST-elevation acute coronary syndrome, *NSTEMI* non-ST-elevation myocardial infarction

disease. Patients with coronary artery disease who have an acute disease presentation are said to have an acute coronary syndrome. The spectrum of acute coronary syndrome consists of unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). The differentiation between these entities is based on ECG and serum biomarker measurements (Fig. 4). On history, patients with an acute coronary syndrome usually have prolonged typical chest pain symptoms or an accelerating pattern of chest pain symptoms that occur on minimal exertion or at rest. UA is not associated with any cardiac biomarker rise. STEMI is associated with persistent ST segment elevation in two or more contiguous ECG leads. NSTEMI is associated with serum cardiac biomarker evidence of myocardial necrosis but without ST segment elevation on ECG.

Ischemic heart disease is the commonest cause of mortality worldwide. The risk factors for ischemic heart disease include hypertension, smoking, dyslipidemia, diabetes mellitus, and obesity. Chronic renal disease and chronic inflammatory conditions such as rheumatoid arthritis are increasingly recognized as also being risk factors for ischemic heart disease. The general pathophysiological principles of ischemic heart disease revolve around the development of atheromatous plaques

causing progressive narrowing of coronary arteries, but it is the rupture of unstable atheromatous plaques that cause the development of acute coronary syndromes.

The comprehensive assessment of a patient with suspected ischemic heart disease begins with history. Classically, chest pain due to myocardial ischemia is described as a pressure or heaviness sensation in the retrosternal area. It is classically brought on by exertion and relieved by rest and nitroglycerin. Other features of the chest pain may include radiation to the left arm, shoulder, neck, and jaw. However, atypical chest pain features do not reliably exclude myocardial ischemia. Women and diabetic patients tend to present with atypical symptoms. Other associated features of acute myocardial infarction include dizziness, pre-syncope, syncope, dyspnea, and diaphoresis.

The fundamental investigation for assessment of acute coronary syndromes is the 12-lead ECG. In STEMI, there is persistent ST segment elevation in two or more contiguous ECG leads (Thygesen et al. 2012). In NSTEMI and UA, the ECG abnormalities include ST segment depression and T wave inversion. These ECG changes could be dynamic and occur during myocardial ischemia. Serial ECGs are important in the assessment of patients presenting with acute chest pain. Evidence of myocardial necrosis can be confirmed by elevation of cardiac specific troponin enzyme levels (troponin I and troponin T). However, it should be noted that elevated troponin is not synonymous with acute coronary syndrome. There are multiple conditions which could cause an elevation in serum troponin (Xu and MacIsaac 2013). In patients presenting with a chest pain syndrome who do not have serum biomarker elevation, noninvasive cardiac imaging investigations play vital roles in the diagnosis of underlying coronary artery disease and the assessment of underlying myocardial ischemia. Multi-detector cardiac computed tomography can effectively diagnose coronary artery disease. It has been used in the emergency department setting to rapidly assess patients presenting with chest pain. Exercise stress ECG is a widely available test that assesses for underlying myocardial ischemia. It is however limited by reduced sensitivity and specificity compared to more advanced imaging modalities for myocardial ischemia, such as exercise stress echocardiography and nuclear stress perfusion study. In the presence of baseline ECG changes and bundle branch block, exercise stress ECG testing cannot be used to reliably assess for myocardial ischemia.

For patients who have been found to have significant CAD on noninvasive imaging techniques and for patients with a confirmed acute coronary syndrome, further assessment should occur with invasive coronary angiography. Coronary angiography allows direct visualization of the coronary arteries. Significant coronary artery lesions can be detected based on visual assessment and/or physiological assessment (fractional flow reserve assessment). In patients presenting with STEMI (Fig. 5), urgent coronary angiography is performed, with a view to perform percutaneous coronary intervention (PCI) and restore coronary artery blood to the region of the myocardium supplied by the occluded artery within 60 min of first medical contact (Fig. 6). In patients with significant coronary artery disease burden, such as triple-vessel coronary artery disease in the setting of diabetes mellitus, coronary artery bypass surgery is generally preferred to PCI. In patients with stable

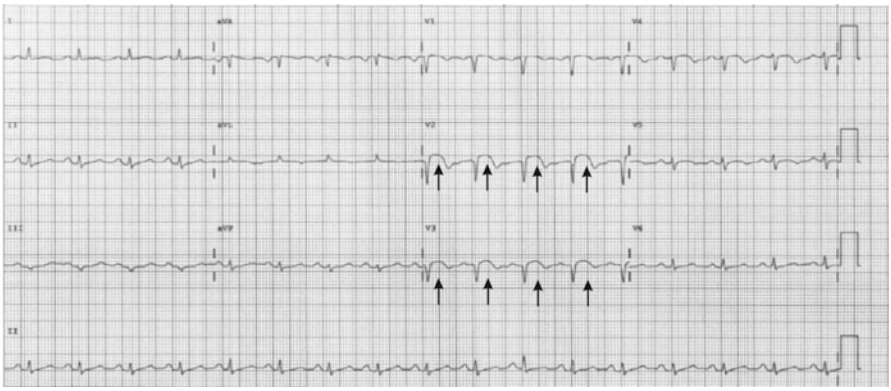


Fig. 5 12-lead electrocardiogram demonstrating 2 mm ST segment elevation in the anterior ECG leads (*black arrows*) for a patient presenting with acute anterior ST-elevation myocardial infarction

coronary artery disease, it has been shown that patients can be effectively managed by optimal medical therapy.

Typical medical therapy of patients with coronary artery disease includes antiplatelet agents (aspirin and another antiplatelet agent such as clopidogrel or ticagrelor), a high-dose lipid-lowering agent (such as a statin), an angiotensin-converting enzyme inhibitor, and a beta-blocker. Lifestyle measures that are of vital importance in the management of coronary artery disease include weight reduction, smoking cessation, and healthy dietary habits (Estruch et al. 2013). Coronary artery disease should not be viewed as a localized disease affecting the coronary arteries, but rather it should be managed as part of a systemic pro-inflammatory atherosclerotic milieu in patients with predisposing cardiovascular risk factors. Therefore, regardless of whether an interventional strategy is pursued (PCI or CABG), ongoing lifestyle measures and optimal medical therapy are of the utmost importance. Addressing the risk factors for coronary artery disease and achieving compliance with optimal medical therapy reduce the progression of atherosclerotic plaque and the risk of further acute coronary syndromes.

Disorders of the Electrical Conduction System: Arrhythmias

Heart Block and Bradyarrhythmias

Bradycardia is defined as a pulse rate less than 60 beats per minute. Heart rhythms which are less than 60 beats per minute are broadly categorized as bradyarrhythmias. Diseases of the conduction system which result in slowed electrical conduction can lead to heart block. When the heart's intrinsic conduction system cannot generate a rhythm that is fast enough to sustain circulation and normal physiology, a device known as the permanent pacemaker (PPM) can be implanted to deliver artificially generated electrical impulses. In general, electrical

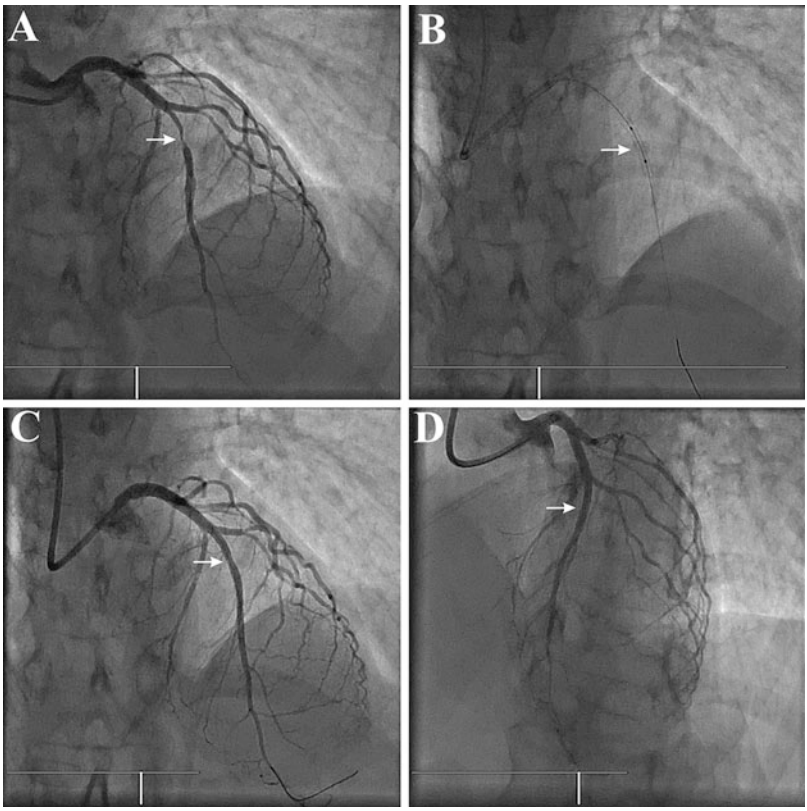


Fig. 6 Emergency percutaneous coronary intervention with angioplasty and stenting to a critical mid-left anterior descending (LAD) artery lesion for a 58-year-old patient presenting with an anterior ST-elevation myocardial infarction. Coronary angiogram demonstrating the severe mid-LAD lesion prior to stenting (anterior-posterior cranial projection) (**a**), fluoroscopy demonstrating the stent deployed at the site of the severe mid-LAD lesion (anterior-posterior cranial projection) (**b**), coronary angiogram demonstrating the successful treatment of the severe mid-LAD lesion by angioplasty and stent deployment (anterior-posterior cranial projection) (**c**), final angiogram after coronary guidewire removal demonstrating excellent final angiographic result (left anterior oblique cranial projection)

signal conduction delay at a level below the AV node indicates more advanced conduction disease and is more often pathological, compared to conduction delay at or above the level of the AV node. First-degree heart block is defined as a prolonged PR interval that is greater than 200 ms. Isolated first-degree heart block is generally asymptomatic and can usually be managed conservatively. However, first-degree heart block may occur as part of more advanced conduction system disease (e.g., as part of tri-fascicular block). Second-degree heart block is divided further into Mobitz type 1 and Mobitz type 2. In Mobitz type 1 heart block, there is progressive prolongation of the PR interval with each subsequent heartbeat, until a P wave is not

followed by a QRS complex, and the cycle resumes. Conduction delay in Mobitz type 1 heart block usually occurs within the AV node, above the level of the bundle of His. Mobitz type 1 heart block can be a normal physiological phenomenon, especially as a result of increased vagal tone during sleep. Mobitz type 1 heart block is generally not associated with syncope. Mobitz type 2 heart block occurs when a P wave is not followed by a QRS complex following a pattern (e.g., 3:1 Mobitz type 2 heart block refers to the situation when for every three P waves, there is only one conducted QRS complex). Mobitz type 2 heart block generally indicates conduction disease below the level of the AV node. In symptomatic patients with pre-syncope or syncope, without a reversible cause (such as beta-blocker medication), treatment with permanent pacing is generally indicated. In third-degree heart block, there is no electrical signal conduction from the atria to the ventricles, causing a phenomenon known as AV dissociation. In these situations, ventricular depolarization relies on the function of other pacemaker cells located within deeper parts of the conduction system, below the level of the AV node. These pacemaker cells generate a slow junctional or ventricular "escape" rhythm, usually at rates of 30–40 beats per minute. Patients with third-degree heart block can present with syncope. Permanent pacing is strongly indicated for all patients with third-degree heart block, unless there is a clear reversible cause or contraindication to permanent pacing (e.g., active systemic sepsis).

Tachyarrhythmias

Tachycardia is defined as a pulse rate greater than 100 beats per minute. Tachyarrhythmias can be broadly divided into those arising from above the ventricular level (supraventricular) and those arising from within the ventricle (ventricular). Supraventricular tachyarrhythmias are generally associated with a narrow QRS complex and are generally benign. Ventricular tachyarrhythmias are generally associated with a broad QRS complex and are often associated with hemodynamic instability and/or cardiac arrest. Supraventricular tachyarrhythmias include arrhythmias associated with accessory conduction pathways such as in the Wolff-Parkinson-White syndrome, junctional tachycardia, atrial tachycardia, atrial flutter, and atrial fibrillation. Generally, these rhythm disorders can be treated with medications. In certain situations, electrophysiological ablation procedures can be performed to ablate the pathways predisposing to these rhythm disorders.

Ventricular tachyarrhythmias include ventricular tachycardia and ventricular fibrillation. Ventricular tachycardia can result from myocardial ischemia, underlying cardiomyopathy, or acquired and congenital causes of prolonged QT interval in patients with a structurally normal heart. Prolonged QT interval can predispose to a specific form of polymorphic ventricular tachycardia known as torsades de pointes (Fig. 7). Ventricular fibrillation most commonly results from myocardial ischemia. Pulseless ventricular tachycardia and ventricular fibrillation should be treated emergently by electrical cardioversion (defibrillation). Ventricular tachyarrhythmias resulting from myocardial ischemia should be treated by revascularization, restoring blood supply to regions of ischemic myocardium. There are specialized pharmacological treatment options for ventricular tachyarrhythmias. In certain

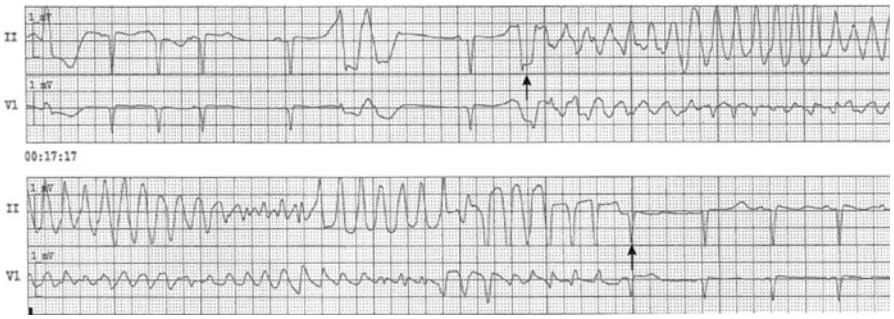


Fig. 7 Rhythm strip demonstrating a run of *torsades de pointes*, a form of polymorphic ventricular tachycardia (*arrows* point to the commencement and termination of the polymorphic ventricular tachycardia)

situations, ICDs are indicated to treat recurrent ventricular tachyarrhythmias in survivors of cardiac arrest. ICDs are also used for the primary prevention of sudden cardiac death in patients with cardiomyopathy and severely impaired left ventricular systolic function. For some patients, electrophysiological procedures can ablate the electrical pathways predisposing to ventricular tachyarrhythmias.

Atrial Fibrillation

Atrial fibrillation (AF) is an increasingly common problem in the aging population. It is the commonest type of arrhythmia encountered in clinical practice. AF is associated with an increased risk for the development of congestive cardiac failure. It is also associated with a twofold increase in risk for all-cause mortality and fivefold increased risk for stroke (Roger et al. 2012). AF is a supraventricular tachyarrhythmia characterized by an irregularly irregular ventricular rhythm and baseline fibrillatory waves (Fig. 8). Common cardiac abnormalities associated with AF include hypertensive heart disease with left ventricular hypertrophy, ischemic heart disease, and valvular heart disease such as mitral valve disease. Sleep-disordered breathing and obesity are being increasingly recognized as risk factors for AF. Temporary precipitants for AF include sepsis, excessive alcohol intake, and hyperthyroidism. Patients with AF can present with palpitations, dyspnea, fatigue, and decreased exercise tolerance. Many patients with AF do not have any subjective symptoms.

The clinical classification of AF includes several categories based on the time course: (1) paroxysmal, if the AF episode terminates spontaneously within 7 days of onset; (2) persistent, if the AF episode lasts for 7 days or longer; and (3) permanent, long-standing AF persisting for more than 1 year, which is refractory to cardioversion. The key management decisions for patients with AF include choosing a management strategy aimed at either rhythm control (attempting to achieve and maintain sinus rhythm) or rate control (controlling the ventricular rate response and accepting the patient's rhythm being AF), followed by an assessment of the individual patient's thromboembolic and stroke risk. In AF, thrombus can

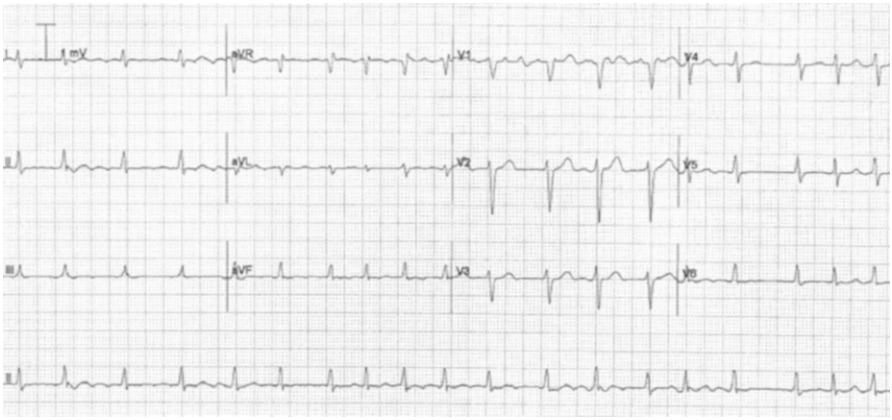


Fig. 8 12-lead electrocardiogram demonstrating atrial fibrillation, characterized by an irregularly irregular ventricular rhythm and baseline fibrillatory waves

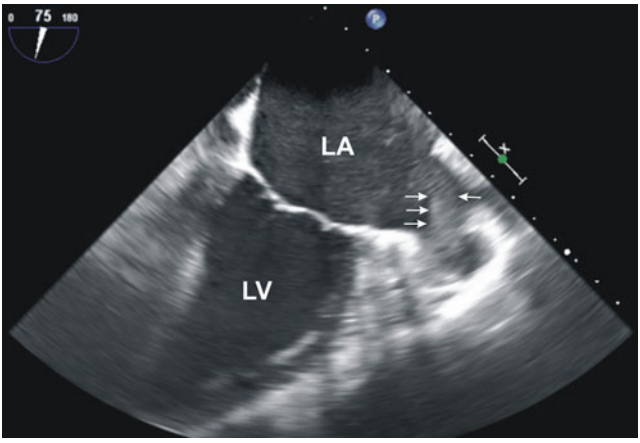


Fig. 9 Transesophageal echocardiogram (mid-esophageal view) demonstrating prominent thrombus (*arrows*) in the left atrial appendage for a patient in chronic atrial fibrillation. Note the severely dilated left atrium. *Abbreviations*: *LA* left atrium, *LV* left ventricle

commonly form in an atrial structure known as the left atrial appendage, which is continuous with the left atrium (Fig. 9). Dislodgment of thrombus from the left atrial appendage can cause systemic embolic phenomena, including stroke. The decision to pursue a rhythm- or rate-control strategy depends on the individual patient's clinical situation. Generally, for a young patient with new-onset AF, attempts are made to pursue rhythm control as these patients often do not tolerate AF well. In comparison, for an elderly patient with multiple comorbidities and dilated left atrium, the rate-control strategy may be reasonable. It has been shown that there are no mortality differences between pursuing either a rhythm-control or

rate-control strategy (Wyse et al. 2002). Validated assessment tools which guide the clinical assessment to individual patient's thromboembolic risk associated with AF are the $CHADS_2$ score and the more recently updated CHA_2DS_2-VASc score. For patients with a CHA_2DS_2-VASc score of ≥ 1, an oral anticoagulant should be considered (Camm et al. 2012). Until recently, warfarin has been the gold-standard and mainstay anticoagulation therapy for patients with non-valvular AF. There are now novel oral anticoagulants which could be used for patients with non-valvular AF: rivaroxaban, apixaban, and dabigatran (Xu and Whitbourn 2012). One major advantage of these novel anticoagulants is that they do not require regular monitoring blood tests. However, at this stage, there are no commercially available reversal agents for these agents in the event of life-threatening hemorrhage.

Cardiomyopathy and Heart Failure

Congestive cardiac failure, or heart failure, is defined as a complex clinical syndrome characterized by structural and/or functional cardiac disorders that lead to impairment of the ability of the ventricles to fill (diastolic heart failure) or eject blood (systolic heart failure) (Camm et al. 2006; Libby et al. 2008). Heart failure is a condition that carries a high morbidity and mortality (Libby et al. 2008; Lily 2007). Early identification and institution of appropriate treatment is important for good patient outcome. Dyspnea at rest and on exertion is a common presenting complaint. Other clinical manifestations include fatigue, decreased exercise tolerance, or fluid retention. Clinical examination may reveal signs of congestion (i.e., pulmonary, hepatic, peripheral) or evidence of organ hypoperfusion secondary to reduced cardiac output (i.e., cool peripheries, confusion, abdominal organ ischemia).

The clinical syndrome of heart failure can be further subdivided into those with reduced left ventricular ejection fraction (HF-REF) and those with preserved left ventricular ejection fraction (HF-PEF). This distinction has significant impact on the selection of appropriate investigations, management strategies, and patient prognosis (Page et al. 2014). There are no major differences in the initial clinical presentation between patients with HF-PEF or HF-REF, but there are important differences in the epidemiological profile between these two patient groups.

It is important to differentiate between predominantly right-sided heart failure, as opposed to left-sided heart failure in order to stratify patients into the appropriate management pathway (Table 1). Right heart failure often presents as a consequence of left heart failure but can also be a consequence of cor pulmonale which reflects a failing right ventricle as a result of increased vascular resistance or high pressures in the lungs (pulmonary hypertension). Cor pulmonale can occur in the context of a variety of conditions including idiopathic pulmonary arterial hypertension, chronic obstructive pulmonary disease (COPD), chronic recurrent pulmonary emboli, interstitial lung disease, and obstructive sleep apnea. The causes of left heart failure are summarized below in the discussion of heart failure with reduced ejection fraction.

Table 1 Clinical features of right- and left-sided heart failure syndromes

Clinical presentation of right heart failure	Clinical presentation of left heart failure
Fatigue	Dyspnea
Dyspnea	Exercise intolerance
Peripheral edema	Orthopnea (dyspnea on lying flat)
Abdominal distension	Paroxysmal nocturnal dyspnea
Syncope on exertion	Dizziness, confusion

Table 2 Clinical conditions associated with heart failure with reduced ejection fraction

Common	Myocardial ischemia/ischemic heart disease (approximately 50 % of new cases)
	Hypertension
Less common	Idiopathic dilated cardiomyopathy
	Familial dilated cardiomyopathy
Uncommon	Valvular heart disease
	Alcohol-associated cardiomyopathy
	Inflammatory cardiomyopathy (i.e., post-viral myocarditis)
	Peripartum cardiomyopathy
	Drug induced (i.e., anthracyclines, cyclophosphamide, paclitaxel)
	Thyroid dysfunction
	Chronic arrhythmia
Rare	Sarcoidosis
	Inherited muscle disorders (i.e., muscular dystrophy, Friedreich's ataxia)

Heart Failure with Reduced Ejection Fraction (HF-REF)

HF-REF is diagnosed in those patients presenting with the clinical syndrome of heart failure with a left ventricular ejection fraction (LVEF) of less than 40 %. The reduced LVEF is identified by cardiac imaging modalities. Transthoracic echocardiography remains the commonest imaging modality used to determine and assess the LVEF. Other imaging modalities such as cardiac magnetic resonance imaging and nuclear imaging can also be used to derive LVEF. HF-REF is associated with a diverse range of conditions (Table 2).

Patients with HF-REF are managed predominantly by cardiologists. Patients require significant counseling, support, and education with regard to non-pharmacological measures such as fluid restriction, avoidance of exacerbating factors (e.g., dietary sodium and alcohol restriction, avoidance of nonsteroidal anti-inflammatory medications), and monitoring for signs of fluid overload. A significant proportion of patients with HF-REF have associated sleep disorders, and these should be screened for and treated where appropriate.

Therapy of HF-REF consists of measures to control congestion (i.e., diuretics, fluid restriction) and disease-modifying pharmacotherapy (angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists). Rarely, a specific etiology may necessitate the use of disease-modifying therapy

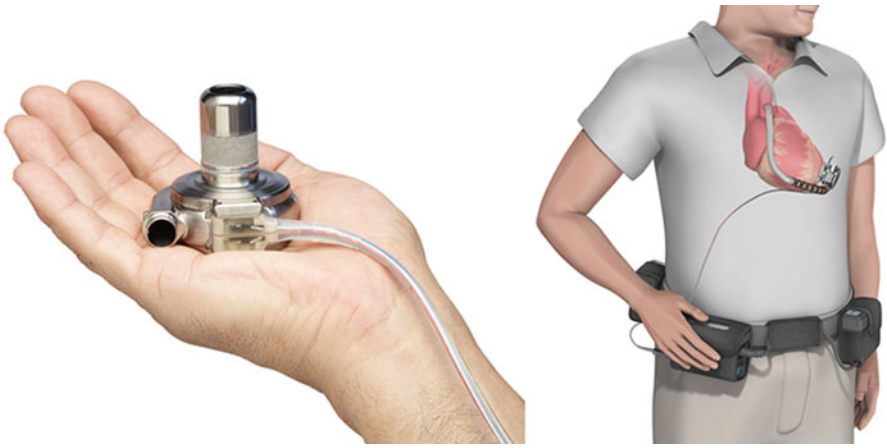


Fig. 10 The HeartWare ventricular assist device. The smaller centrifugal pump contains a single moving impeller part. The pump is implanted in the pericardial space. The driveline connects the pump to a power source externally (Adapted with permission from HeartWare: http://www.heartware.com)

(e.g., corticosteroid therapy in myocarditis or sarcoidosis). In patients with persisting symptoms and reduced left ventricular ejection fraction despite medical therapy, device therapy is used where appropriate which includes ICD and CRT.

Another important management consideration for patients with severe heart failure and refractory clinical symptoms is the use of left ventricular assist devices (Fig. 10) and assessment of candidacy for cardiac transplantation. These treatments can be considered for patients who have failed standard medical therapy and have persisting limiting symptoms, recurrent hospitalizations with heart failure, and/or worsening organ function from persistently low cardiac output.

Heart Failure with Preserved Ejection Fraction (HF-PEF)

HF-PEF is diagnosed in those patients presenting with the clinical syndrome of heart failure but who have intact left ventricular systolic function (i.e., LVEF >50 %). This can be a difficult group of patients to characterize as they are frequently older, have variable symptoms, and commonly possess a number of comorbidities, some of which may also be associated with breathlessness (Table 3).

Diagnosis of HF-PEF can be difficult to confirm, as many patients have symptoms only on exertion. Initial cardiac investigations such as baseline transthoracic echocardiography may not provide a clear diagnosis; however, there are specific features on echocardiography that can guide the clinician toward a diagnosis of HF-PEF (Table 4). Detection of elevated cardiac biomarkers, B-natriuretic peptide (BNP) and N-terminal-pro BNP, is of diagnostic and prognostic significance. These biomarkers are secreted by myocytes in response to ventricular pressure or volume overload. An elevated serum BNP (e.g., >500 ng/L) indicates a high likelihood of underlying heart failure.

Table 3 Risk factors and comorbidities associated with heart failure with preserved ejection fraction (HF-PEF)

Elderly
Female gender
Systemic hypertension
Diabetes mellitus
Chronic renal failure
Obstructive sleep apnea
Obesity

Table 4 Features on echocardiography suggestive of possible underlying heart failure. Echocardiographic parameters should always be correlated with the individual patient's clinical findings

Echocardiography parameter(s)	Findings suspicious for heart failure
Chamber size and wall thickness	Left or bi-atrial enlargement
	Left ventricular dilation
	Left ventricular hypertrophy
Left ventricular ejection fraction	Reduced
Right ventricular ejection fraction	Reduced
Valvular function	Significant (i.e., severe regurgitation or stenosis)
Pulmonary pressures	Right ventricular systolic pressure (RVSP) >35 mmHg
	Pulmonary artery systolic pressure (PASP) >35 mmHg
Regional wall motion	Abnormal (i.e., hypokinesis, dyskinesis, akinesis)
Diastolic function	E/E' ratio >15
	Conclusion comments
	"suspicious for diastolic dysfunction"
	"features consistent with elevated mean left atrial pressure"

Evidence for pharmacological therapy in HF-PEF providing prognostic and mortality benefit is scant. Because of the tendency for HF-PEF patients to possess comorbidities, a high level of diligence should apply to the assessment and management of sleep disorders, obesity, airway disease, and general deconditioning. Clinical trials in HF-PEF have largely failed to provide support for efficacy for the common agents used in HF-REF such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and spironolactone. This may reflect the fact that the HF-PEF population is a heterogeneous patient group with different pathologies, comorbidities, and clinical stages. International guidelines recommend HF-PEF treatment to encompass the management of congestion with diuretics, control of hypertension, management of coexisting symptomatic coronary artery disease, and management of atrial fibrillation. Blood pressure should be targeted to <130/80 mmHg.

Cardiac exercise programs may also provide patients with improved muscle function and conditioning which may assist with weight loss and symptoms. Depression should also be screened for and treated when identified.

Table 5 Clinical profiles of patients with common valvular pathologies

Diagnosis	When to suspect
Aortic stenosis	Elderly patients
	Ejection systolic murmur
	Associated with bicuspid aortic valve (aortic stenosis can occur in younger patients with congenitally bicuspid aortic valve)
Aortic regurgitation	Early diastolic murmur with dyspnea
	Associated with bicuspid aortic valve, hypertension, connective tissue diseases, aortopathy
Mitral stenosis	Rheumatic fever
	Murmurs in indigenous Australians, Pacific Islanders, and patients from developing countries
	Atrial fibrillation
	Dyspnea in pregnancy
Mitral regurgitation	Pansystolic murmur and left-sided heart failure
	Mitral valve prolapse (all age groups)
	Secondary functional mitral regurgitation in ischemic cardiomyopathy

Valvular Heart Disease

Valvular heart disease (VHD) may present with breathlessness, fatigue, syncope, as well as chest pain and palpitations. VHD encompasses a wide range of valvular pathologies in different clinical settings. Suspicion for VHD should be raised in the presence of dyspnea and other relevant clinical findings such as a cardiac murmur or clinical findings suggestive of heart failure. A patient's age and epidemiological profile provide useful information regarding potential etiology. Degenerative or calcific valvular disorders (e.g., severe calcific aortic stenosis) are much more common in the older population (Vahanian et al. 2012). Younger patients with valvular lesions are much more likely to have a primary valvular abnormality (e.g., mitral valve prolapse, congenitally bicuspid aortic valve) (Vahanian et al. 2012).

Transthoracic echocardiography is the gold-standard first-line investigation for the assessment of the etiology of a cardiac murmur and of the severity of the associated valvular pathology. See Table 5 for a summary of the clinical profiles of patients with common valvular pathologies.

Identification of a significant valvular lesion requires assessment by a cardiologist. Management of valvular disease depends upon a number of factors including the etiology of the valvular lesion, its severity, and the patient's symptoms related to the lesion (Vahanian et al. 2012). Monitoring with serial transthoracic echocardiograms and clinical review is appropriate for most valvular lesions in the mild to moderate severity range. Once a valvular lesion is graded as severe and the patient develops symptoms consistent with valvular dysfunction, consideration for valve repair and/or replacement must be considered.

Medical therapy has some role in the management of VHD by providing relief of pulmonary congestion (with diuretics), reducing afterload and ventricular

remodeling (with neurohormonal antagonists and beta-blockers), and reducing thromboembolic complications if atrial fibrillation or flutter is present (with anticoagulants). For direct intervention on valvular disease, open-heart surgery (to allow valve repair or replacement) is performed in the majority of cases. However, percutaneous therapies provided by interventional cardiologists now play a significant and expanding role. Percutaneous treatment options for valvular heart disease include transcatheter aortic valve replacement (TAVR) in the treatment of elderly patients with severe symptomatic aortic stenosis, who are deemed not fit for open-heart surgery, and percutaneous balloon valvuloplasty in appropriate cases of severe rheumatic mitral stenosis.

Infective endocarditis is a condition that can involve any of the four heart valves. Clinical presentation of infective endocarditis can be acute or subacute. Patients commonly present with a fever and a new cardiac murmur. Other associated features include systemic symptoms, such as night sweats, weight loss, joint pains, and embolic phenomena. Infective endocarditis carries significant morbidity and mortality. Its management needs to be led by cardiologists in a multidisciplinary environment, with the support of infectious disease specialists and cardiothoracic surgeons.

Congenital Heart Disease

Congenital heart disease consists of a broad range of disorders that may affect heart structure and function (Elliott et al. 2012). These conditions are present from birth but can progress in their severity through life and may not present clinically until late in adulthood. Congenital heart disorders vary significantly in their presentation, consequences, and prognosis. Congenital heart disease may be diagnosed prenatally via ultrasound which may allow for early planning for the appropriateness of closure of defects such as ventricular septal defects, atrial septal defects, or patent ductus arteriosus. Timing of an intervention to close a defect is an important consideration in congenital disease, weighing the risks and hemodynamic and clinical consequences of the defect with the risks of intervention which include surgery or percutaneous treatments.

In certain situations, prompt treatment is required to sustain life in the early postnatal period. For instance, in D-transposition of the great vessels, there is ventriculo-arterial discordance. In this condition, deoxygenated blood from the venous system enters the right side of the heart. Instead of then traveling through the lungs, the right ventricle is connected to the aorta, and deoxygenated blood travels out through the systemic circulation. Blood which has been oxygenated travels into the left ventricle; however, it is then pumped back through the lungs through the main pulmonary artery because of this ventriculo-arterial discordance. Infants born with this condition often have other heart defects such as an atrial septal defect, ventricular septal defect, or patent ductus arteriosus which all allow some mixing of blood and therefore some oxygenated blood within the systemic circulation. Without the presence of an interatrial or interventricular shunt, there is

a lack of oxygenated blood supplying the systemic circulation, and these infants require an early intervention to sustain life.

A number of congenital heart conditions represent abnormal communications between different heart chambers or vessels and are included in this group of disorders (e.g., atrial septal defects, ventricular septal defects, and patent ductus arteriosus). Some congenital heart conditions may require long-term follow-up for complications. For instance, a bicuspid aortic valve commonly leads to the development of aortic stenosis or regurgitation. Diseases of the great vessels (e.g., coarctation of the aorta and truncus arteriosus) are often repaired surgically at a young age but can present later in life with complications associated with the original condition (e.g., re-coarctation). There are a number of other congenital heart diseases which are due to abnormal formation of a part of the heart's structure. These include tricuspid atresia and hypoplastic left heart syndrome, which both usually require early surgical treatments to sustain life.

There is now a growing population of surviving adults who underwent surgical or percutaneous corrective procedures of a congenital cardiac condition at a young age. These patients are often at risk of late complications and may present many years later as an adult with dyspnea, fatigue, palpitations, syncope, or poor effort tolerance. Unfortunately, a significant proportion of patients with congenital heart disease are often lost to follow-up during the transition from pediatric to adult cardiology clinics. To appropriately manage a patient with congenital heart disease, it is important for the clinician to be aware of the patient's original primary diagnosis and the details of surgical and/or percutaneous procedures performed.

Conclusion

This chapter has summarized the fundamentals of cardiac anatomy, physiology and pathology. For those involved in the management of cardiac patients, it provides an overview of the various clinical presentations, investigations and management strategies. The chapter provides an overview of the various sub-specialities within cardiology including interventional cardiology, electrophysiology, heart failure, congenital heart disease and cardiac imaging.

Glossary

Acute coronary syndrome The spectrum of clinical disorders describing patients presenting with acute or unstable chest pain syndromes due to underlying unstable coronary artery disease. This consists of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA). The differentiation between these clinical entities is based on electrocardiographic (ECG) changes and serum biomarker levels.

Afterload The resistance the ventricles need to overcome to eject the volume of blood.

Anatomy The study of the structures of the human body. This chapter focuses on the anatomy of the heart.

Bradyarrhythmias Rhythm disorders of the heart with a heart rate less than 60 beats per minute.

Cardiac cycle The cardiac cycle consists of systole, the phase of contraction, and diastole, the phase of relaxation.

Cardiac output The volume of blood ejected from the left ventricle each minute. It can be derived by multiplying *stroke volume* with *heart rate*, the number of heartbeats per minute.

Contractility The intrinsic contractile ability of the cardiac muscle.

Coronary angiography An invasive interventional cardiology technique commonly performed via femoral or radial arterial access, in which the lumen of the coronary arteries is visualized in detail using special contrast and fluoroscopy X-ray equipment. Coronary angiography provides the basis for percutaneous coronary intervention, in which special guidewires, angioplasty balloons, and stents are used to treat significant coronary artery lesions.

Coronary arteries Arteries which provide blood supply to the heart muscle.

Coronary artery disease Disease of the coronary arteries. The commonest cause of coronary artery disease is atherosclerosis, the buildup of cholesterol-rich inflammatory material, resulting in progressive narrowing of the coronary arteries.

Echocardiography The study of the human heart by ultrasound. It is a useful noninvasive imaging technique that provides detailed assessment of the structure, function, and physiology of the human heart.

Embryology The study of the development of the human body during fetal life. This chapter briefly discusses the fetal development of the human heart.

Heart failure A complex clinical syndrome characterized by cardiac disorders that lead to impairment of the ability of the ventricles to fill (diastolic heart failure) or eject blood (systolic heart failure).

Physiology The study of the normal function of human organs. This chapter provides an overview of the function of the human heart in health (*physiology*) and in common disease states (*pathophysiology*).

Preload The degree of stretch in the heart before contraction.

Stroke volume The volume of blood ejected by the left ventricle with each contraction.

Tachyarrhythmias Rhythm disorders of the heart with a heart rate greater than 100 beats per minute.

Valvular heart disease Disorders affecting the heart valves. They consist of a wide range of pathologies in different clinical settings. Common symptoms of valvular heart disease include dyspnea, pre-syncope, and fatigue.

References

Ailani, J. (2014). Migraine and patent foramen ovale. *Current Neurology and Neuroscience Reports, 14*, 426–430.

Camm, A. J., Luscher, T. F., & Serruys, P. W. (2006). *The ESC textbook of cardiovascular medicine*. Antipolis: Blackwell.

Camm, A. J., Lip, G. Y. H., De Caterina, R., et al. (2012). 2012 focused update of the ESC guidelines for the management of atrial fibrillation. *European Heart Journal, 33*, 2719–2747.

Elliott, P., Lambiase, P. D., & Kumar, D. K. (2012). *Inherited cardiac disease*. New York: Oxford University Press.

Estruch, R., Ros, E., Salas-Salvado, J., et al. (2013). Primary prevention of cardiovascular disease with a Mediterranean diet. *The New England Journal of Medicine, 368*, 1279–1290.

Guyton, A. C., & Hall, J. E. (2000). *Textbook of medical physiology*. Pennsylvania: WB Saunders Company.

Libby, P., Bonow, R. O., Mann, D. L., & Zipes, D. P. (2008). *Braunwald's heart disease: A textbook of cardiovascular medicine*. Philadelphia: Saunders of Elsevier.

Lily, L. S. (2007). *Pathophysiology of heart disease*. Baltimore: Lippincott Williams & Wilkins.

Oostra, R.-J., & Moorman, A. F. M. (2009). Development of the heart. In C. H., Rodeck, J. Queenan (Eds.), *Fetal medicine* (2nd ed., Chap. 5, pp. 47–59). Churchill Livingstone, an imprint of Elsevier Inc., London.

Page, K., Marwick, T. H., Lee, R., et al. (2014). A systematic approach to chronic heart failure care: A consensus statement. *The Medical Journal of Australia, 201*(3), 146–150.

Preeta, D., Leatherbury, L., Lo, C. W., & Donofrio, M. T. (2012). Human cardiac development in the first trimester. In C. S. Kleinman, & I. Seri (Eds.), *Hemodynamics and cardiology: Neonatology questions and controversies* (2nd ed., Chap. 18, pp. 377–389). Saunders, an imprint of Elsevier Inc., Philadelphia.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., et al. (2012). Heart disease and stroke statistics—2012 update: A report from the American Heart Association. *Circulation, 125*, e2–e220.

Thygesen, K., Alpert, J. S., Jaffe, A. S., Simoons, M. L., Chaitamn, B. R., & White, H. D. (2012). Third universal definition of myocardial infarction. *Circulation, 126*, 2020–2035.

Vahanian, A., Alfieri, O., Andreotti, F., et al. (2012). Guidelines on the management of valvular heart disease. *European Heart Journal, 33*, 2451–2496.

Watanabe, M., & Wikenheiser, J. (2015). Cardiac embryology. In R. J., Martin, A. A., Fanaroff, M. C., Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine* (Chap. 79, pp. 1188–1197). Saunders, an imprint of Elsevier Inc., Philadelphia.

Wyse, D. G., Waldo, A. L., Dimarco, J. P., et al. (2002). A comparison of rate control and rhythm control in patients with atrial fibrillation. *The New England Journal of Medicine, 347*, 1825–1833.

Xu, B., & MacIsaac, A. I. (2013). What does an elevated troponin mean? An update on the definition of myocardial infarction. *Australian Family Physician, 42*(8), 554–559.

Xu, B., & Whitbourn, R. (2012). Novel anticoagulants for non-valvular atrial fibrillation. *Heart, Lung & Circulation, 21*(8), 463–467.

Epidemiology of Cardiovascular Disease

Christopher Reid and Alice Owen

Contents

Abstract

Noncommunicable diseases such as cardiovascular diseases and cancers are key threats to maintaining health and well-being in the twenty-first century. In 2008, 30 % of global deaths were due to cardiovascular disease, a mortality burden felt by countries across the income/development spectrum. The middle of the twentieth century saw the advent of epidemiological studies which have made significant advances in understanding the factors driving cardiovascular disease risk. Studies such as the Seven Countries Study gathered data from across the globe on clinical and lifestyle factors and their relationship to rates of cardiovascular disease. Other landmark studies such as the Framingham Study set the

C. Reid (✉) • A. Owen
School of Public Health and Preventive Medicine, CCRE Therapeutics, Monash University, Melbourne, VIC, Australia
e-mail: chris.reid@monash.edu; alice.owen@monash.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_5

scene for a detailed understanding of the magnitude of risk conferred by clinical factors.

An increasingly sedentary lifestyle and energy-dense diet facilitated by urbanization have contributed to epidemics of obesity, hypertension, and diabetes, which are all major cardiovascular risk factors. These risks, coupled with aging populations (age being another key risk factor), drive the need to develop and implement prevention strategies that will be effective and accessible for high- and lower-income countries. The worldwide framework for tobacco control and working with the food industry to develop healthier accessible foods are key examples of lifestyle-related strategies for prevention. Low-cost preventive medications such as the multicomponent "polypill" also hold promise as cost-effective strategies to reduce the burden of cardiovascular disease; however further evidence of the efficacy across different population and age groups is required.

Keywords
Cardiovascular risk • Prevention • Risk factors • Epidemiology • Blood pressure • Lipids

Introduction

Since early civilization, mankind has faced the coming and going of major threats to human health and well-being. Environmental threats including famine, communicable diseases, and human conflict underpinned the major challenges to survival for most of the first 2,000 years of human civilization. The industrial revolution and advances in technology, urbanization, wealth, and communication have fueled the epidemiological transition (Fig. 1) to a state where new epidemics and major threats to life emerged. Noncommunicable diseases such as cardiovascular diseases and cancers are now the key threats to maintaining health and well-being in the twenty-first century.

This chapter will examine how information has been gathered to identify the key factors underpinning the cardiovascular disease epidemic of the twentieth century. It will also examine how prevention and treatment strategies have been developed and implemented and what challenges low- to middle-income countries face to avoid a repeat of the epidemic which at its peak in the mid-1960s claimed over 20,000 lives per year in the USA alone.

Gathering the Evidence

Cardiovascular disease epidemiology had its roots in the observation from autopsies conducted on young soldiers killed in combat during the First and Second World Wars that many, even in their early 20s, had developed atherosclerotic plaques (Meade 2001; Rosenthal 1934). At that time, in the 1930s and 1940s, coronary heart disease was starting to emerge as a significant cause of death in

Stages of Development	Life Expectancy	Deaths From CVD: % of Total Deaths	Predominant CVDs and Risk Factors
Stage 1. Pestilence and famine	35 years	5–10	Rheumatic heart disease, infections, and nutritional cardiomyopathies
Stage 2. Receding pandemics	50 years	10–35	As above + hypertensive heart disease and haemorrhagic strokes
Stage 3. Degenerative and man-made diseases	>60 years	35–65	All forms of strokes, ischemic heart disease at young ages, increasing obesity, and diabetes
Stage 4. Delayed degenerative diseases	>70 years	<50	Stroke and ischemic heart disease at old age

Fig. 1 Epidemiological transition for CVD (From Gersh et al. 2010)

industrialized Western countries such as the USA. Infant mortality rates had subsided due to improvement in sanitation systems and clean water provision in more densely populated areas. Disparities among cardiovascular disease rates in countries at similar stages of industrialization sparked the interest of Ancel Keys to establish the Seven Countries Study in the 1950s (Keys 1970). The aim of the Seven Countries Study was to gather data from across the globe on clinical and lifestyle factors to examine the association of these factors with the rates of cardiovascular disease.

Observational Epidemiology

Commencing in the 1950s and involving population cohorts in the USA, Japan, Italy, Yugoslavia, Finland, the Netherlands, and Greece, the Seven Countries Study was one of the first to examine the association between major clinical and lifestyle factors and the risk of cardiovascular disease (Keys 1970). Importantly, it also identified clinical factors and modifiable lifestyle behaviors associated with cardiovascular risk factors, which have been the substrate of decades of research into whether modulating these risk factors influenced cardiovascular disease outcome.

The Framingham Study (Dawber 1980) is another early and well-known epidemiological study examining risk factors for cardiovascular disease. Baseline data collection commenced in 1950, and the original population sample consisted of 5,127 male and female residents of the small town of Framingham, Massachusetts, USA, aged 30–59 years old and free of coronary heart disease. The Framingham Study has contributed key information about the epidemiology of cardiovascular

disease, particularly the relationships between blood pressure, smoking, cholesterol, and cardiovascular disease.

At the start of the twenty-first century, the INTERHEART study led by Salim Yusuf has been the most influential global study of cardiovascular epidemiology in recent times (Yusuf et al. 2004). A case-control study of acute myocardial infarction (MI) conducted in 52 countries across all inhabited continents, using population attributable risk methodology INTERHEART, identified nine key modifiable factors driving risk of MI. Smoking, raised ApoB/ApoA1 (a marker of high LDL/HDL cholesterol ratio), hypertension, diabetes, abdominal obesity, and psychosocial stress (domains of stress at work and at home, financial stress, and major life events over the preceding year) were associated with increased risk, whereas daily consumption of fruit and vegetables, regular physical activity, and low-moderate consumption of alcohol were associated with decreased risk (Yusuf et al. 2004).

These and other seminal observational studies have shaped the understanding of the role of lifestyle and behavior on cardiovascular morbidity and mortality and also provided a clear picture of the role of other major risk factors, such as blood pressure and blood cholesterol.

Cigarette Smoking

The association between cigarette smoking and cardiovascular disease was observed in the Seven Countries Study (Keys et al. 1984) and also in a number of other population-based studies around the world. The British Doctors' Study (Doll and Peto 1976) undertaken by Sir Richard Doll in the UK, the Whitehall Study (Reid et al. 1976), and the Honolulu Heart Study (Kagan et al. 1975) are just a sample of the numerous studies which have supported the association between cigarette smoking and cardiovascular diseases, particularly coronary heart disease and stroke. Bradford-Hill's rules of causality require reversal of a risk factor to reduce the incidence of the outcome, and observational study data support this for cigarette smoking. While estimates of the time required vary, smokers who give up smoking have been shown to revert to coronary heart disease rates similar to nonsmokers (Cook et al. 1986; Gordon et al. 1974). Despite there being no randomized trial evidence available for smoking cessation, the overwhelming body of evidence for the association between cigarette smoking and coronary disease and the benefit of cessation has led to major public health campaigns and health policy changes to reduce prevalence. The World Health Organization has been instrumental in driving global efforts to combat smoking through its Framework Convention on Tobacco Control. In some countries, control measures include a ban on tobacco advertising, smoke-free workplace policies, and more recently plain tobacco packaging laws, which have been introduced in Australia and New Zealand (Zacher et al. 2014). The impact of these research findings and their translation to policy initiatives have led to a reduction in cigarette smoking rates in a number of countries over the past decades (Fig. 2).

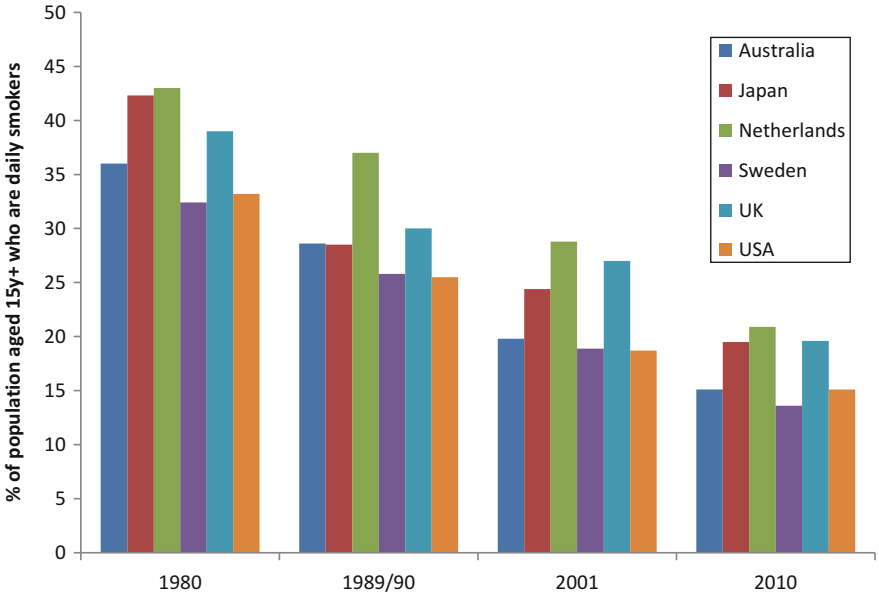


Fig. 2 Changes in smoking rates in six countries from 1980 to 2010

Diabetes

Diabetes is a disease characterized by chronic dysregulation of glucose homeostasis. Since the middle of the last century, there has been a substantial increase in diabetes prevalence, driven by a growing and aging population, urbanization, and increasing prevalence of obesity and physical inactivity. Research suggests that the burden of diabetes will continue to grow: the prevalence for all age groups worldwide was estimated to be 2.8 % in 2000 and is projected to rise to 4.4 % in 2030 (Wild et al. 2004).

Diabetes was established as a cardiovascular disease risk factor by early observational studies. Recent analysis of data from Framingham has shown that over the past half-century, the proportion of cardiovascular disease attributable to diabetes has increased from 5.4 to 8.9 % in this cohort (Fox et al. 2007). Globally, the INTERHEART study found diabetes accounted for 10 % of the population attributable risk of MI (Yusuf et al. 2004).

Dietary Intake

Dietary intake of excess calories and increased saturated fats is strongly associated with the development of obesity, elevated blood cholesterol, and diabetes. Obesity and diabetes are reaching epidemic proportions across the globe in both high-income and low- to middle-income countries. The Ni-Hon-San study was an early observation of the role of a changing diet on cardiovascular disease.

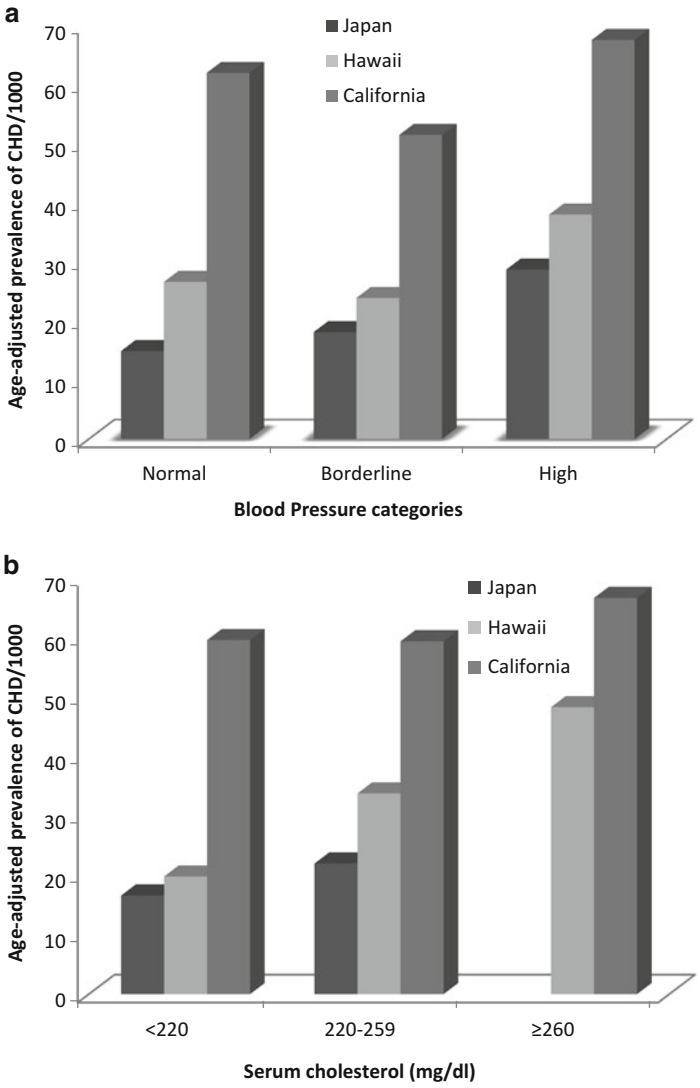


Fig. 3 Blood pressure (a) and serum cholesterol levels (b) in Japanese populations lining in Japan, Hawaii and California

It examined people migrating from Japan (a country with one of the lowest rates of cardiovascular disease) to Honolulu and San Francisco (the USA having a very high rate of cardiovascular disease). The Japanese migrants had increasing exposure to dietary fat and cholesterol intake and a "Western diet." As exposure increased, so did blood pressure and cholesterol levels, levels of obesity and diabetes, and also rates of coronary artery disease (Fig. 3) (Marmot et al. 1975).

Dietary fat content has been a focus of much research activity, and the work of Ancel Keys was an early driver of this. Keys' eponymous equation quantified the effect of saturated and polyunsaturated fats on plasma cholesterol (Fetcher et al. 1967). Understanding of the effect of dietary fats on cardiovascular disease and its risk factors has evolved and expanded and continues to be an active area of research. It is now known that some unsaturated fats, such as the long-chain polyunsaturated omega-3 fats found in fish and seafood, are cardioprotective. Conversely, *trans* fats produced by partial hydrogenation of vegetable oils have, on a per calorie basis, the strongest relationship with cardiovascular disease of any macronutrient (Mozaffarian et al. 2006).

Another dietary factor related to a major cardiovascular disease risk factor is sodium chloride (salt) intake. Salt intake is directly related to blood pressure, and it is estimated that a population-wide reduction of salt intake by 6 g/day could reduce rates of stroke by 24 % and coronary heart disease by 18 % (He and MacGregor 2003).

Physical Activity and Sedentary Behavior

Energy (calorie) intake is a key driver of obesity and diabetes, but the other side of the energy balance equation is, of course, energy expenditure. People in more physically active occupations have been shown to have lower rates of obesity, diabetes, and coronary heart disease than their sedentary counterparts. The London Bus Drivers Study (Morris et al. 1953) and the San Francisco Longshoremen's study (Brand et al. 1979) are two early examples of epidemiological studies which demonstrated the relationship between increased physical activity and reduced rates of coronary disease. While these observations have been questioned in regard to selection bias, there is good evidence to show that increasing physical activity in formerly sedentary people can reduce body weight, lower LDL cholesterol and raise HDL cholesterol, and improve insulin sensitivity suggesting an important role in coronary heart disease etiology and prevention.

Recent analysis from the INTERHEART study found that across all global regions leisure-time physical activity and mild-moderate occupational physical activity (but not heavy physical occupation activity) were associated with reduced risk of MI, while key drivers of sedentary behavior (ownership of a car and a television) were associated with increased risk of MI (Held et al. 2012). A key point to distinguish here is that physical activity and sedentary behavior are not necessarily opposite ends of a single "activity" scale. It has been shown that even in those whose level of leisure-time physical activity might meet guideline recommendations, being largely sedentary for the remaining hours of the day is a significant risk factor for cardiovascular disease (van der Ploeg et al. 2012; Chomistek et al. 2013). Preventive strategies to reduce sedentary behavior (e.g., reducing "sitting" time) are different to the preventive strategies one might employ to encourage adherence to physical activity recommendations.

Obesity

Rates of obesity have been growing worldwide, fueled by increasingly sedentary lifestyles and increases in dietary energy density. The World Health Organization estimates that in 2008, 35 % of adults worldwide were overweight, and 10 % of men and 14 % of women were obese (Organisation 2013). There is considerable geographic variation in levels of obesity, but it remains a major global health challenge. Obesity is associated with development of cardiovascular risk factors, including hypertension, dyslipidemia, and diabetes. It is likely a combination of these strong associations between obesity, blood pressure, plasma lipids, and glucose homeostasis, in addition to the evolution toward a more sedentary lifestyle and energy-dense diet, which confounded early studies looking at associations between body mass index (BMI) and cardiovascular disease. A recent analysis pooling data from 97 cohort studies (collectively 1.8 million participants) found that risk of coronary heart disease was 27 % higher for each 5 kg/m^2 increment in BMI (Lu et al. 2014). Elevations in blood pressure, cholesterol, and glucose accounted for around half of that increased risk, so this suggests that addressing excess body weight itself remains a critical issue.

Socioeconomic Status

Significant regional disparities in cardiovascular mortality in Scotland, which had one of the highest coronary heart disease death rates in the world in the 1980s, led Hugh Tunstall-Pedoe and colleagues to undertake a series of studies which clearly identified socioeconomic factors, particularly unemployment and housing tenure, as being associated with cardiovascular morbidity and mortality. More socioeconomically disadvantaged groups had greater risk factor levels, including smoking, poor diet, and heavy alcohol consumption, but even after accounting for these factors, socioeconomic status remained a significant risk factor for cardiovascular disease (Smith et al. 1990).

Alcohol Intake

Alcohol intake illustrates an interesting case in the evolution of our understanding of behavioral risk factors for cardiovascular disease. Early epidemiological studies such as two occupational cohort studies conducted in Chicago in the 1970s (Dyer et al. 1981) were just two of the many early cohort studies noting that heavy alcohol consumption was associated with increased rates of cardiovascular disease. Over the following decades, studies of alcohol consumption and cardiovascular disease suggested the existence of a J-shaped association, such that low-moderate alcohol consumers had lower rates of cardiovascular disease than nondrinkers (Ronksley et al. 2011). Emerging evidence from INTERHEART suggests that this association may differ between geographic regions, and low-moderate alcohol consumption may not offer the same cardiovascular benefit in South Asian populations (Leong et al. 2014).

Mental Health and Cardiovascular Disease

The interrelationships between cardiovascular health and mental health and well-being have been documented across a variety of populations and settings (Bunker et al. 2003). The National Heart Foundation of Australia has recently updated their

2003 position paper on evidence supporting the role of chronic stressors and coronary heart disease. Chronic stressors with varying degrees of evidence for a link with coronary disease include chronic work stress and job strain, effort-reward imbalance, organizational injustice, and social isolation and lack of support. Acute mental stresses included bereavement and acute emotional responses, job loss, sporting events, and natural disasters (Colquhoun et al. 2013b).

Depression is an important independent risk factor for first and recurrent coronary heart disease events. The prevalence of depression is particularly high in patients with coronary disease, and it has a significant impact on the patient's quality of life and adherence to therapy and an independent effect on prognosis (Colquhoun et al. 2013a). The previously mentioned INTERHEART study included 11,119 patients with MI from 52 countries reported that perceived stress and depression together accounted for 32.5 % of the population attributable risk (PAR) for coronary heart disease (Yusuf et al. 2004). Together, these factors were as important as smoking and more important than diabetes (PAR, 9.9 %) and hypertension (PAR, 17.9 %) as risk factors. Rates of major depressive disorder of around 15 % have been reported in patients after myocardial infarction or coronary artery bypass grafting.

Randomized Controlled Clinical Trials

The introduction of a more rigorous approach to experimental epidemiology involving the conduct of randomized controlled trials has greatly improved understanding of effective prevention and treatment strategies for coronary heart disease. Following the Second World War, clinical experimentation on human subjects became more highly regulated, and as the pharmaceutical industry developed medications to reduce the burden of cardiovascular disease, so did the requirement for higher levels of evidence to support the use of medications for primary and secondary disease prevention.

Blood Pressure and Lipids

The relationship between blood pressure, changes in blood pressure, and subsequent cardiovascular disease events has been one of the most intensively researched areas of clinical medicine over the past 50 years. Again, leading from the observational epidemiological studies both within and between populations, a near-linear relationship has been demonstrated between levels of blood pressure and the risk of stroke and coronary heart disease (Fig. 4) (Lewington et al. 2002). This has been paralleled with major therapeutic developments targeted toward the mechanisms underlying the development of high blood pressure. Broadly, these include targeting the central nervous system, the renin-angiotensin system, the arterial vascular system, and homeostasis. Clinical trials, starting with the early Veterans Administration Trial (Veterans Administration Cooperation Study on

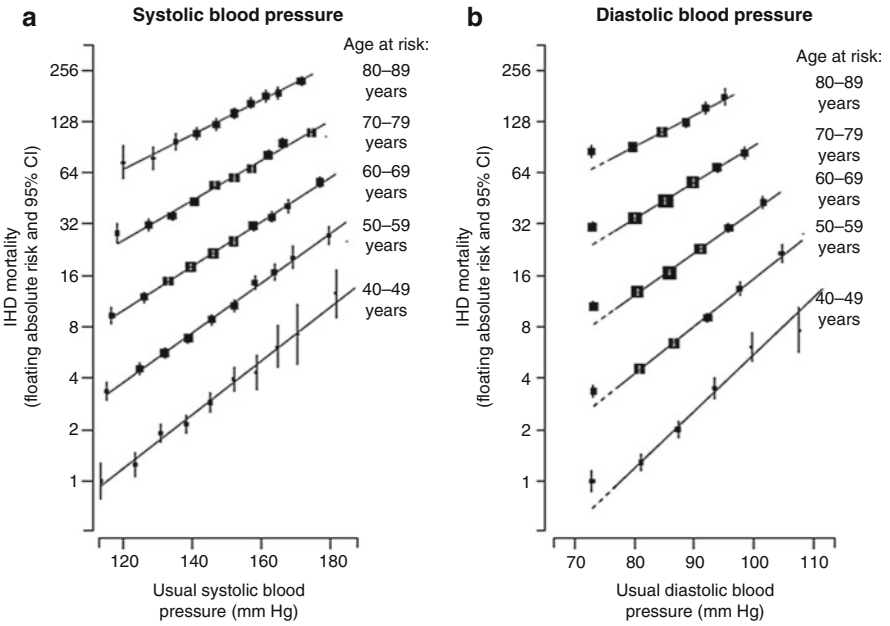
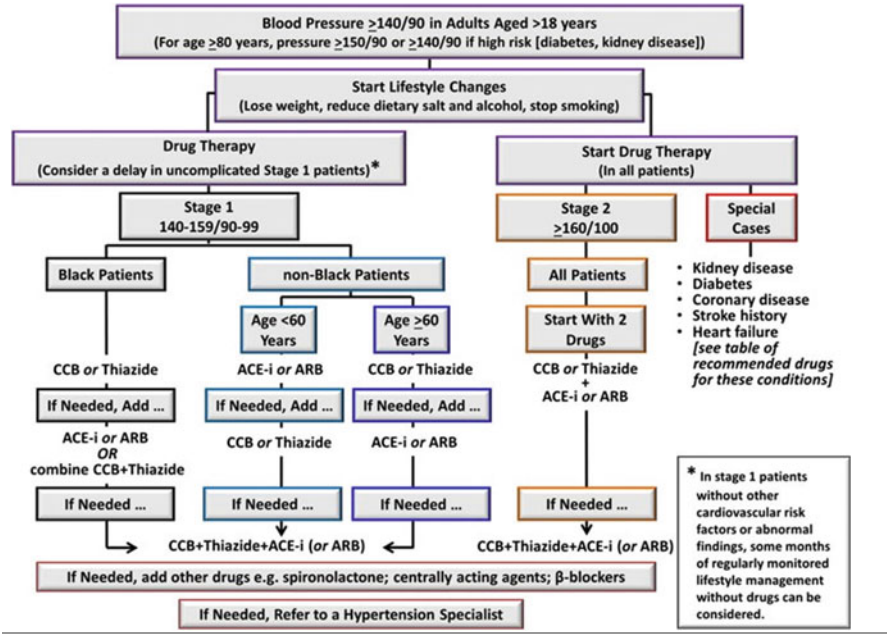


Fig. 4 Levels of systolic and diastolic blood pressure and age-related risk of Ischaemic Heart Disease

Antihypertensive Agents 1970) and the Hypertension Detection and Follow-up Program (Hypertension Detection Follow-up Program Cooperative Group 1979), through to SYST-EUR (Staessen et al. 1997), HYVET (Bulpitt et al. 2012), ALLHAT (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002), ANBP2 (Wing et al. 2003), and ASCOT trials (Dahlöf et al. 2005) have demonstrated that lowering high blood pressure, in virtually any population group, reduces the risk of coronary heart disease and particularly stroke. As a result, clinical guidelines for the identification, treatment, and prevention of high blood pressure have been developed and promulgated over the past decades (Table 1), the most recent in 2014 (Members et al. 2013; Weber et al. 2014). While clinical societies continue to argue regarding preferences for initial choice of therapy, treatment targets, and even how best to measure blood pressure (clinic, ambulatory, home, arterial, central, etc.), the commonality among them remains clear – high blood pressure is a major risk factor and reducing high blood pressure reduces the risk of cardiovascular disease.

Elevated blood cholesterol, in particular high levels of low-density lipoprotein (LDL) cholesterol, was also identified in the Seven Countries Study as being associated with increasing rates of cardiovascular disease, in particular coronary heart disease. The buildup of atheroma and unstable plaque formation leading to potential rupture and subsequent thrombosis precipitated many of the ever-increasing coronary heart disease events occurring in developed countries across

Table 1 American Society of Hypertension and International Society of Hypertension Clinical Practice Guidelines Algorithm (Weber et al. 2014)



CCB denotes calcium channel blocker; ACE-i, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; thiazide, thiazide or thiazide-like diuretics. Blood pressure values are systolic/diastolic blood pressure in mmHg

the globe. Therapeutic development led to the use of bile acid sequestrants, nicotinic acid, and finally statins to effectively lower blood lipid levels and also reduce fatal and nonfatal coronary event rates. Starting with the Coronary Drug Project in the 1960s in patients with existing coronary heart disease (Friedman et al. 1983), secondary prevention was firmly established, and trials such as the West of Scotland Primary Prevention Study (Shepherd et al. 1995), the 4S Study (The Scandinavian Simvastatin Survival Study Group 1994), and the LIPID study (The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998) have demonstrated the value of lowering of LDL cholesterol in patients with high and "normal cholesterol" levels. As with blood pressure, guideline development for the control of elevated blood lipids and cardiovascular disease prevention has thrived backed by a myriad of cholesterol-lowering trials in various populations (Psaty and Weiss 2014).

Novel targets, such as the trialing of HDL-raising drugs (Verma and Figueredo 2014), suppression of inflammation (Everett et al. 2010), and renal denervation of sympathetic nerves (Krum et al. 2014), are examples of new therapeutic interventions in recent years to refine and improve the control of these two major risk factors that have been strongly associated with disease prevalence and incidence.

Multifactorial Risk

The Multiple Risk Factor Intervention Trial was one of the key trials to demonstrate interrelationships between coronary heart disease risk factors (Neaton and Wentworth 1992). This trial (conducted in men only, in the 1980s) showed that those individuals who had even mild elevations of multiple risk factors were at greater risk of coronary disease than those who had larger elevations of single factors. This observation led to a field of epidemiological research in modeling and risk prediction that has tried to better identify those individuals who may benefit most from targeted intervention. Models derived from the Framingham cohort study (Dawber 1980) are among the most widely adopted for use to estimate risk of developing coronary disease.

Controversy still exists on the role of absolute risk assessment for targeting interventions for individuals (D'Agostino Sr. et al. 2013). Age is the most dominant risk factor for coronary heart disease, and when risk thresholds are recommended (e.g., a 10 % 5 year Framingham risk), then the majority of individuals over the age of 65 years and virtually all of those over the age of 70 years would be targeted for preventive interventions irrespective of the individuals' blood pressure or blood lipid levels. Unfortunately most of the evidence derived for the benefits of blood pressure lowering and cholesterol lowering have arisen from clinical trials in middle-aged populations, and with global aging populations, the need for further evidence directly relevant to the elderly is an imperative.

Genetics

The Framingham Offspring Study (which as the name suggests, recruited offspring of participants from the original Framingham Study) showed that having a parent with premature cardiovascular disease more than doubled the risk of developing cardiovascular disease (Lloyd-Jones et al. 2004). For some time it had been established that there were Mendelian disorders associated with development of severe and premature cardiovascular disease, such as familial hypercholesterolemia (caused by mutations in the LDL receptor gene or Apo B gene, leading to substantially elevated circulating LDL cholesterol levels), and mutations in ion channel genes (notably of sodium, calcium, and potassium channels) leading to cardiac rhythm disorders. However the widespread association with family history suggested that genetic effects on cardiovascular disease extended beyond these relatively rare gene variants.

The increasing accessibility of genetic analysis for application in epidemiological studies is driving a new wave of research looking at common gene variants and risk of cardiovascular disease. These include gene variants which have been found to be associated with cardiovascular events (e.g., APOE polymorphisms), as well as gene variants associated with the development of cardiovascular risk factors such as hypertension, high cholesterol or triglyceride levels, or low HDL levels. Additionally, gene variants have been identified which influence the response to commonly used cardiovascular drugs, fueling the quest for "personalized medicine" in cardiovascular disease prevention and treatment.

Another growing area of genetic research is the interaction between genes and environment/behavior. For example, in a Han Chinese population, it was recently shown that possession of a single nucleotide polymorphism in the rs671 allele of the acetaldehyde dehydrogenase 2 gene was associated with a greater risk of hypertension and adverse lipid profiles only in those who drank alcohol (Wang et al. 2013). This highlights the complexity of genetics and genomics in cardiovascular disease epidemiology.

Inflammation

A link between acute infection and heart disease, e.g., myocarditis, pericarditis, and endocarditis, has been long established. Over the past half-century, epidemiological studies have revealed associations between lower-grade systemic inflammation and cardiovascular disease. In 1974, Friedman and colleagues published results from the Kaiser-Permanente case-control study showing that a previous (>1 year prior) elevated white cell count was strongly associated with the risk of having an MI (Friedman et al. 1974). Evolution of the understanding of the pathophysiological processes underpinning development of atherosclerotic plaques has highlighted the role of inflammation in development of atherosclerotic cardiovascular disease, and epidemiological studies are revealing associations between biomarkers of inflammation, obesity, insulin resistance, and cardiovascular disease risk factors. A recent example is severe periodontal disease (gum bleeding) which has been found to be associated with increased systolic blood pressure (Tsakos et al. 2010) and risk of atherosclerotic disease (Dietrich et al. 2013).

Aspirin and related salicylate compounds were used as antipyretic and pain-relieving agents in the nineteenth century. In the latter half of the twentieth century, the discovery that aspirin's anti-inflammatory activity was related to inhibition of prostaglandin synthesis earned Vane, Samuelsson, and Bergstrom a Nobel Prize in Medicine (Bishopric 2013). In addition, as understanding of the pathophysiology of cardiovascular disease evolved, aspirin's ability to inhibit platelet aggregation prompted a series of clinical trials confirming aspirin's role in secondary prevention of cardiovascular disease (Antiplatelet Triallists Collaboration 1994). More recent studies have focused on the role of aspirin for primary prevention; aspirin confers benefits but also increased bleeding risks, and consideration of this balance of risk to benefit should be applied to the use of aspirin in the primary prevention setting (ASPREE Study Group 2013).

Strategies for Prevention

In higher-income countries, the major targets for cardiovascular disease prevention strategies include tobacco use, poor diet and physical inactivity, excessive alcohol consumption, high blood pressure, high blood glucose, and dyslipidemia. The strategies for low-middle-income countries share some commonalities with

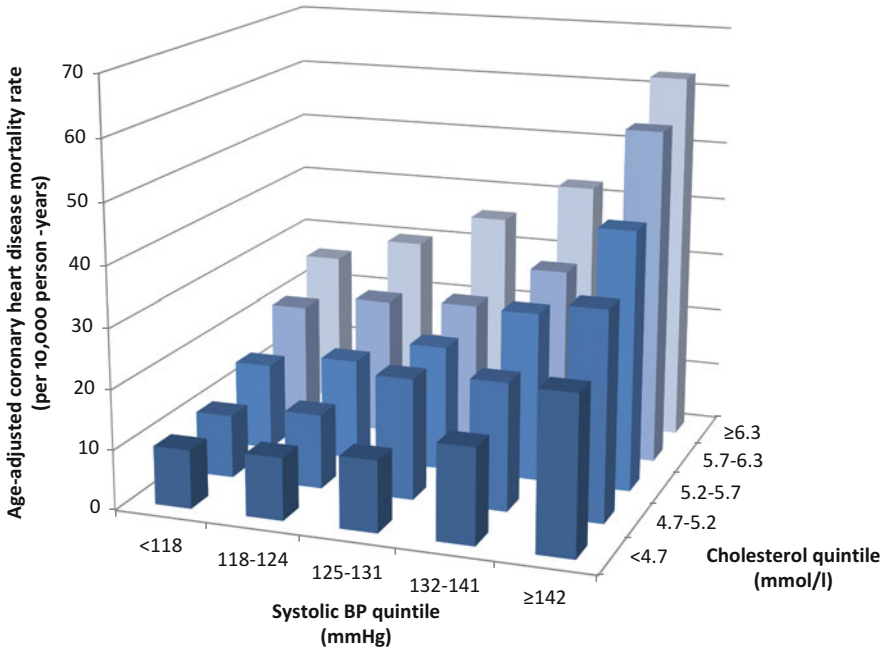


Fig. 5 Interaction between blood pressure and cholesterol levels on age adjusted coronary heart disease mortality rates

higher-income countries, but in low-middle-income countries, other factors such as low birth weight, severe nutritional deficiencies (e.g., folate deficiency), and infectious disease (e.g., rheumatic fever) are more frequent. The intersection between these factors and the lifestyle changes which come with increasing urbanization present challenges for prevention of cardiovascular disease in low-resource settings.

With a limited resource pool, even in higher-income countries, how does one best target cardiovascular prevention strategies? Ideally strategies that can address many risk factors simultaneously are needed, and while population-wide strategies are required, there is also need to target population subgroups most affected – i.e., those at highest risk. These concepts proposed by Geoffrey Rose in the 1970s and 1980s remain valid in terms of the high-risk and population-based approaches toward chronic disease prevention (Rose 1985). These concepts highlight the benefits for the individual through a high-risk approach to risk factor reduction (blood pressure, lipids, etc.) and the benefits to the community through population-wide changes in risk factors levels (smoking, blood pressure, etc.). For coronary heart disease, at present the majority of deaths in the population are occurring in those with risk factor levels in the middle of the distribution; therefore the maximum benefit to the community is likely to be achieved through population-wide risk factor reduction (Fig. 5) (Neaton and Wentworth 1992).

For the high-risk approach, ensuring accessibility of primary and secondary prevention drugs for those at highest risk, notably antihypertensive agents, aspirin, and lipid-lowering "statins" has been a key focus. A "polypill" (a single pill combining all of the aforementioned preventive agents) has been put forward as simple strategy that might improve adherence and accessibility, but uncertainty remains regarding long-term cost-effectiveness and risk benefit in the primary prevention setting (Patel et al. 2014).

At the population level, reducing the *trans* fat and salt content of the food supply are major public health challenges. Achieving salt reductions will require strategies not only to convince people to add less salt to their cooking and food at home but also require engagement with the food industry – processed foods make a major contribution to salt intake. Organizations such as the World Action on Salt & Health are working to drive change at the level of government and food industry around the globe. The partial hydrogenation of vegetable oils, which results in production of *trans*-fatty acids, provides these oils with a longer shelf life, solidity at room temperature, and greater stability during deep frying, characteristics which increase their appeal to food manufacturers and consumers. In some low-income countries, these oils are often used in home cooking, while in high-income countries they are more widely used in bakery products and processed foods. Efforts to reduce industrially produced *trans* fats in the food supply require engagement with industry in addition to public health messages but have been successfully tackled through policy and legislation in places such as Denmark and New York.

Future Challenges for Cardiovascular Disease Prevention

In 2008, 80 % of global deaths due to cardiovascular disease occurred in low-middle-income countries. In addition, the rates of premature death from cardiovascular disease (occurring below the age of 60 years) in low-middle-income countries were more than double that of high-income countries (Organization 2011). Worldwide, half of the burden of ischemic heart disease and stroke is attributable to high blood pressure (Lawes et al. 2008), and the incidence of hypertension continues to grow steadily across India, China, and Asia. This second wave of CVD epidemic is well underway in developing nations across Africa, Asia, and China, and the lessons learned in responding to the challenge in the 1950s and 1960s need to be adapted, tested, and applied in many resource-poor settings.

The other major future challenge for cardiovascular disease prevention is the amelioration of "upstream factors" such as social status, self-empowerment, education, and financial income on health (Fig. 6). These factors are not only relevant to the developing world but are also relevant to continuing the reductions in cardiovascular disease deaths seen in most high-income countries over the past decades. Hotchkiss and colleagues recently reported that the falls in cardiovascular mortality seen in Scotland between 2000 and 2010, through reductions in smoking

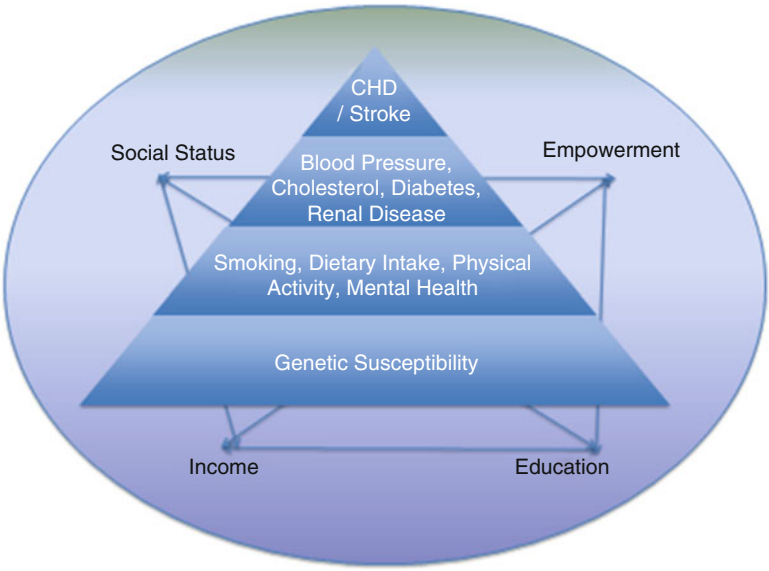


Fig. 6 Upstream factors influencing cardiovascular health and well-being

and treatments for blood pressure and lipids, were being offset by increases in obesity and diabetes which were strongly related to upstream factors influencing social status (Hotchkiss et al. 2014).

Conclusion

Cardiovascular disease remains the major cause of global burden of disease and will continue to do so for many years to come. While great progress has been made in understanding the etiology, treatment, and prevention of the disease at both the individual and community level, future initiatives in population-wide prevention strategies and reducing social disadvantage for both developed and developing countries remain at the forefront of tackling the second cardiovascular disease epidemic across the world.

References

Allhat Officers and Coordinators for the Allhat Collaborative Research Group. (2002). Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA, 288*, 2981–2997.

Antiplatelet Triallists Collaboration. (1994). Collaborative overview of randomised trials of antiplatelet treatment. *British Medical Journal, 308*, 235–246.

Aspree Study Group. (2013). Study design of ASPirin in Reducing Events in the Elderly (ASPREE): A randomized, controlled trial. *Contemporary Clinical Trials, 36*, 555–564.

Bishopric, N. H. (2013). Toward a genomic definition of aspirin resistance∗. *Journal of the American College of Cardiology, 62*, 1277–1279.

Brand, R. J., Paffenbarger, R. S., Jr., Sholtz, R. I., & Kampert, J. B. (1979). Work activity and fatal heart attack studied by multiple logistic risk analysis. *American Journal of Epidemiology, 110*, 52–62.

Bulpitt, C. J., Beckett, N. S., Peters, R., Leonetti, G., Gergova, V., Fagard, R., Burch, L. A., Banya, W., & Fletcher, A. E. (2012). Blood pressure control in the Hypertension in the Very Elderly Trial (HYVET). *Journal of Human Hypertension, 26*, 157–163.

Bunker, S., Colquhoun, D. J., Esler, M., Hickie, I., Hunt, D., Jelinek, M., Oldenburg, B., Peach, H., Ruth, D., Tennant, C., & Tonkin, A. (2003). "Stress" and coronary heart disease: Psychosocial risk factors. *Medical Journal of Australia, 178*, 272–276.

Chomistek, A. K., Manson, J. E., Stefanick, M. L., Lu, B., Sands-Lincoln, M., Going, S. B., Garcia, L., Allison, M. A., Sims, S. T., Lamonte, M. J., Johnson, K. C., & Eaton, C. B. (2013). Relationship of sedentary behavior and physical activity to incident cardiovascular disease: Results from the Women's Health Initiative. *Journal of the American College of Cardiology, 61*, 2346–2354.

Colquhoun, D., Bunker, S., Clarke, D., Glozier, N., Hare, D. L., Hickie, I. B., Tatoulis, J., Thompson, D. R., Tofler, G. H., Wilson, A., & Branagan, M. G. (2013a). Screening, referral and treatment for depression in patients with coronary heart disease. *Medical Journal of Australia, 198*, 483–484.

Colquhoun, D. M., Bunker, S. J., Clarke, D. M., Hare, D. L., Hickie, I. B., Tatoulis, J., Thompson, D. R., Wilson, A., & Branagan, M. G. (2013b). Psychosocial risk factors for coronary heart disease. *The Medical Journal of Australia, 199*, 1–6.

Cook, D. G., Shaper, A. G., Pocock, S. J., & Kussick, S. J. (1986). Giving up smoking and the risk of heart attacks. *Lancet, ii*, 1376–1380.

D'Agostino, R. B., Sr., Pencina, M. J., Massaro, J. M., & Coady, S. (2013). Cardiovascular disease risk assessment: Insights from Framingham. *Global Heart, 8*, 11–23.

Dahlöf, B., Sever, P. S., Poulter, N. R., Wedel, H., Beevers, D. G., Caulfield, M., Collins, R., Kjeldsen, S. E., Kristinsson, A., Mcinnes, G. T., Mehlsen, J., Nieminen, M., O'Brien, E., & Östergren, J. (2005). Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *The Lancet, 366*, 895–906.

Dawber, T. R. (1980). *The Framingham study*. Cambridge, MA: Harvard University Press.

Dietrich, T., Sharma, P., Walter, C., Weston, P., & Beck, J. (2013). The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. *Journal of Periodontology, 84*, S70–S84.

Doll, R., & Peto, R. (1976). Mortality in relation to smoking: 20 years' observations on male British doctors. *British Medical Journal, 2*, 1525–1536.

Dyer, A. R., Stamler, J., Paul, O., Berkson, D. M., Shekelle, R. B., Lepper, M. H., Mckean, H., Lindberg, H. A., Garside, D., & Tokich, T. (1981). Alcohol, cardiovascular risk factors and mortality: The Chicago experience. *Circulation, 64*, III 20–III 27.

Everett, B. M., Glynn, R. J., Macfadyen, J. G., & Ridker, P. M. (2010). Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein: Justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin (JUPITER). *Circulation, 121*, 143–150.

Fetcher, E. S., Foster, N., Anderson, J. T., Grande, F., & Keys, A. (1967). Quantitative estimation of diets to control serum cholesterol. *American Journal of Clinical Nutrition, 20*, 475–492.

Fox, C. S., Coady, S., Sorlie, P. D., D'Agostino, R. B., Sr., Pencina, M. J., Vasan, R. S., Meigs, J. B., Levy, D., & Savage, P. J. (2007). Increasing cardiovascular disease burden due to diabetes mellitus: The Framingham Heart Study. *Circulation, 115*, 1544–1550.

Friedman, G. D., Klatsky, A. L., & Siegelaub, A. B. (1974). The leukocyte count as a predictor of myocardial infarction. *New England Journal of Medicine, 290*, 1275–1278.

Friedman, L., Wenger, N. K., & Knatterud, G. L. (1983). Impact of the coronary drug project findings on clinical practice. *Controlled Clinical Trials, 4*, 513–522.

Gersh, B. J., Sliwa, K., Mayosi, M. B., Yusuf, S. (2010). Novel therapeutic concepts. The epidemic of cardiovascular disease in the developing world: global implications. *Eur Heart J, 31*(6), 642–648.

Gordon, T., Kannel, W. B., Mcgee, D., & Dawber, T. (1974). Death and coronary attacks in men after giving up cigarette smoking. *Lancet, ii*, 1345–1348.

He, F. J., & Macgregor, G. A. (2003). How far should salt intake be reduced? *Hypertension, 42*, 1093–1099.

Held, C., Iqbal, R., Lear, S. A., Rosengren, A., Islam, S., Mathew, J., & Yusuf, S. (2012). Physical activity levels, ownership of goods promoting sedentary behaviour and risk of myocardial infarction: Results of the INTERHEART study. *European Heart Journal, 33*, 452–466.

Hotchkiss, J. W., Davies, C. A., Dundas, R., Hawkins, N., Jhund, P. S., Scholes, S., Bajekal, M., O'Flaherty, M., Critchley, J., Leyland, A. H., & Capewell, S. (2014). Explaining trends in Scottish coronary heart disease mortality between 2000 and 2010 using IMPACTSEC model: Retrospective analysis using routine data. *BMJ, 348*, g1088.

Hypertension Detection Follow-Up Program Cooperative Group. (1979). Five-year findings of the hypertension detection and follow-up program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA, 242*, 2562–2571.

Kagan, A., Gordon, T., Rhoads, G. G., & Schiffman, J. C. (1975). Some factors related to coronary heart disease incidence in Honolulu Japanese men: The Honolulu Heart Study. *International Journal of Epidemiology, 4*, 271–279.

Keys, A. (1970). Coronary heart disease in seven countries. Summary. *Circulation, 41*, I186–I195.

Keys, A., Menotti, A., Aravanis, C., Blackburn, H., Djordevic, B. S., Buzina, R., Dontas, A. S., Fidanza, F., Karvonen, M. J., Kimura, N., et al. (1984). The seven countries study: 2,289 deaths in 15 years. *Preventive Medicine, 13*, 141–154.

Krum, H., Schlaich, M. P., Sobotka, P. A., Böhm, M., Mahfoud, F., Rocha-Singh, K., Katholi, R., & Esler, M. D. (2014). Percutaneous renal denervation in patients with treatment-resistant hypertension: Final 3-year report of the symplicity HTN-1 study. *The Lancet, 383*, 622–629.

Lawes, C. M., Vander Hoorn, S., & Rodgers, A. (2008). Global burden of blood-pressure-related disease, 2001. *Lancet, 371*, 1513–1518.

Leong, D. P., Smyth, A., Teo, K. K., McKee, M., Rangarajan, S., Pais, P., Liu, L., Anand, S. S., & Yusuf, S. (2014). Patterns of alcohol consumption and myocardial infarction risk: Observations from 52 countries in the INTERHEART Case-Control Study. *Circulation, 130*(5), 390–398.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., & Collins, R. (2002). Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet, 360*, 1903–1913.

Lloyd-Jones, D. M., Nam, B. H., D'Agostino, R. B., Sr., Levy, D., Murabito, J. M., Wang, T. J., Wilson, P. W., & O'Donnell, C. J. (2004). Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: A prospective study of parents and offspring. *JAMA, 291*, 2204–2211.

Lu, Y., Hajifathalian, K., Ezzati, M., Woodward, M., Rimm, E. B., & Danaei, G. (2014). Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: A pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet, 383*, 970–983.

Marmot, M. G., Syme, S. L., Kagan, A., Kato, H., Cohen, J. B., & Belsky, J. (1975). Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: Prevalence of coronary and hypertensive heart disease and associated risk factors. *American Journal of Epidemiology, 102*, 514–525.

Meade, T. (2001). Cardiovascular disease – Linking pathology and epidemiology. *International Journal of Epidemiology, 30*, 1179–1183.

Members, A. T. F., Mancia, G., Fagard, R., Narkiewicz, K., Redon, J., Zanchetti, A., Böhm, M., Christiaens, T., Cifkova, R., De Backer, G., Dominiczak, A., Galderisi, M., Grobbee, D. E., Jaarsma, T., Kirchhof, P., Kjeldsen, S. E., Laurent, S., Manolis, A. J., Nilsson, P. M., Ruilope, L. M., Schmieder, R. E., Sirnes, P. A., Sleight, P., Viigimaa, M., Waeber, B., Zannad, F., Council, E. S., Burnier, M., Ambrosioni, E., Caufield, M., Coca, A., Olsen, M. H., Tsioufis, C., Van de Borne, P., Guidelines, E. C. F. P., Zamorano, J. L., Achenbach, S., Baumgartner, H., Bax, J. J., Bueno, H., Dean, V., Deaton, C., Erol, C., Ferrari, R., Hasdai, D., Hoes, A. W., Knuuti, J., Kolh, P., Lancellotti, P., Linhart, A., Nihoyannopoulos, P., Piepoli, M. F., Ponikowski, P., Tamargo, J. L., Tendera, M., Torbicki, A., Wijns, W., Windecker, S., Reviewers, D., Clement, D. L., Gillebert, T. C., Rosei, E. A., Anker, S. D., Bauersachs, J., Hitij, J. B., Caulfield, M., De Buyzere, M., De Geest, S., Derumeaux, G. A., Erdine, S., Farsang, C., Funck-Brentano, C., Gerc, V., Germano, G., Gielen, S., Haller, H., Jordan, J., Kahan, T., Komajda, M., Lovic, D., Mahrholdt, H., Ostergren, J., Parati, G., Perk, J., Polonia, J., Popescu, B. A., Reiner, Ž., Rydén, L., Sirenko, Y., Stanton, A., Struijker-Boudier, H., Vlachopoulos, C., Volpe, M., & Wood, D. A. (2013). 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European Heart Journal, 34*, 2159–2219.

Morris, J. N., Heady, J. A., Raffle, P. A., Roberts, C. G., & Parks, J. W. (1953). Coronary heart-disease and physical activity of work. *Lancet, 265*, 1111–1120. concl.

Mozaffarian, D., Katan, M. B., Ascherio, A., Stampfer, M. J., & Willett, W. C. (2006). Trans fatty acids and cardiovascular disease. *New England Journal of Medicine, 354*, 1601–1613.

Neaton, J. D., & Wentworth, D. (1992). Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Archives of Internal Medicine, 152*, 56–64.

World Health Organisation. (2013). *Global Health Observatory (GHO): Obesity 2008*. WHO, Geneva, Switzerland. http://www.who.int/gho/ncd/risk_factors/obesity_text/en/.

Mendis, S. P. P., & Norrving, B. (Eds.). (2011). *Global atlas on cardiovascular disease prevention and control*. Geneva: World Health Organization.

Patel, A., Cass, A., Peiris, D., Usherwood, T., Brown, A., Jan, S., Neal, B., Hillis, G.S., Rafter, N., Tonkin, A., Webster, R., Billot, l., Bompoint, S., Burch, C., Burke, H., Hayman, N., Molanus, B., Reid, C.M., Shiel, l., Togni, S., Rodgers, A., Kanyini Guidelines Adherence with the Polypill (Kanyini GAP) Collaboration. (2014). A pragmatic randomized trial of a polypill-based strategy to improve use of indicated preventive treatments in people at high cardiovascular disease risk. *European Journal of Preventive Cardiology*. doi:10.1177/2047487314530382. Paper version Eur J Prev Cardiol 2015, 22(7), 920–930

Psaty, B. M., & Weiss, N. S. (2014). 2013 acc/aha guideline on the treatment of blood cholesterol: A fresh interpretation of old evidence. *JAMA, 311*, 461–462.

Reid, D. D., Hamilton, P. J., McCartney, P., Rose, G., Jarrett, R. J., & Keen, H. (1976). Smoking and other risk factors for coronary heart-disease in British civil servants. *Lancet, 2*, 979–984.

Ronksley, P. E., Brien, S. E., Turner, B. J., Mukamal, K. J., & Ghali, W. A. (2011). Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. *BMJ, 342*, d671.

Rose, G. (1985). Sick individuals and sick populations. *International Journal of Epidemiology, 14*, 32–38.

Rosenthal, S. R. (1934). Studies in atherosclerosis: Chemical, experimental, and morphologic. *Archives of Pathology, 18*, 473–506.

Shepherd, J., Cobbe, S. M., Ford, I., Isles, C. G., Ross, L. A., Macfarlane, P. W., Mckillop, J. H., Packard, C. J., & West of Scotland Coronary Prevention Study Group. (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *The New England Journal of Medicine, 333*, 1301–1307.

Smith, W. C., Shewry, M. C., Tunstall-Pedoe, H., Crombie, I. K., & Tavendale, R. (1990). Cardiovascular disease in Edinburgh and north Glasgow – A tale of two cities. *Journal of Clinical Epidemiology, 43*, 637–643.

Staessen, J. A., Fagard, R., Thijs, L., Celis, H., & For the Syst-Eur Trial Investigators. (1997). Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet, 350*, 757–764.

The Long-Term Intervention with Pravastatin in Ischaemic Disease (Lipid) Study Group. (1998). Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *New England Journal of Medicine, 339*, 1349–1357.

The Scandinavian Simvastatin Survival Study Group. (1994). Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *The Lancet, 344*, 1383–1389.

Tsakos, G., Sabbah, W., Hingorani, A. D., Netuveli, G., Donos, N., Watt, R. G., & D'Aiuto, F. (2010). Is periodontal inflammation associated with raised blood pressure? Evidence from a National US survey. *Journal of Hypertension, 28*, 2386–2393.

Van der Ploeg, H. P., Chey, T., Korda, R. J., Banks, E., & Bauman, A. (2012). Sitting time and all-cause mortality risk in 222 497 Australian adults. *Archives of Internal Medicine, 172*, 494–500.

Verma, N., & Figueredo, V. M. (2014). HDL cholesterol: All hope is not lost after the torcetrapib setback – Emerging therapeutic strategies on the horizon. *American Journal of Therapeutics, 21*, 222–232. doi:10.1097/MJT.0b013e318249a1b5.

Veterans Administration Cooperation Study on Antihypertensive Agents. (1970). Effects of treatment of morbidity in hypertension. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. *JAMA, 213*, 1143.

Wang, Y., Zhang, Y., Zhang, J., Tang, X., Qian, Y., Gao, P., & Zhu, D. (2013). Association of a functional single-nucleotide polymorphism in the ALDH2 gene with essential hypertension depends on drinking behavior in a Chinese Han population. *Journal of Human Hypertension, 27*, 181–186.

Weber, M. A., Schiffrin, E. L., White, W. B., Mann, S., Lindholm, L. H., Kenerson, J. G., Flack, J. M., Carter, B. L., Materson, B. J., Ram, C. V. S., Cohen, D. L., Cadet, J.-C., Jean-Charles, R. R., Taler, S., Kountz, D., Townsend, R. R., Chalmers, J., Ramirez, A. J., Bakris, G. L., Wang, J., Schutte, A. E., Bisognano, J. D., Touyz, R. M., Sica, D., & Harrap, S. B. (2014). Clinical practice guidelines for the management of hypertension in the community. *The Journal of Clinical Hypertension, 16*, 14–26.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care, 27*, 1047–1053.

Wing, L., Reid, C., Ryan, P., Beilin, L., Brown, M., Jennings, G., Johnston, C., Mcneil, J., Marley, J., Morgan, T., Shaw, J., Steven, I., & West, M. (2003). A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for the treatment of hypertension in the elderly. *New England Journal of Med, 348*, 583–592.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., Mcqueen, M., Budaj, A., Pais, P., Varigos, J., & Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*, 937–952.

Zacher, M., Bayly, M., Brennan, E., Dono, J., Miller, C., Durkin, S., Scollo, M., & Wakefield, M. (2014). Personal tobacco pack display before and after the introduction of plain packaging with larger pictorial health warnings in Australia: An observational study of outdoor café strips. *Addiction, 109*, 653–662.

Cardiovascular Risk Factors: Role of Lifestyle

Gautam Vaddadi

Contents

Abstract

Cardiovascular disease (CVD) is the leading cause of death and disability in the developed world. Lifestyle factors are thought to account for up to 90 % of attributable risk of myocardial infarction worldwide. Smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, consumption of fruits and vegetables, psychosocial factors, and physical activity are the key components of this risk. Interventions to reduce risk such as exercise, smoking cessation, and dietary change are valuable in lowering CVD risk at any age; however, instituting the "right" lifestyle choices from childhood or even from conception is likely to

G. Vaddadi (✉)
Department of Cardiology, The Alfred Hospital, Melbourne, VIC, Australia
e-mail: drgvaddadi@gmail.com

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_6

have the greatest impact on reducing the long-term burden of disease. The "sitting time" is now recognized to add to the risk of CVD, even in people who are physically active at other times. Sitting more than 10 h per day increases all-cause mortality. TV watching is a strong predictor of CVD risk and is more profound than "screen time" which may include video games. This may relate to increased snacking and poor dietary choices when watching TV. If we are to reduce CVD, a paradigm shift is needed in how our "Western" society operates. Fundamental changes are needed in infrastructure, travel, use of cars, work patterns, food industry, and education from birth to grave.

Keywords
Cardiovascular • Myocardial infarction • Hypertension • Obesity • Sitting

Cardiovascular disease (CVD) is the leading cause of death and disability in the developed world (Murray and Lopez 2013). Globally it is thought to account for 17.3 million deaths annually (Laslett et al. 2012) and includes the following common conditions:

- Ischemic heart disease
- Cerebrovascular disease (stroke)
- Peripheral vascular disease
- Atherosclerotic disease of the aorta including aortic aneurysms

In the Framingham Heart Study, the lifetime risk of developing coronary heart disease at age 40 years was 42.4 % for men and 24.9 % for women (Lloyd-Jones et al. 1999). Lifetime risk continues to remain high at age 70 being 1 in 3 for men and 1 in 4 for women. In the developed world, the burden of ischemic heart disease has escalated by 29 % between 1990 and 2010 with 55 % of this increase being accounted for by a combination of population growth and aging (Moran et al. 2014). The World Health Organization states that "Coronary heart disease (CHD) is now the leading cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders."

A healthy lifestyle is essential to the prevention of CVD, the leading cause of morbidity and mortality worldwide. Preventative lifestyle measures can modify many of the risk factors for CVD. In the INTERHEART population study, potentially modifiable risk factors for myocardial infarction were assessed in 52 countries. Ninety percent of the attributable risk of a myocardial infarct worldwide in both sexes and all age groups was potentially modifiable, including smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol consumption, and physical activity (Yusuf et al. 2004). Prevention begins at a young age, ideally during pregnancy, and is lifelong. Sadly much of our focus on prevention of CVD begins in middle age and beyond. Evidence is accruing that the risk of CVD starts at a very young age. Exposure to risk factors in utero has also been demonstrated to

play a role as was seen in the offspring of women who were pregnant during the Dutch famine of the Second World War (Eriksson et al. 1999; Forsen et al. 1999).

Risk factor intervention does result in reduced CVD event rates. In recent times there has been a steady decline in mortality from CHD in developed countries only in part attributable to therapeutic advances such as pharmaceuticals and coronary intervention (stents and bypass surgery). Changes in risk factors account for approximately half of this effect (Capewell 1999; Perk et al. 2012). It is widely believed that lifestyle interventions at a population level would take decades to result in an impact on CVD event rates, but in fact a large body of data supports the idea that lifestyle interventions such as smoking cessation and dietary change (more fruit and vegetables, less meat/animal fat) can result in rapid changes (months to a few years) to CVD event rates in a population (Capewell and O'Flaherty 2011). Therefore lifestyle interventions could potentially play a huge role in reducing the burden of CVD globally, especially if these interventions are applied throughout life.

The Role of Diet

The mantra "you are what you eat" is apt. Dietary factors are being increasingly demonstrated to play a major role in the development of the modifiable risk factors for CVD. Dietary changes at a population level have been demonstrated to have a rapid impact on CVD events and mortality (Capewell and O'Flaherty 2011).

A balanced healthy diet should contain the following:

- Saturated fat <10 % of total energy intake. Fat intake replaced by poly- and monounsaturated fats.
- Trans-unsaturated fats at an absolute minimum. Ideally these should not be present in processed food.
- <5 g of salt per day (Recent data from the PURE sodium study (O'Donnell et al. 2014) suggests that current guidelines advocating very low salt intake for the general population of 1.5 g/day are not beneficial and that targeting the 3–4 g/day zone is reasonable).
- 30–45 g of fiber per day from fruits, whole grains, and vegetables.
- Two to three serves of fruits per day.
- Two to three serves of vegetables per day.
- Fish 1–2 $\times$/week (oily fish such as salmon preferred).
- Alcohol limited to two standard drinks per day for men and one for women.

Fat

It has been recognized for over 50 years that replacing saturated fats in the diet with polyunsaturated fats reduces serum cholesterol. However the impact of saturated fat intake on the occurrence of CVD remains controversial. Evidence from a broad

range of studies supports the notion that replacing 1 % of energy from saturated fats with polyunsaturated fats reduces risk of CHD by 2–3 % (Astrup et al. 2011). The same has not been shown for replacement of saturated fat with carbohydrate or monounsaturated fats.

Unsaturated fats are by and large the "good fats." Polyunsaturated fats (PUFAs) will lower LDL cholesterol levels when they are used to replace saturated fat in the diet. PUFAs can be divided into two main subgroups, n-6 fatty acids which are principally sourced from plants and n-3 fatty acids which are usually found in oily fish. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are members of the n-3 family of PUFAs and have been shown to reduce CHD mortality (He et al. 2004) which is thought to perhaps represent an anti-arrhythmic effect.

Interestingly "trans" fats which are also unsaturated have been demonstrated to increase cholesterol and decrease HDL. These are geometric isomers of the good fats, essentially mirror images. But this small difference results in subtle alterations in physical properties which has deadly consequences for human health. A meta-analysis has shown that a higher trans-fat intake of just 2 % of daily energy expenditure is associated with a 23 % increased risk of CHD (Mensink and Katan 1990; Michels and Sacks 1995; Mozaffarian et al. 2006). Trans fats are commonly found in fried and baked food produced commercially. Intake should be virtually zero.

Salt

High sodium intake has been strongly linked to increased blood pressure, arguably one of the most significant modifiable risk factors for CVD. There is currently great controversy in establishing what the right sodium intake is for the general healthy population. Current guidelines advocate a maximum of 2.3 g/day sodium intake (National Heart Foundation of Australia), and a level of 1.5 g/day is a goal sodium intake set by the American Heart Association (He and MacGregor 2001; He et al. 2013). The PURE sodium study (O'Donnell et al. 2014), the largest study to investigate the links between sodium and health outcomes, has cast doubt on these recommendations. It has shown that virtually no population anywhere in the world reaches current targets for sodium intake. Furthermore, in a healthy population, only those individuals consuming more than 5 g/day of sodium, which is very high, had an adverse effect on blood pressure and cardiovascular outcomes. This new research is likely to result in a significant shift in the guidelines for salt intake as it applies to the healthy general population. It should be noted that patients with hypertension and the elderly may still benefit from much lower sodium intakes more in line with current guidelines. Processed food is thought to account for approximately 75 % of our sodium intake. All guidelines for the prevention of CVD strongly advocate minimal intake of processed food of all types.

Potassium, Vitamins, and Fiber

Potassium is primarily sourced from fruit and vegetables, the classic example being bananas. A high potassium intake will result in increased sodium excretion in the urine in order to maintain cationic balance. High potassium intake has been shown to reduce stroke risk by up to 40 % (He and MacGregor 2001).

Vitamins A, E, B6, folic acid, and B12 have no convincing data that can support their use in the prevention of CVD (Perk et al. 2012).

Diets high in dietary fiber confer a reduced CHD risk by mechanisms that are not clear. Fiber has a beneficial effect on lipid levels and lowers glucose levels in the postprandial state, thus potentially reducing the deleterious effects of high insulin levels. The American Heart Association recommends a minimum of 25 g of fiber per day.

Fruit and Vegetables

Diets that are rich in fresh fruit and vegetables confer a reduced risk of CVD. Most of our data comes from prospective cohort studies which may be confounded by the fact that people who eat a lot of fruit and vegetables are often different from people who don't in other ways such as smoking, saturated fat intake, and physical activity. Attempts have been made to correct for these biases statistically, and a meta-analysis has demonstrated a 4 % decrease in CHD risk and 5 % decrease in stroke risk for each additional serving of fruit and vegetables per day (Dauchet et al. 2004, 2005, 2006).

Fruits and vegetables could be beneficial for a variety of reasons including being a major source of fiber. They are high in potassium and thus can help lower sodium intake and blood pressure. This was demonstrated in the DASH trial which showed that the marked reduction in blood pressure in the intervention arm could be attributed to the high consumption of fresh fruit and vegetables (Appel et al. 1997; Greenland 2001; Sacks et al. 2001).

Fish

Fish is high in n-3 polyunsaturated fatty acids which is thought to be why fish confers cardiovascular protection. Eating fish at least once a week reduces the risk of CHD by 15 % (He et al. 2004). It has been estimated that a modest increase in fish intake among the general population could result in a 36 % reduction in CHD mortality and a 17 % reduction in all-cause mortality (Mozaffarian and Rimm 2006). European guidelines recommend two serves of fish per week, one serve being oily fish.

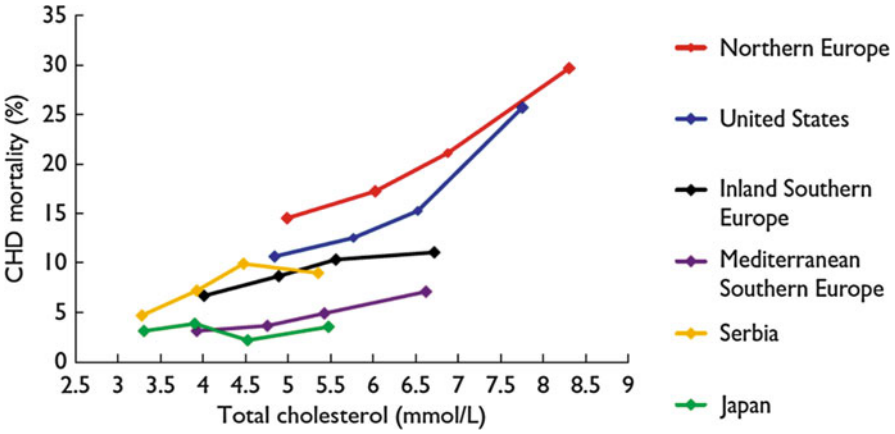


Fig. 1 Cumulative 25-year coronary heart disease (CHD) mortality rates in different cohorts of the Seven Countries Study, according to baseline quartiles of total cholesterol level, adjusted for age, smoking, and blood pressure

Soft Drinks

In the USA, sugar-based soft drinks account for a large proportion of daily calorie intake. In children and adolescents, 10–15 % of calorie intake may be sourced from these products (Perk et al. 2012). Regular consumption of sugar-sweetened drinks (one to two serves/day) has been associated with a 35 % higher risk of CHD in women when compared with one serve/month even when adjusted for other unhealthy lifestyle factors. Regular soft drink consumption has been linked to obesity and type 2 diabetes. Soft drinks that are artificially sweetened have not been associated with CHD (Fung et al. 2009).

Mediterranean Diet

A Mediterranean diet is thought to underlie the lower incidence of CHD mortality in southern Europe compared to northern Europe independent of cholesterol levels. This diet is dominated by many of the foods and dietary choices discussed thus far including fruits and vegetables, polyunsaturated fats, olive oil, legumes, grains, fiber, and low consumption of red meat and saturated animal fat. The figure below demonstrates the dramatic regional differences in CHD mortality according to cholesterol levels (Fig. 1).

Physical Activity, Inactivity, and Exercise

Aerobic exercise has been shown to decrease CVD in healthy subjects, people with risk factors, and those patients with underlying CHD (Perk et al. 2012). Aerobic exercise has a plethora of positive effects including reducing blood pressure, improving glycemic control, and slowing the onset of type 2 diabetes and enhances coronary blood flow and the microcirculation within the heart which may protect the heart from damage during myocardial infarction. In a study of 55,137 adults, leisure running reduced all-cause mortality by 30 % and cardiovascular mortality risk by 45 % over 15 years of follow-up when compared to non-runners (Lee et al. 2014). In contrast sedentary activities such as car riding and TV watching (Stamatakis et al. 2013) increase CVD risk starting in childhood (Smith et al. 2014). Playing computer games and other "active" screen-based activities may not have the same negative effect on CVD risk, perhaps due to the association between poor "snacking habits" and TV watching (Ouwens et al. 2012). A recently published 32-year longitudinal British study has shown that TV watching time in childhood tracks into adulthood, suggesting that we should place an increased emphasis on early lifestyle interventions to reduce risky behavioral choices (Smith et al. 2014). Increasing levels of occupation and leisure-time physical activity are inversely associated with most of the CVD risk factors and are also independently related to a reduced risk of MI (Held et al. 2012). Strenuous occupation-related physical activity was, however, not significantly associated with decreased risk. These relationships are consistent in both sexes and across the young and elderly (Held et al. 2012). Globally there is an increasing use of technology associated with a more sedentary lifestyle such as the television and car. The INTERHEART study has shown an adverse relationship between ownership of a car and TV with CVD risk across all economic and geographic regions. Furthermore, ownership of a car or TV is an independent risk factor for MI (Held et al. 2012). Excessive hours lying down per day is associated with increased all-cause and cardiovascular mortality; this effect persists in an ameliorated form in those individuals who are otherwise physically active (Holtermann et al. 2014).

Sitting is an activity many of us do in abundance, driving cars, taking the train, at our desks at work, and in restaurants, to name but a few. An increasing body of evidence supports the notion that sitting time is increasing our risk of CVD, even among those who are physically active during their leisure time (Owen et al. 2010; van Uffelen et al. 2010; Gardiner et al. 2011). A recent Danish study has shown that excessive sitting time, >10 h per day, is associated with increased all-cause mortality, compared with individuals who sit <6 h per day (Bjork Petersen et al. 2014). The effect is particularly stark among physically inactive adults who have a high sitting time. This evidence supports the need for fundamental lifestyle changes at work, at home, and at all levels of operation within our society.

The positive effects of exercise seem to extend across both sexes and in all age groups including the elderly. In the EU it has been estimated that <50 % of people

are involved in regular aerobic leisure activity or work-related physical activity (Perk et al. 2012). The risk of adverse cardiovascular events due to exercise is extremely low; however, people who undertake significant physical exercise only occasionally appear to be at higher risk for acute cardiac events (Thompson et al. 2007) when compared to those who exercise more regularly. It is therefore recommended that people begin exercise programs gradually, and the aim should be to perform 30 mins of aerobic exercise five times per week. Medical screening for heart disease prior to commencing exercise in the general population is controversial. Logic would suggest that screening should be tailored to the individual patients' cardiovascular risk profile and the type of exercise they wish to undertake, especially in middle age and beyond.

Alcohol

In 2010 alcohol consumption was estimated to be a factor in >2.5 million deaths globally due to a range of adverse effects including trauma, cancer, cardiovascular disease, and liver cirrhosis (Lim et al. 2012). A range of studies have suggested that low to moderate regular alcohol consumption reduces the risk of myocardial infarction (heart attack) (Mukamal et al. 2003, 2006, 2010; Ronksley et al. 2011). These studies have all been conducted in high-income countries, and thus we cannot generalize the data to all countries and ethnic groups. The INTERHEART study was a case-control study of MI undertaken in 12,461 individuals with first MI and 14,637 age- and sex-matched controls from 52 countries in Asia, Europe, Middle East, Africa, Australia, and the Americas (Leong et al. 2014). The authors found that across all patients, alcohol consumption in the preceding 12 months was associated with a significant reduction in MI risk, 6–20 % ($p < 0.001$). The benefit was greater in women and those over 45 years of age but was restricted to individuals who consumed alcohol <4 times/week. It is interesting to note that alcohol did not have a protective effect in Bangladesh, India, Nepal, Pakistan, and Sri Lanka and this is not thought to be genetic because the protective effect holds true for people from the South Asian ethnic grouping who live outside the region. Heavy drinking (>6 drinks) during a 24 h period was associated with a 40 % increased risk of MI in the cohort overall ($p = 0.01$), adding further support to existing data (Leon et al. 2007a, b).

Body Weight

Body fat content, in particular abdominal fat and visceral adipose tissue (fat around the organs), is now well recognized as a significant contributor to CVD risk. Being overweight and obese are both associated with an increased risk of CVD death (Haslam and James 2005). There is a progressive linear relationship between all-cause mortality and degree of obesity (body mass index (BMI)). A BMI of between 20 and 25 kg/m^2 is associated with the lowest mortality. At 30–35 kg/m^2,

median survival is reduced by 2–4 years; at 40–45 kg/m^2, it is reduced by 8–10 years (which is comparable with the effects of smoking) (Prospective Studies et al. 2009).

Obesity Paradox

It is intriguing to note that patients who are overweight or obese appear to have a better prognosis when they have established coronary artery disease than patients with CHD and a normal BMI (Lavie et al. 2009a, b; Hastie et al. 2010). The reasons for this are less than clear and are at odds with the clear deleterious effect of increasing BMI on health outcomes for the general population.

Conclusions

Lifestyle factors play a key role in the development of cardiovascular disease. Society as a whole needs to be encouraged to make fundamental changes to our day to day lives. We need to eat more fresh fruit and vegetables; reduce our consumption of saturated fat, animal fat, and processed foods; and increase physical activity. Physical activity and exercise needs to come both in leisure time and be integrated with the way we work and travel. Structural changes in Western cities encouraging walking, bicycle riding, and other human-powered modes of transport will assist in reducing CVD risk. This will require people to live closer to work and have access to fast efficient public transport to reduce dependency on the car. Finally, lifestyle interventions must begin at birth in order to "nudge" us toward healthier choices, and this intervention must continue throughout life.

References

Appel, L. J., Moore, T. J., Obarzanek, E., Vollmer, W. M., Svetkey, L. P., Sacks, F. M., Bray, G. A., Vogt, T. M., Cutler, J. A., Windhauser, M. M., Lin, P. H., & Karanja, N. (1997). A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *New England Journal of Medicine, 336*(16), 1117–1124.

Astrup, A., Dyerberg, J., Elwood, P., Hermansen, K., Hu, F. B., Jakobsen, M. U., Kok, F. J., Krauss, R. M., Lecerf, J. M., LeGrand, P., Nestel, P., Riserus, U., Sanders, T., Sinclair, A., Stender, S., Tholstrup, T., & Willett, W. C. (2011). The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: Where does the evidence stand in 2010? *American Journal of Clinical Nutrition, 93*(4), 684–688.

Bjork Petersen, C., Bauman, A., Gronbaek, M., Wulff Helge, J., Thygesen, L. C., & Tolstrup, J. S. (2014). Total sitting time and risk of myocardial infarction, coronary heart disease and all-cause mortality in a prospective cohort of Danish adults. *International Journal of Behavioral Nutrition and Physical Activity, 11*, 13.

Capewell, S. (1999). Survival trends, coronary event rates, and the MONICA project. Monitoring trends and determinants in cardiovascular disease. *Lancet, 354*(9181), 862–863. author reply 863-864.

Capewell, S., & O'Flaherty, M. (2011). Rapid mortality falls after risk-factor changes in populations. *Lancet, 378*(9793), 752–753.

Dauchet, L., Ferrieres, J., Arveiler, D., Yarnell, J. W., Gey, F., Ducimetiere, P., Ruidavets, J. B., Haas, B., Evans, A., Bingham, A., Amouyel, P., & Dallongeville, J. (2004). Frequency of fruit and vegetable consumption and coronary heart disease in France and northern Ireland: The PRIME study. *British Journal of Nutrition, 92*(6), 963–972.

Dauchet, L., Amouyel, P., & Dallongeville, J. (2005). Fruit and vegetable consumption and risk of stroke: A meta-analysis of cohort studies. *Neurology, 65*(8), 1193–1197.

Dauchet, L., Amouyel, P., Hercberg, S., & Dallongeville, J. (2006). Fruit and vegetable consumption and risk of coronary heart disease: A meta-analysis of cohort studies. *Journal of Nutrition, 136*(10), 2588–2593.

Eriksson, J. G., Forsen, T., Tuomilehto, J., Winter, P. D., Osmond, C., & Barker, D. J. (1999). Catch-up growth in childhood and death from coronary heart disease: Longitudinal study. *BMJ, 318*(7181), 427–431.

Forsen, T., Eriksson, J. G., Tuomilehto, J., Osmond, C., & Barker, D. J. (1999). Growth in utero and during childhood among women who develop coronary heart disease: Longitudinal study. *BMJ, 319*(7222), 1403–1407.

Fung, T. T., Malik, V., Rexrode, K. M., Manson, J. E., Willett, W. C., & Hu, F. B. (2009). Sweetened beverage consumption and risk of coronary heart disease in women. *American Journal of Clinical Nutrition, 89*(4), 1037–1042.

Gardiner, P. A., Healy, G. N., Eakin, E. G., Clark, B. K., Dunstan, D. W., Shaw, J. E., Zimmet, P. Z., & Owen, N. (2011). Associations between television viewing time and overall sitting time with the metabolic syndrome in older men and women: The Australian Diabetes, Obesity and Lifestyle study. *Journal of American Geriatrics Society, 59*(5), 788–796.

Greenland, P. (2001). Beating high blood pressure with low-sodium DASH. *New England Journal of Medicine, 344*(1), 53–55.

Haslam, D. W., & James, W. P. (2005). Obesity. *Lancet, 366*(9492), 1197–1209.

Hastie, C. E., Padmanabhan, S., Slack, R., Pell, A. C., Oldroyd, K. G., Flapan, A. D., Jennings, K. P., Irving, J., Eteiba, H., Dominiczak, A. F., & Pell, J. P. (2010). Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. *European Heart Journal, 31*(2), 222–226.

He, F. J., & MacGregor, G. A. (2001). Fortnightly review: Beneficial effects of potassium. *BMJ, 323*(7311), 497–501.

He, K., Song, Y., Daviglus, M. L., Liu, K., Van Horn, L., Dyer, A. R., & Greenland, P. (2004). Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation, 109*(22), 2705–2711.

He, F. J., Li, J., & Macgregor, G. A. (2013). Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ, 346*, f1325.

Held, C., Iqbal, R., Lear, S. A., Rosengren, A., Islam, S., Mathew, J., & Yusuf, S. (2012). Physical activity levels, ownership of goods promoting sedentary behaviour and risk of myocardial infarction: Results of the INTERHEART study. *European Heart Journal, 33*(4), 452–466.

Holtermann, A., Mork, P. J., & Nilsen, T. I. (2014). Hours lying down per day and mortality from all-causes and cardiovascular disease: The HUNT study, Norway. *European Journal of Epidemiology, 29*(8), 559–565.

Laslett, L. J., Alagona, P., Jr., Clark, B. A., 3rd, Drozda, J. P., Jr., Saldivar, F., Wilson, S. R., Poe, C., & Hart, M. (2012). The worldwide environment of cardiovascular disease: Prevalence, diagnosis, therapy, and policy issues: A report from the American College of Cardiology. *Journal of the American College of Cardiology, 60*(25 Suppl), S1–S49.

Lavie, C. J., Milani, R. V., Artham, S. M., Patel, D. A., & Ventura, H. O. (2009a). The obesity paradox, weight loss, and coronary disease. *American Journal of Medicine, 122*(12), 1106–1114.

Lavie, C. J., Milani, R. V., & Ventura, H. O. (2009b). Obesity and cardiovascular disease: Risk factor, paradox, and impact of weight loss. *Journal of the American College of Cardiology, 53* (21), 1925–1932.

Lee, D. C., Pate, R. R., Lavie, C. J., Sui, X., Church, T. S., & Blair, S. N. (2014). Leisure-time running reduces all-cause and cardiovascular mortality risk. *Journal of the American College of Cardiology, 64*(5), 472–481.

Leon, D. A., Saburova, L., Tomkins, S., Andreev, E., Kiryanov, N., McKee, M., & Shkolnikov, V. M. (2007a). Hazardous alcohol drinking and premature mortality in Russia: A population based case-control study. *Lancet, 369*(9578), 2001–2009.

Leon, D. A., Saburova, L., Tomkins, S., McKee, M., & Shkolnikov, V. M. (2007b). Alcohol consumption and public health in Russia. *Lancet, 370*(9587), 561.

Leong, D. P., Smyth, A., Teo, K. K., McKee, M., Rangarajan, S., Pais, P., Liu, L., Anand, S. S., Yusuf, S., & I. Investigators. (2014). Patterns of alcohol consumption and myocardial infarction risk: Observations from 52 countries in the INTERHEART case-control study. *Circulation, 130*(5), 390–398.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., Amann, M., Anderson, H. R., Andrews, K. G., Aryee, M., Atkinson, C., Bacchus, L. J., Bahalim, A. N., Balakrishnan, K., Balmes, J., Barker-Collo, S., Baxter, A., Bell, M. L., Blore, J. D., Blyth, F., Bonner, C., Borges, G., Bourne, R., Boussinesq, M., Brauer, M., Brooks, P., Bruce, N. G., Brunekreef, B., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Bull, F., Burnett, R. T., Byers, T. E., Calabria, B., Carapetis, J., Carnahan, E., Chafe, Z., Charlson, F., Chen, H., Chen, J. S., Cheng, A. T., Child, J. C., Cohen, A., Colson, K. E., Cowie, B. C., Darby, S., Darling, S., Davis, A., Degenhardt, L., Dentener, F., Des Jarlais, D. C., Devries, K., Dherani, M., Ding, E. L., Dorsey, E. R., Driscoll, T., Edmond, K., Ali, S. E., Engell, R. E., Erwin, P. J., Fahimi, S., Falder, G., Farzadfar, F., Ferrari, A., Finucane, M. M., Flaxman, S., Fowkes, F. G., Freedman, G., Freeman, M. K., Gakidou, E., Ghosh, S., Giovannucci, E., Gmel, G., Graham, K., Grainger, R., Grant, B., Gunnell, D., Gutierrez, H. R., Hall, W., Hoek, H. W., Hogan, A., Hosgood, H. D., 3rd, Hoy, D., Hu, H., Hubbell, B. J., Hutchings, S. J., Ibeanusi, S. E., Jacklyn, G. L., Jasrasaria, R., Jonas, J. B., Kan, H., Kanis, J. A., Kassebaum, N., Kawakami, N., Khang, Y. H., Khatibzadeh, S., Khoo, J. P., Kok, C., Laden, F., Lalloo, R., Lan, Q., Lathlean, T., Leasher, J. L., Leigh, J., Li, Y., Lin, J. K., Lipshultz, S. E., London, S., Lozano, R., Lu, Y., Mak, J., Malekzadeh, R., Mallinger, L., Marcenes, W., March, L., Marks, R., Martin, R., McGale, P., McGrath, J., Mehta, S., Mensah, G. A., Merriman, T. R., Micha, R., Michaud, C., Mishra, V., Mohd Hanafiah, K., Mokdad, A. A., Morawska, L., Mozaffarian, D., Murphy, T., Naghavi, M., Neal, B., Nelson, P. K., Nolla, J. M., Norman, R., Olives, C., Omer, S. B., Orchard, J., Osborne, R., Ostro, B., Page, A., Pandey, K. D., Parry, C. D., Passmore, E., Patra, J., Pearce, N., Pelizzari, P. M., Petzold, M., Phillips, M. R., Pope, D., Pope, C. A., 3rd, Powles, J., Rao, M., Razavi, H., Rehfuess, E. A., Rehm, J. T., Ritz, B., Rivara, F. P., Roberts, T., Robinson, C., Rodriguez-Portales, J. A., Romieu, I., Room, R., Rosenfeld, L. C., Roy, A., Rushton, L., Salomon, J. A., Sampson, U., Sanchez-Riera, L., Sanman, E., Sapkota, A., Seedat, S., Shi, P., Shield, K., Shivakoti, R., Singh, G. M., Sleet, D. A., Smith, E., Smith, K. R., Stapelberg, N. J., Steenland, K., Stockl, H., Stovner, L. J., Straif, K., Straney, L., Thurston, G. D., Tran, J. H., Van Dingenen, R., van Donkelaar, A., Veerman, J. L., Vijayakumar, L., Weintraub, R., Weissman, M. M., White, R. A., Whiteford, H., Wiersma, S. T., Wilkinson, J. D., Williams, H. C., Williams, W., Wilson, N., Woolf, A. D., Yip, P., Zielinski, J. M., Lopez, A. D., Murray, C. J., Ezzati, M., AlMazroa, M. A., & Memish, Z. A. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380* (9859), 2224–2260.

Lloyd-Jones, D. M., Larson, M. G., Beiser, A., & Levy, D. (1999). Lifetime risk of developing coronary heart disease. *Lancet, 353*(9147), 89–92.

Mensink, R. P., & Katan, M. B. (1990). Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *New England Journal of Medicine, 323*(7), 439–445.

Michels, K., & Sacks, F. (1995). Trans fatty acids in European margarines. *New England Journal of Medicine, 332*(8), 541–542.

Moran, A. E., Forouzanfar, M. H., Roth, G. A., Mensah, G. A., Ezzati, M., Flaxman, A., Murray, C. J., & Naghavi, M. (2014). The global burden of ischemic heart disease in 1990 and 2010: The Global Burden of Disease 2010 study. *Circulation, 129*(14), 1493–1501.

Mozaffarian, D., & Rimm, E. B. (2006). Fish intake, contaminants, and human health: Evaluating the risks and the benefits. *JAMA, 296*(15), 1885–1899.

Mozaffarian, D., Katan, M. B., Ascherio, A., Stampfer, M. J., & Willett, W. C. (2006). Trans fatty acids and cardiovascular disease. *New England Journal of Medicine, 354*(15), 1601–1613.

Mukamal, K. J., Conigrave, K. M., Mittleman, M. A., Camargo, C. A., Jr., Stampfer, M. J., Willett, W. C., & Rimm, E. B. (2003). Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *New England Journal of Medicine, 348*(2), 109–118.

Mukamal, K. J., Chiuve, S. E., & Rimm, E. B. (2006). Alcohol consumption and risk for coronary heart disease in men with healthy lifestyles. *Archives of Internal Medicine, 166*(19), 2145–2150.

Mukamal, K. J., Chen, C. M., Rao, S. R., & Breslow, R. A. (2010). Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002. *Journal of the American College of Cardiology, 55*(13), 1328–1335.

Murray, C. J., & Lopez, A. D. (2013). Measuring the global burden of disease. *New England Journal of Medicine, 369*(5), 448–457.

O'Donnell, M., Mente, A., Rangarajan, S., McQueen, M. J., Wang, X., Liu, L., Yan, H., Lee, S. F., Mony, P., Devanath, A., Rosengren, A., Lopez-Jaramillo, P., Diaz, R., Avezum, A., Lanas, F., Yusoff, K., Iqbal, R., Ilow, R., Mohammadifard, N., Gulec, S., Yusufali, A. H., Kruger, L., Yusuf, R., Chifamba, J., Kabali, C., Dagenais, G., Lear, S. A., Teo, K., Yusuf, S., & P. Investigators. (2014). Urinary sodium and potassium excretion, mortality, and cardiovascular events. *New England Journal of Medicine, 371*(7), 612–623.

Ouwens, M. A., Cebolla, A., & van Strien, T. (2012). Eating style, television viewing and snacking in pre-adolescent children. *Nutrición Hospitalaria, 27*(4), 1072–1078.

Owen, N., Healy, G. N., Matthews, C. E., & Dunstan, D. W. (2010). Too much sitting: The population health science of sedentary behavior. *Exercise and Sport Sciences Reviews, 38*(3), 105–113.

Perk, J., De Backer, G., Gohlke, H., Graham, I., Reiner, Z., Verschuren, M., Albus, C., Benlian, P., Boysen, G., Cifkova, R., Deaton, C., Ebrahim, S., Fisher, M., Germano, G., Hobbs, R., Hoes, A., Karadeniz, S., Mezzani, A., Prescott, E., Ryden, L., Scherer, M., Syvanne, M., Scholte op Reimer, W. J., Vrints, C., Wood, D., Zamorano, J. L., Zannad, F., P. European Association for Cardiovascular, Rehabilitation, & E. S. C. C. f. P. Guidelines. (2012). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *European Heart Journal, 33*(13), 1635–1701.

Prospective Studies C., Whitlock, G., Lewington, S., Sherliker, P., Clarke, R., Emberson, J., Halsey, J., Qizilbash, N., Collins, R., & Peto, R. (2009). Body-mass index and cause-specific mortality in 900 000 adults: Collaborative analyses of 57 prospective studies. *Lancet, 373* (9669), 1083–1096.

Ronksley, P. E., Brien, S. E., Turner, B. J., Mukamal, K. J., & Ghali, W. A. (2011). Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. *BMJ, 342*, d671.

Sacks, F. M., Svetkey, L. P., Vollmer, W. M., Appel, L. J., Bray, G. A., Harsha, D., Obarzanek, E., Conlin, P. R., Miller, E. R., 3rd, Simons-Morton, D. G., Karanja, N., Lin, P. H., & D. A.-S. C. R. Group. (2001). Effects on blood pressure of reduced dietary sodium and the Dietary

Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *New England Journal of Medicine, 344*(1), 3–10.

Smith, L., Gardner, B., & Hamer, M. (2014). Childhood correlates of adult TV viewing time: A 32-year follow-up of the 1970 British Cohort Study. *Journal of Epidemiology and Community Health*. doi:10.1136/jech-2014-204365.

Stamatakis, E., Coombs, N., Jago, R., Gama, A., Mourao, I., Nogueira, H., Rosado, V., & Padez, C. (2013). Type-specific screen time associations with cardiovascular risk markers in children. *American Journal of Preventive Medicine, 44*(5), 481–488.

Thompson, P. D., Franklin, B. A., Balady, G. J., Blair, S. N., Corrado, D., Estes, N. A., 3rd, Fulton, J. E., Gordon, N. F., Haskell, W. L., Link, M. S., Maron, B. J., Mittleman, M. A., Pelliccia, A., Wenger, N. K., Willich, S. N., Costa, F., American Heart Association Council on Nutrition, Metabolism, Physical Activity, American Heart Association Council on Clinical Cardiology, & American College of Sports Medicine. (2007). Exercise and acute cardiovascular events placing the risks into perspective: A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation, 115*(17), 2358–2368.

van Uffelen, J. G., Wong, J., Chau, J. Y., van der Ploeg, H. P., Riphagen, I., Gilson, N. D., Burton, N. W., Healy, G. N., Thorp, A. A., Clark, B. K., Gardiner, P. A., Dunstan, D. W., Bauman, A., Owen, N., & Brown, W. J. (2010). Occupational sitting and health risks: A systematic review. *American Journal of Preventive Medicine, 39*(4), 379–388.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., Lisheng, L., & INTERHEART Study Investigators. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*(9438), 937–952.

Smoking and Cardiovascular Risk: Role of Stress in the Genesis of Smoking Behavior

Don Byrne and Jason Mazanov

Contents

Abstract

Smoking is an acknowledged – and significant – risk factor for cardiovascular disease (CVD). Research into the causes of smoking behavior is extensive, but few would disagree that smoking is a discretionary human behavior acquired through the operation of a combination of well-understood psychological

D. Byrne (✉)
The Medical School, The Australian National University, Canberra, ACT, Australia
e-mail: Don.Byrne@anu.edu.au

J. Mazanov
School of Business, UNSW-Canberra, Canberra, ACT, Australia
e-mail: j.mazanov@adfa.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_7

mechanisms. This chapter considered the role of psychological stress in its many forms – and including psychological illness – in the genesis of smoking behavior. While the evidence is both widespread and various, the collective view is that stress plays a very clear role in the maintenance of smoking behavior, and in the frequency of tobacco consumption, in well-established adult smokers. More than this, however, there is growing evidence that psychological distress experienced in adolescence is causally related to the onset of smoking behavior in that age group. Public health programs to prevent smoking onset among adolescents – as part of continuing efforts to lower the incidence of CVD in adults – must therefore include components of stress reduction and management in addressing this crucial issue.

Keywords
Cigarette smoking • CVD risk • Stress • Emotional distress • Adolescence

Introduction

Smoking and Cardiovascular Disease

The negative health consequences of cigarette smoking are now established beyond any reasonable doubt. Smoking has been consistently, convincingly, and causally related to a host of cardiovascular, peripheral vascular, and cerebrovascular diseases, and this assertion has clear epidemiological support (Tanuseputro et al. 2003: Lloyd-Jones et al. 2006; Erhardt 2009). It holds across genders and cultures (Kurian and Cardarelli 2007) and for passive as well as active smoking (Whincup et al. 2004). Moreover, CVD risk among smokers decreases with smoking cessation (Wannamethee et al. 2005). And well-understood pathophysiological mechanisms are available to explain the links between smoking and CVD risk (Ambrose and Barua 2004).

In the large majority of cases, CVD becomes manifest in middle or late adulthood, though cigarette smoking has its origins firmly in early to middle adolescence. Despite this recognition, and the consequent application of a multitude of smoking prevention programs targeted at early and middle adolescents (Byrne and Mazanov 2005), rates of smoking behavior remain high in this crucial developmental stage. Large numbers in developed countries report themselves to be regular smokers, and females do so at rates generally greater than do males. Moreover, adults continue to smoke in large numbers and across national and cultural boundaries (Ng et al. 2014). The problem is therefore obvious, and a substantial and ongoing research effort remains directed at both the determinants of smoking onset and the drivers of that behavior once it has been established. And an emerging research effort has recently been focused on the most effective means of preventing smoking behavior among adolescents or of the usefulness of smoking cessation strategies in adults once the behavior has been established.

Determinants of the Onset of Smoking Behavior

A comprehensive overview of factors bearing on the onset of cigarette smoking clearly favors the notion that it is, above all, a socio-behavioral phenomenon. Tyas and Pederson (1998) have suggested a four-category typology of causal influences, involving sociodemographic, environmental, behavioral, and personal influences. Sociodemographic factors such as age, gender, and socioeconomic status are self-evident. Ethnicity and race have been related to smoking but not in any consistent manner, and while urban or rural location has been investigated, there is little which is conclusive about that evidence. Environmental factors include parental smoking behaviors and attitudes, and the influence of siblings and peers is equally clear. Moreover, a host of influences which can loosely be grouped under the umbrella of both state and trait personality attributes – to be discussed in another chapter – have attracted a great deal of attention. Yet longitudinal studies testing multivariate causal models (e.g., Byrne and Reinhart 1998) have provided conclusive support neither for specific combinations of causal variables nor for the rank-ordered importance of those variables. Methodological issues related to both sampling and measurement have conspicuously impaired the capacity to clearly interpret the evidence. But one irreducible factor draws this evidence together. Cigarette smoking is a discretionary human behavior – it is acquired and maintained largely (if not exclusively) by way of the complex and dynamic interaction of individuals with their psychosocial environments. And in line with this view, the prevention or cessation of smoking behavior follows the same set of psychological principles. The issue which is still to be resolved is, of course, what those psychological principles are.

The experience of psychological stress has been linked anecdotally to smoking behavior for decades. Yet in contrast to such diverse areas as the sociodemographic contexts of smoking behavior, and of the role of individual personality, the influence of stress on smoking behavior has only recently been seriously explored in systematic research studies. This chapter reviews that evidence.

Stress and Smoking

Examination of the research linking stress and smoking behavior must be viewed in the context of three important caveats. First, research into stress and smoking has largely been empirically driven and is often lacking in a clear theoretical foundation. Second, definitions and conceptualizations of stress have historically been challenged. And third, Nesbitt's paradox (Nesbitt 1973), in which ... *smoking generates physiological and psychological changes which are normally incompatible* ... (as stated by Parrott 1998), poses a perplexing discord between anecdotal and clinical reports of smoking and stress reduction, on the one hand, and relevant theory and empirical evidence on the other.

Nonetheless, the popular view that smoking reduces stress, and that smoking behavior is therefore reinforced through its stress-reducing properties, prevails in the lay literature. An Internet search using the term *stress and smoking* yields an abundance of sites, the large majority offering either folk wisdom (typically some statement that stress promotes smoking behavior) or various intervention packages, evidence-based or otherwise, to assist with stress management during smoking cessation. There is a relatively small scientific literature, and even then often indirect, documenting associations between stress and smoking. The hypothesized relationship was first canvassed three decades ago (Schachter et al. 1977), but few studies since have directly addressed the fundamental issues either of whether stress causes (or contributes to) the onset of smoking behavior or whether, among those who have already commenced smoking, stress simply increases the frequency of cigarette consumption.

Much of the evidence addressing the latter issue is largely indirect, and it is also mostly focused on the adult population of smokers (Spigner et al. 2005), not surprisingly since it is the adult population in which the greatest numbers of regular smokers are to be found. This evidence can best be captured under the four groupings of: (a) cumulative exposure to psychosocial stress and smoking, (b) sufferers of stress-related psychiatric disorders and smoking, (c) stress and smoking in high occupational risk populations, and (d) stress and its impact on attempts at smoking cessation.

Exposure to Psychosocial Stress and Smoking

The relationship between psychosocial stress and smoking behavior – and the issue of why those experiencing stress should turn to cigarette smoking – lies at the heart of Nesbitt's paradox. Nonetheless, it is clear from the evidence that among regular adult smokers at least, the experience of stress corresponds to an increase in tobacco consumption rates (Michal et al. 2013). This is seen broadly across age groups, from adolescents (Fields et al. 2009), young adults (Conrad et al. 2013; Tavolacci et al. 2013), and adults in both the mid (Ng and Jeffery 2003; Slopen et al. 2012) and later years (Choi and Dinitto 2011). And the relationship appears also to hold for tobacco craving (Childs and de Wit 2010; Saladin et al. 2012). While psychosocial stress generally has been clearly associated with cigarette use, stress arising from more specific sources, for example, unemployment (De Vogli and Santinello 2014), the aftermath of the September 11 terrorist attacks (Vlahov et al. 2002), and perceived racial discrimination Purnell et al. 2012), also manifests the relationship. Alarmingly, psychosocial stress has been associated with smoking behavior in both pregnant women (Varescon et al. 2013) and young mothers (Hauge et al. 2012; Sperlich et al. 2013). The evidence, collectively, therefore confirms the general link between stress and smoking behavior.

Traumatic Stress, Stress-Related Mood Disorders, and Smoking

Many psychiatric disorders either claim stress as a causal contributor or manifest stress-like symptoms as part of their clinical presentation (see American Psychiatric Association, DSM V, 2013). It is reasonable then to expect that if stress and smoking are related, smoking rates should be elevated among those suffering such disorders.

Morissette et al. (2006) examined smoking behavior among individuals with anxiety disorders and reported smoking to be higher in those with anxiety sensitivity, higher levels of anxiety symptoms, agoraphobic avoidance, negative affect, and life interference of anxiety. Smokers were not different from nonsmokers, however, on measures of social anxiety, worry, or obsessive-compulsive symptoms. A broad influence of anxiety on smoking behavior could therefore be claimed.

But of the anxiety-based psychiatric disorders, post-traumatic stress disorder (PTSD) shows the most consistent association with smoking behavior. PTSD identified by structured interview in the general population was related to the probability of smoking and of nicotine dependence and also to a (low) probability of remission from nicotine dependence (Hapke et al. 2005) leading to the conclusion that smokers with PTSD may need particular help with cessation. Thorndike et al. (2006) looked for PTSD in current regular smokers (rather than assessing smoking in those with PTSD) and found PTSD to be related to nicotine dependence but not to numbers of cigarettes consumed daily. Smoking behavior assessed in various ways has now also been clearly, consistently, and causally linked to the experience of major traumatic events, both civilian (Olff et al. 2006) and war related (Koenen et al. 2006). An examination of event triggers in a sample of smokers with PTSD (Beckham et al. 2005) indicated that negative affect, PTSD symptoms, and restlessness were reliable precipitants of smoking behavior.

Survivors of the attack on the World Trade Center on 11 September 2001 have recently provided a large group for study in relation to PTSD and smoking. Assessment of a random sample of New York residents 5–8 weeks after the attack showed rates of smoking increased noticeably following the event (Vlahov et al. 2002), and symptoms of PTSD were associated with this increase (Arijit et al. 2005). Even US populations geographically distant from New York at the time of the attack showed traumatic event-related increases in smoking behavior in the following week (Formann-Hoffman et al. 2005). Interestingly, reexamination of these data controlling for depression eliminated associations between PTSD and smoking, raising the possibility that mood disorders other than those based on anxiety are associated with smoking behavior. Depression has been prominent in this regard (Knox et al. 2006; Dierker et al. 2005; Campo-Arias et al. 2006), though associations have not been universally strong (Johnson and Breslau 2006).

And beyond the anxiety-based syndromes, both depression (Matthews et al. 2011) and negative mood more broadly defined (Perkins et al. 2012) have been reported to be significantly associated with smoking behavior.

The use of mood disorders as a proxy index of stress has not provided unambiguous support for the view that stress and smoking are linked in anything but a coincidental manner, but the evidence is sufficiently persuasive to warrant further investigation. While the evidence is strongest for PTSD as a predictor of smoking status, it is confounded in at least one study by the coexistence of depression.

Smoking in Potentially Stress-Prone Occupational Populations

Some populations of individuals through occupational choice are subjected to greater exposure to stress during periods of their lives than are other populations. If smoking were linked to stress, then more individuals in these populations would be expected to be smokers, and among those smokers, the behavior would be expected to covary with fluctuations in stressor load.

Rates of smoking among nurses are high relative to the population at large, and the stress of the nursing workplace has been implicated in this finding (McKenna et al. 2003); while there was no evidence to indicate a causal influence, the maintenance effects of stress on smoking behavior in nurses were clearly apparent.

Armed service personnel, whether current or retired, constitute another population at apparent risk; rates of smoking in military populations are recognized to be high (Feigelman 1994), and speculation has linked this phenomenon to the stress of a potentially hazardous occupation (Prendergast et al. 1973). Smoking rates rise generally when young recruits enter military service (Chisick et al. 1998) and the experience of combat conditions (Wynd and Ryan-Wenger 1998; Ismali et al. 2000) strengthens links. This has also been evident among those engaged in the provision of medical care during wartime (Creson et al. 1996; Britt and Adler 1999; Boos and Croft 2004). And high rates of smoking in military personnel continue into civilian life after discharge (Klevens et al. 1995; Whitlock et al. 1995; op den Velde et al. 2002). There is evidence to suggest however that continuation is mediated in part by the development of PTSD (op den Velde et al. 2002) or depression (Whitlock et al. 1995). There is therefore consistent evidence linking smoking with military service, and by inference with the stress of military life, but much of this is indirect and does not inform the debate on stress and smoking in any specific way. Much the same may be said for stress and smoking among police officers (Smith et al. 2005). Empirical evidence for this has been reported in a number of countries including the USA (Franke et al. 1998), Australia (Richmond et al. 1998), and France (Bonnet et al. 2005). Importantly, however, this empirical finding has been specifically linked to the occupational stress arising from police work (Bonnet et al. 2005; Smith et al. 2005).

Most directly, however, occupational stress has been related to cigarette smoking in studies extending beyond specific occupational groups with putative high stress levels. Kouvonen et al. (2005) found that high effort-reward imbalance in the workplace was a predictor of smoking behavior. High levels of job strain and job demand were also related to cigarette smoking, and low job effort was associated with ex-smoker status. The stress of job loss too has been related to increases in

cigarette consumption and to relapse into smoking among those who had previously quit (Falba et al. 2005). Occupational stress is therefore clearly associated with smoking behavior. Interestingly, stress specific to the workplace has been found to impede smoking cessation attempts (Yasin et al. 2012), and workplace smoking bans, conversely, result in the experience of further stress (Azagaba and Sharaf 2012). But whether this evidence extends to a causal influence on work stress on smoking onset or is limited to some covariation between work stress and smoking behavior among already established smokers remains to be confirmed by prospective investigation.

Stress and Smoking Cessation

Clinical observations have consistently indicated that stress impacts adversely on smoking cessation (Baddini-Martinez and de Padua 2013). Recent studies report that perceived stress is associated with lower quit rates in those undergoing a smoking cessation intervention (Norman et al. 2006) and with a failure to maintain abstinence following intervention (Manning et al. 2005; Nakajima and al'Absi 2012). Stress has also been associated with relapse among initially successful quitters (Slopen et al. 2013). Moreover, failure to quit following a definite attempt resulted in increased levels of psychological distress (van der Deen et al. 2011). Successful smoking cessation has been associated with decreases in the experience of anxiety, though correspondingly, anxiety appears to increase when cessation attempts are unsuccessful (McDermott et al. 2013). Depression alone, however, has not been shown to predict failure in smoking cessation (Hall 2004; Lerman et al. 2004). A recent meta-analysis of 26 empirical studies on smoking cessation (Taylor et al. 2014) found that successful smoking cessation resulted in positive mental health outcomes across the areas of depression, anxiety, stress, and mood generally. However, autonomic arousal during the early stages of smoking abstinence following intervention does exacerbate withdrawal symptoms and contributes to rapid relapse for most smokers (al'Absi 2006). Clinical anecdote is therefore borne out by systematic investigation. Since it is highly likely that the experience of stress interferes in some way with smoking cessation, many practitioners in the area now advocate the inclusion of a stress management component into smoking cessation interventions.

Overview of the Evidence

The evidence is sufficiently consistent now that, in line with both anecdote and observation, stress has been generally linked with smoking in adult smokers in a range of empirical investigations. The bulk of this evidence, however, comes from studies inferring stress either from the presence of diagnosed psychological dysfunction or membership of an occupational group assumed to be stressful. Few studies have reported covariations of smoking behavior with naturalistic

assessments of stressor exposure and impact. Nonetheless, the broad coexistence of stress and smoking appears to be well established. But the target populations for these studies have been regular smokers typically in adulthood, and as we earlier stated, smoking onset is overwhelmingly to be found in adolescents. The evidence linking stress and adolescent smoking, both causally (to smoking onset) and as a maintaining influence once smoking has been established, must now be examined.

Stress and Smoking Onset in Adolescents

The theme of this chapter rests on the view that the primary theoretical objection to a causal link between stress and smoking onset in adolescence lies with (1973) Nesbitt's paradox. This aside, however, the past decade has seen a great deal of evidence linking stress with smoking behavior in adolescence. Most of this evidence falls within the three broad categories of: (a) stress and either current smoking behavior or smoking onset, (b) smoking in adolescents suffering from a psychological disorder linked with stress, or (c) stress as an impediment to smoking prevention strategies in adolescents. These are now considered in turn.

Stress and Adolescent Smoking (Onset or Current Behavior)

The experience of high levels of stress, often in association with poor mobilization of effective coping skills, has consistently been associated with current smoking behavior in adolescents. Siqueira et al. (2000) examined 954 patients aged between 12 and 21 attending an urban multidisciplinary clinic; 25 % were current smokers and this was clearly related to both high levels of experienced stress and the use of negative coping strategies. The nature of the reported stressors was broadly based but those involving the family were prominent. Family stress was also found to be a correlate of both adolescent smoking behavior and daily smoking levels in a large population sample (Miller and Volk 2002).

A study of normal secondary school adolescents (Karatzias et al. 2001) looked both at experimental smoking (having tried smoking) and the maintenance of established smoking behavior. School stress was the best predictor of experimental smoking, but the maintenance of the behavior, once established, was better predicted by poor quality of school life. While this study was essentially retrospective, the finding that (school) stress predicted experimental smoking but not smoking maintenance hints at the possible link between stress and smoking onset. A large population study (van den Breen et al. 2004) further reinforced the importance of school stress, reporting associations between stress in the school context and both initiation and progression of smoking among adolescents. High levels of stress predicted progression along a trajectory of smoking in school-aged adolescents (Hunt 2005). And findings such as these have gone beyond Western samples of adolescents, with similar results recently reported from samples of adolescents in China (Unger et al. 2001; Li et al. 2003; Liu 2003).

Much of this evidence rests on cross-sectional examination of adolescent smoking behavior; however, a number of studies have attempted to move to a more predictive assessment of stress and smoking. In a large sample of sixth and seventh graders, Jones (2004) showed not only that perceived stress related to current smoking behavior but that measures of perceived stress in sixth graders predicted smoking when these adolescents were prospectively examined as seventh graders. And reported adolescent intention to smoke is clearly predicted by prior stress (Straub et al. 2003; Booker et al. 2004). In a truly prospective study (relatively rare in this area), Wills et al. (2002) examined directional hypotheses in regard to stress and smoking in a large sample of adolescents initially assessed at intake (with a mean age of 12.4 years) and followed up at three yearly intervals. The experience of negative life events significantly predicted smoking onset over the follow-up period, and because of the prospective design, the evidence supported the view that stress is associated with smoking onset and not simply current smoking behavior.

This finding was largely confirmed by Finkelstein et al. (2006) in a study of smoking onset in a sample of more than 1000 school-aged adolescents. The link between stress and smoking onset, however, appeared to be influenced by social status as a proxy measure of social inequality.

And in this light, while exposure to stressors in general has constituted the dominant measure in studies linking stress and adolescent smoking, some work has examined more specific components of stress in relation to the postulated link. Work by van Jaarsveld et al. (2007), for example, found that early maturing – as evidenced by assessments of pubertal timing – was associated with adolescent smoking behavior. And adolescent smoking has also been linked with low body image satisfaction, particularly among young adult females (Croghan et al. 2006). These findings are again based on proxy measures of stress but add overall weight to statistical links between the experience of stress and smoking behavior among adolescents.

The paucity of prospective evidence on stress and adolescent smoking onset – in contrast to the more abundant associations between stress and current smoking behavior – has however limited the conclusions which might be drawn in this area. A quasi-prospective study of more than 6500 Australian adolescents (Byrne et al. 1995) reported significant associations between stress and smoking onset in previously nonsmoking adolescents followed up over a year, with associations represented across a broad range of stressors. Unfortunately, while smoking onset was assessed over the follow-up year, stress was retrospectively measured only at follow-up, and so predictive relationships based on levels of stress at intake could not be claimed.

This issue was addressed in a further study (Byrne and Mazanov 1999) in which both stress and current smoking were assessed in a large sample of Australian adolescents. Stressor experience was clearly related to current smoking, and while associations were stronger for girls than for boys, most domains of adolescent stressors were correlated with smoking behavior. The sample was followed up a year after intake; scores on scales of adolescent stress were only weakly predictive of smoking onset in boys. For girls, however, prospective associations were far stronger and more broadly represented across the domains of adolescent stress, indicating that stress may exert a causal influence on the onset of smoking at least

for adolescent girls (Byrne and Mazanov 2003). Results indicated a broad range of stressor categories (Byrne et al. 2007) as precursors to adolescent smoking, particularly among girls. The breadth of stressors associated with smoking attests to the complex nature of adolescent stress. Examination of intention to smoke in this same cohort revealed that dimensions of stress usefully predicted adolescents' indicated intention to be smokers (or nonsmokers) at some time into the future (Mazanov and Byrne 2002). Intention to smoke is a contentious outcome variable, however, since it is not perfectly correlated with the actual behavioral outcome, though it is often used as a variable of convenience where a true prospective methodology is not feasible. Droomers et al. (2005) extended the reasoning to the broader psychosocial contexts in which adolescents live, linking smoking to the stress of low socioeconomic class, though findings such as these are prone to a range of interpretations.

But two particular sources of adolescent stress have emerged from the recent literature as worthy of further attention. First, gender differences in relation to stress and smoking are clearly evident (Koval et al. 2000). Female gender has also been associated with smoking rates, with girls tending to have higher rates of smoking than boys, at least in Western samples (Byrne and Reinhart 1998). Adolescent girls also appear to experience higher levels of stress than boys (Byrne et al. 2007). The possibility that these issues may be linked (Croghan et al. 2006) cannot be overlooked. One pathway which may explain the link is that of pubertal timing. Early puberty in girls has been associated with the experience of stress (Simon et al. 2003) and with both having tried smoking (Simon et al. 2003) and early initiation and greater frequency of smoking (Dick et al. 2000). The potential to understand high smoking rates in adolescent girls through the mechanism of stress associated with early puberty deserves further exploration.

And second, as societies around the world become more multiethnic, adolescents in minority groups are experiencing racial discrimination and stress arising from that (Fisher et al. 2000). Early evidence is emerging that stress from this source is associated with adolescent smoking. Guthrie et al. (2002) looked at racial discrimination among African-American adolescent girls and reported a clear association between the experience of discrimination and smoking. Controlling for levels of stress arising from discrimination significantly reduced the size of the relationship between discrimination and smoking, underscoring the importance of stress in understanding the link. Udry et al. (2003) extended this reasoning to adolescents of mixed race origins, associating elevated risk of smoking in mixed race adolescents to stress arising from this situation. This potential link between stress and adolescent smoking also requires vigorous examination.

Anxiety, Depression, and Adolescent Smoking

In a manner identical to evidence relating stress to established smoking in adults, it would be expected that where adolescents suffer a psychological disorder involving affective distress, smoking behavior should vary in some way in relation to the onset or course of that psychological disorder (Morissette et al. 2007).

Investigation of a population sample of adolescents (Acierno et al. 2000) assessed traumatic stress in relation to cigarette use. Depression was associated with smoking only in girls and in contrast to the adult literature reviewed earlier; PTSD was not independently related to an increased risk of smoking. Gender differences in relation to depression and smoking were also evident in a study of early adolescents using electronic diary data collection (Whalen et al. 2001; Henker et al. 2002). While "depressive dispositions" were related both to smoking urges and risk of smoking in this sample, depression was related to a reduction in smoking risks in boys, but only where smoking risks were associated with externalizing (aggressive and delinquent) behaviors. By contrast, a telephone survey of girls and young women drawn from a representative population sample revealed that smoking was related to the report of depressive symptoms (Pirkle and Richter 2006).

Botello Cabrera (2005) reported broader links between mood disorders and smoking in adolescents, where smoking is related to having any psychiatric disorder. A study of current adolescent smoking behavior (Koval et al. 2004) indicated that while psychosocial variables relate to current smoking, effects are more evident for boys than for girls, leading to the conclusion that for older boys at least, smoking may be used as a coping strategy against depression. Broadening the field further, an extensive study of young people aged 7–18 with symptoms of hyperactivity-inattention (Galera et al. 2005) suggested that while these symptoms did not independently predict risk of smoking, symptoms of conduct disorder were significantly related to smoking in both genders. High activity levels were associated with smoking only in boys, but shy girls showed a lower risk of smoking.

Some studies have questioned the direction of causality of the link between psychological disorder and smoking in adolescents. Goodwin et al. (2005) followed a large group of adolescents over three time points from adolescence to young adulthood and found that daily smoking at intake was related to the experience of panic attacks at the first follow-up and to conspicuous panic disorder at the final data collection. While these results were attenuated when the presence of parental anxiety was taken into account, they suggest that smoking may lead to anxiety rather than the reverse. Data from a further population sample (Steuber and Banner 2006) indicated that adolescent smoking status at intake was associated with the report of depression at follow-up and that this finding was most prominent for girls. McGee et al. (2005) reported that early smoking in adolescents predicted suicidal ideation sometime later, though this relationship disappeared when coexisting depression was controlled for.

The evidence linking affective distress with adolescent smoking is therefore tantalizing but not conclusive in regard to adolescent smoking. While firmer conclusions are attractive, the complexity of adolescent mental health issues potentially confounds the data.

Stress and Adolescent Smoking Prevention and Cessation

The health consequences of adolescent smoking are sufficiently important that a good deal of research is now devoted either to prevention of smoking in younger

adolescents or cessation of smoking among those who have already acquired the behavior. As with the adult literature, there is emerging evidence that stress exerts an influence on the ease with which adolescents are either able to resist the behavior or give it up once acquired.

Common practice in the field of adolescent smoking cessation consistently involves the teaching of stress management as an integral component of intervention (Singleton and Pope 2000; O'Connell et al. 2004). Indeed, a study of smoking cessation interventions (Turner et al. 2004) actually found that stress predicted attendance at cessation sessions; those with high reported stress were less likely to attend than those with low stress. And stress posed a significant barrier to smoking cessation in another sample interviewed on their likelihood of quitting smoking (Amos et al. 2006). A small qualitative study of young female smokers (Gilbert 2005) advocated that smoking cessation programs should be targeted to the needs of young people and that the common belief that smoking leads to stress relief should for a focus for such programs.

Unlike the adult literature, however, few studies have examined stress (or mental health status) in relation to actual outcomes in smoking cessation programs. Horn et al. (2004) studied a relatively small sample of rural adolescents either undergoing a purpose-designed program to quit smoking or offered a brief, single intervention. The cessation program was modestly successful, but the coexistence of depression or anxiety reduced the effectiveness of cessation outcomes. On that basis these authors recommended the inclusion of coping and stress management skills into smoking cessation programs for adolescents.

The literature on smoking prevention in adolescents is, unfortunately, not encouraging (Bruvold 1993), and there has been little to systematically link stress with the achievement of prevention. Byrne and Mazanov (2005) did present data evaluating an extensive smoking prevention program in a large sample of Australian adolescents which does bear on the role of stress. Three approaches to smoking prevention based respectively on the health consequences of smoking, the fitness consequences of smoking, and resistance to peer pressure were trialed in a 1-year prospective study. While the intervention program focusing on the health consequences of smoking was most effective in reducing smoking onset immediately following intervention, 1-year follow-up demonstrated that resistance to peer pressure based on stress management was a more effective long-term prevention strategy.

Conclusions

The evidence relating adolescent smoking to stress then is broadly persuasive but not absolutely clear-cut. Much of the support has been implied from studies of established adult smokers and focused on the apparent stress-reducing properties of smoking behavior. And Nesbitt's (1973 paradox remains a thorny theoretical issue. Yet the empirical evidence continues to support a link between stress and adolescent smoking, and some evidence (Byrne and Mazanov 1999, 2003, 2005) suggests

that this link may be causal. Prospective evidence restricts the link largely to girls but associations still remain evident in boys. And interestingly, there is little evidence that stress influences smoking behavior over time in adolescents once the behavior has been established (Mazanov and Byrne 2006). But the best evidence on whether stress relates causally to the onset of adolescent smoking will finally rest with intervention studies, and there is now sufficient of that evidence to indicate that stress management should be a prominent component of all new programs focusing on the prevention of smoking behavior among school-aged adolescents.

Acknowledgment Portions of this chapter are based on revisions of an earlier publication by the present authors (Personality, stress and the determination of smoking behaviour in adolescents, in G.J. Boyle, G. Matthews and D.H. Salkofske (Eds) (2008) *The Sage Handbook of Personality Theory and Assessment*. Los Angeles: Sage Publications Inc. (Chapter 34, pp 698–719). Used with the publisher's permission.

References

Acierno, R., Kilpatrick, D. G., Resnick, H., Saunders, B., De Arellano, M., & Best, C. (2000). Assault, PTSD, family substance use, and depression as risk factors for cigarette use in youth: Findings from the National Survey of Adolescents. *Journal of Traumatic Stress, 13*(3), 381–396.

al'Absi, M. (2006). Hypothalamic-pituitary-adrenocortical responses to psychological stress and risk for smoking relapse. *International Journal of Psychophysiology, 59*(3), 218–227.

Ambrose, J. A., & Barua, R. S. (2004). The pathophysiology of cigarette smoking and cardiovascular disease. *Journal of the American College of Cardiology, 43*(10), 1731–1737.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Washington, DC: APA.

Amos, A., Wiltshire, S., Haw, S., & McNeill, A. (2006). Ambivalence and uncertainty: Experiences of and attitudes towards addiction and smoking cessation in the mid-to-late teens. *Health Education Research, 21*(2), 181–191.

Arijit, N., Galea, S., Ahern, J., & Vlahov, D. (2005). Probable cigarette dependence, PTSD, and depression after an urban disaster: Results from New York City residents 4 months after September 11, 2001. *Psychiatry: Interpersonal Biological Processes, 68*(4), 299–310.

Azgaba, S., & Sharaf, M. F. (2012). The association between workplace smoking bans and self-perceived, work-related stress among smoking workers. *BMC Public Health*. doi:10.1186/1471-2458-12-123.

Baddini-Martinez, J., & de Padua, A. I. (2013). Can an index of smokers' emotional status predict the chances of success in attempts to quit smoking? *Medical Hypotheses, 80*(6), 722–725.

Beckham, J. C., Feldman, M., Vrana, S. R., Mozley, S. L., Erkanli, A., & Clancy, C. P. (2005). Immediate Antecedents of cigarette smoking in smokers with and without posttraumatic stress disorder: A preliminary study. *Experimental and Clinical Psychopharmacology, 13*(3), 219–228.

Bonnet, A., Fernandez, L., Marpeaux, V., Graziani, P., Pedinielli, J.-L., & Rouan, G. (2005). Stress, tobacco smoking and other addictive behaviours in the police force. *Alcoologie et Addictologie, 27*(2 Suppl), 26S–36S.

Booker, C. L., Gallaher, P., Unger, J. B., Ritt-Olson, A., & Johnson, C. A. (2004). Stressful life events, smoking behavior, and intentions to smoke among a multiethnic sample of sixth graders. *Ethnicity & Health, 9*(4), 369–397.

Boos, D. J., & Croft, A. M. (2004). Smoking rates in the staff of a military field hospital before and after wartime deployment. *Journal of the Royal Society of Medicine, 97*(1), 20–22.

Botello Cabrera, M. T. (2005). DSM-IV psychiatric disorders and cigarette smoking among adolescents living in Puerto Rico. *Dissertation Abstracts International: Section B The Sciences and Engineering, 66*(5-B), 2538.

Britt, T. W., & Adler, A. B. (1999). Stress and health during medical humanitarian assistance missions. *Military Medicine, 164*(4), 275–279.

Bruvold, W. H. (1993). A meta-analysis of adolescent smoking prevention programs. *American Journal of Public Health, 83*(6), 872–880.

Byrne, D. G., & Mazanov, J. (1999). Sources of adolescent stress, smoking and the use of other drugs. *Stress Medicine, 15*(4), 215–227.

Byrne, D. G., & Mazanov, J. (2002). Sources of stress in Australian adolescents: Factor structure and stability over time. *Stress and Health, 18*(4), 185–192.

Byrne, D. G., & Mazanov, J. (2003). Adolescent stress and future smoking behaviour: A prospective investigation. *Journal of Psychosomatic Research, 54*(4), 313–321.

Byrne, D. G., & Mazanov, J. (2005). Prevention of adolescent smoking: A prospective test of three models of intervention. *Journal of Substance Use, 10*(6), 363–374.

Byrne, D. G., & Reinhart, M. I. (1998). Psychological determinants of adolescent smoking behaviour: A prospective study. *Australian Journal of Psychology, 50*(1), 29–34.

Byrne, D. G., Byrne, A. E., & Reinhart, M. I. (1995). Personality, stress and the decision to commence smoking in adolescence. *Journal of Psychosomatic Research, 39*(1), 53–62.

Byrne, D. G., Davenport, S. C., & Mazanov, J. (2007). Profiles of adolescent stress: The development of the adolescent stress questionnaire. *Journal of Adolescence, 30*(3), 393–416.

Campo-Arias, A., Diaz-MartineZ, L. A., Rueda-Jaimes, G. E., Rueda-Sanchez, M., Farelo-Palacin, D., Diaz, F. J., et al. (2006). Smoking is associated with schizophrenia, but not with mood disorders, within a population with low smoking rates: A matched case-control study in Bucaramanga. *Colombiana Schizophrenia Research, 83*(2–3), 269–276.

Childs, E., & de Wit, H. (2010). Effects of acute psychosocial stress on cigarette craving and smoking. *Nicotine Tobacco Research, 12*(4), 449–453.

Chisick, M. C., Poindexter, F. R., & York, A. K. (1998). Comparing tobacco use among incoming recruits and military personnel on active duty in the United States. *Tobacco Control, 7*(3), 236–240.

Choi, N. G., & Dinitto, D. M. (2011). Drinking, smoking, and psychological distress in middle and late life. *Aging Mental Health, 15*(6), 720–731.

Conrad, M., Wardle, M., King, A., & de Wit, H. (2013). Relationship of self-reported and acute stress to smoking in emerging adult smokers. *Journal of Clinical Psychology, 69*(7), 710–717.

Creson, D., Schmitz, J. M., & Arnoutovic, A. (1996). War-related changes in cigarette smoking: A survey study of health professionals in Sarajevo. *Substance Use & Misuse, 31*(5), 639–646.

Croghan, I. T., Bronars, C., Patten, C. A., Schroeder, D. R., Nirelli, L. M., Thomas, J. L., et al. (2006). Is smoking related to body image satisfaction, stress, and self-esteem in young adults? *American Journal of Health Behavior, 30*(3), 322–333.

De Vogli, R., & Santinello, M. (2014). Unemployment and smoking: Does psychosocial stress matter? *Tobacco Control, 2005*(14), 389–395.

Dick, D. M., Rose, R. J., Viken, R. J., & Kaprio, J. (2000). Pubertal timing and substance use: Associations between and within families across late adolescence. *Developmental Psychology, 36*(2), 180–189.

Dierker, L. C., Ramirez, R. R., Chavez, L. M., & Canino, G. (2005). Association between psychiatric disorders and smoking stages among Latino adolescents. *Drug and Alcohol Dependence, 80*(3), 361–368.

Droomers, M., Schrijvers, C. T. M., Casswell, S., & Mackenbach, J. P. (2005). Father's occupational group and daily smoking during adolescence: Patterns and predictors. *American Journal of Public Health, 95*(4), 681–689.

Erhardt, L. (2009). Cigarette smoking: An undertreated risk factor for cardiovascular disease. *Atherosclerosis, 205*, 23–32.

Falba, T., Teng, H.-M., Sindelar, J. L., & Gallo, W. T. (2005). The effect of involuntary job loss on smoking intensity and relapse. *Addiction, 100*(9), 1330–1339.

Feigelman, W. (1994). Cigarette smoking among former military service personnel: A neglected social issue. *Preventive Medicine, 23*(2), 235–241.

Fields, S., Leraas, K., Collins, C., & Reynolds, B. (2009). Delay discounting as a mediator of the relationship between perceived stress and cigarette smoking status in adolescents. *Behavioural Pharmacology, 20*(5–6), 455–460.

Finkelstein, D. M., Kubzansky, L. D., & Goodman, E. (2006). Social status, stress, and adolescent Smoking. *Journal of Adolescent Health, 39*, 678–685.

Fisher, C. B., Wallace, S. A., & Fenton, R. E. (2000). Discrimination distress during adolescence. *Journal of Youth and Adolescence, 29*(6), 679–695.

Formann-Hoffman, V., Riley, W., & Pici, M. (2005). Acute impact of the September 11 tragedy on smoking and early relapse rates among smokers attempting to quit. *Psychology of Addictive Behaviors, 19*(3), 277–283.

Franke, W. D., Collins, S. A., & Hinz, P. N. (1998). Cardiovascular disease morbidity in an Iowa law enforcement cohort, compared with the general Iowa population. *Journal of Occupational and Environmental Medicine, 40*(5), 441–444.

Galera, C., Fombonne, E., Chastang, J.-F., & Bouvard, M. (2005). Childhood hyperactivity-inattention symptoms and smoking in adolescence. *Drug and Alcohol Dependence, 78*(1), 101–108.

Gilbert, E. (2005). Contextualising the medical risks of cigarette smoking: Australian young women's perceptions of anti-smoking campaigns. *Health Risk and Society, 7*(3), 227–245.

Goodwin, R. D., Lewinsohn, P. M., & Seeley, J. R. (2005). Cigarette smoking and panic attacks among young adults in the community: The role of parental smoking and anxiety disorders. *Biological Psychiatry, 58*(9), 686–693.

Guthrie, B. J., Young, A. M., Williams, D. R., Boyd, C. J., & Kintner, E. K. (2002). African American girls' smoking habits and day-to-day experiences with racial discrimination. *Nursing Research, 51*(3), 183–190.

Hall, S. M. (2004). History of depression and smoking cessation outcome: A meta-analysis: The Covey-Hitsman exchange. *Nicotine & Tobacco Research, 6*(4), 751–752.

Hapke, U., Schumann, A., Rumpf, H. J., John, U., Konerding, U., & Meyer, C. (2005). Association of smoking and nicotine dependence with trauma and posttraumatic stress disorder in a general population sample. *Journal of Nervous and Mental Disease, 193*(12), 843–846.

Hauge, L. J., Torgersen, L., & Vollrath, M. (2012). Associations between maternal stress and smoking: Findings from a population-based prospective cohort study. *Addiction, 107*(6), 1168–1173.

Henker, B., Whalen, C. K., Jamner, L. D., & Delfino, R. J. (2002). Anxiety, affect, and activity in teenagers: Monitoring daily life with electronic diaries. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(6), 660–670.

Horn, K., Dino, G., Kalsekar, I., Massey, C. J., Manzo-Tennant, K., & McGloin, T. (2004). Exploring the relationship between mental health and smoking cessation: A study of rural teens. *Prevention Science, 5*(2), 113–126.

Hunt, Y. (2005). Generalized expectancies for negative mood regulation and patterns of substance use in adolescents. *Dissertation Abstracts International: Section B The Sciences and Engineering, 65*(7-B), 3745.

Ismali, K., Blatchley, N., Hotopf, M., Hull, L., Palmer, I., Unwin, C., et al. (2000). Occupational risk factors for ill health in Gulf veterans of the United Kingdom. *Journal of Epidemiology and Community Health, 54*(11), 834–838.

Johnson, E. O., & Breslau, N. (2006). Is the association of smoking and depression a recent phenomenon? *Nicotine & Tobacco Research, 8*(2), 257–262.

Jones, L. R. (2082). Gender and ethnic differences in perceived stress as a predictor of smoking behaviors in rural adolescents. *Dissertation Abstracts International: Section B The Sciences and Engineering, 65*(4-B), 2082.

Karatzias, A., Power, K. G., & Swanson, V. (2001). Predicting use and maintenance of use of substances in Scottish adolescents. *Journal of Youth and Adolescence, 30*(4), 465–484.

Klevens, R. M., Giovino, G. A., Peddicord, J. P., Nelson, D. E., Mowery, P., & Grummer-Strawn, L. (1995). The association between veteran status and cigarette-smoking behaviors. *American Journal of Preventive Medicine, 11*(4), 245–250.

Knox, S., Barnes, A., Kiefe, C., Lewis, C. E., Iribarren, C., Matthews, K. A., et al. (2006). History of depression, race, and cardiovascular risk in CARDIA. *International Journal of Behavioral Medicine, 13*(1), 44–50.

Koenen, K. C., Hitsman, B., Lyons, M. J., Stroud, L., Niaura, R., McCaffery, J., et al. (2006). Posttraumatic stress disorder and late-onset smoking in the Vietnam era twin registry. *Journal of Consulting and Clinical Psychology, 74*(1), 186–190.

Kouvonen, A., Kivimaki, M., Virtanen, M., Pentti, J., & Vahtera, J. (2005). Work stress, smoking status, and smoking intensity: An observational study of 46,190 employees. *Journal of Epidemiology and Community Health, 59*(1), 63–69.

Koval, J. J., Pederson, L. L., Mills, C. A., McGrady, G. A., & Carvajal, S. C. (2000). Models of the relationship of stress, depression, and other psychosocial factors to smoking behavior: A comparison of a cohort of students in Grades 6 and 8. *Preventive Medicine, 30*(6), 463–477.

Koval, J. J., Pederson, L. L., & Chan, S. S. H. (2004). Psychosocial variables in a cohort of students in grades 8 and 11: A comparison of current and never smokers. *Preventive Medicine, 39*(5), 1017–1025.

Kurian, A. K., & Cardarelli, K. (2007). Racial and ethnic differences in cardiovascular disease risk factors: A systematic review. *Ethnicity & Disease, 17*(1), 143–152.

Lerman, C., Niaura, R., Collins, B. N., Wileyto, P., Audrain-McGovern, J., Pinto, A., et al. (2004). Effect of Bupropion on depression symptoms in a smoking cessation clinical trial. *Psychology of Addictive Behaviors, 18*(4), 362–366.

Li, Y., Unger, J., Gong, J., Chen, X., Chou, C., & Johnson, C. A. (2003). Stressful life events and smoking in adolescents in Wuhan, China. *Chinese Mental Health Journal, 17*(2), 113–116.

Liu, X. (2003). Cigarette smoking, life stress and behavioural problems in Chinese adolescents. *Journal of Adolescent Health, 33*(3), 189–192.

Lloyd-Jones, D. M., Leip, E. P., Larson, M. G., D'Agostino, R. B., Beiser, A., Wilson, P. W. F., Wolf, P. A., & Levy, D. (2006). Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation, 113*(6), 791–798.

Manning, B. K., Catley, D., Harris, K. J., Mayo, M. S., & Ahluwalia, J. S. (2005). Stress and quitting among African American smokers. *Journal of Behavioral Medicine, 28*(4), 325–333.

Matthews, R. R. S., Hall, W. D., & Gartner, C. E. (2011). Depression and psychological distress in tobacco smokers and people with cannabis dependency in the National Survey of Mental Health and Wellbeing. *Medical Journal of Australia, 195*(3 Suppl 1), S12–S15.

Mazanov, J. and Byrne, D.G. (2002). A comparison of predictors of adolescent intention to smoke with adolescent current smoking using discriminant function analysis. *British Journal of Health Psychology*, 7, 185–201

Mazanov, J., & Byrne, D. G. (2006). An evaluation of the stability of perceptions and frequency of adolescent risk taking over time and across samples. *Personality and Individual Differences, 40*(4), 725–735.

McDermott, M. S., Marteau, T. M., Hollands, G. J., Hankins, M., & Aveyard, P. (2013). Change in anxiety following successful and unsuccessful attempts at smoking cessation: Cohort study. *British Journal of Psychiatry, 202*(1), 62–67.

McGee, R., Williams, S., & Shymala, N.-R. (2005). Is cigarette smoking associated with suicidal ideation among young people? *American Journal of Psychiatry, 162*(3), 619–620.

McKenna, H., Slater, P., McCance, T., Bunting, B., Spiers, A., & McElwee, G. (2003). The role of stress, peer influence and education levels on the smoking behaviour of nurses. *International Journal of Nursing Studies, 40*(4), 359–366.

Michal, M., Wiltink, J., Kirschner, Y., Wild, P. S., Schulz, A., Zwiener, I., Blettner, M., & Beutel, M. E. (2013). Association of mental distress with smoking status in the community: Results from the Gutenberg Health Study. *Journal of Affective Disorders, 146*(3), 355–360.

Miller, T. Q., & Volk, R. J. (2002). Family relationships and adolescent cigarette smoking: Results from a national longitudinal survey. *Journal of Drug Issues, 32*(3), 945–972.

Morissette, S. B., Brown, T. A., Kamholz, B. W., & Gulliver, S. B. (2006). Differences between smokers and nonsmokers with anxiety disorders. *Journal of Anxiety Disorders, 20*(5), 597–613.

Morissette, S. B., Tull, M. T., Gulliver, S. B., Kamholz, B. W., & Zimering, R. T. (2007). Anxiety, anxiety disorders, tobacco use and nicotine: A critical review of interrelationships. *Psychological Bulletin, 133*(2), 245–272.

Nakajima, M., & al'Absi, M. (2012). Predictors of risk for smoking relapse in men and women: A prospective examination. *Psychology of Addictive Behaviors, 26*(3), 633–637.

Nesbitt, P. D. (1973). Smoking, physiological arousal and emotional response. *Journal of Personality and Social Psychology, 25*(1), 137–144.

Ng, D. M., & Jeffery, R. W. (2003). Relationships between perceived stress and health behaviours in a sample of working adults. *Health Psychology, 22*(6), 638–642.

Ng, M., Freeman, M. K., Fleming, T. D., Robinson, M., Dwyer-Lindgren, L., Thomson, B., Wollum, A., Sanman, E., Sulf, S., Lopez, A. D., Murray, C. J. L., & Gakidou, E. (2014). Smoking prevalence and cigarette consumption in 187 countries, 1980 to 2012. *Journal of the American Medical Association, 311*(2), 183–192.

Norman, S. B., Norman, G. J., Rossi, J. S., & Prochaska, J. O. (2006). Identifying high- and low-success smoking cessation subgroups using signal detection analysis. *Addictive Behaviors, 31*(1), 31–41.

O'Connell, M. L., Freeman, M., Jennings, G., Chan, W., Greci, L. S., Manta, I. D., et al. (2004). Smoking cessation for high school students: Impact evaluation of a novel program. *Behavior Modification, 28*(1), 133–146.

Olff, M., Meewisse, M. L., Kleber, R. J., van der Velden, P. G., Drogendijk, A. N., van Amsterdam, J. G., et al. (2006). Tobacco usage interacts with post-disaster psychopathology on circadian salivary cortisol. *International Journal of Psychophysiology, 59*(3), 251–258.

op den Velde, W., Aarts, P. G. H., Falger, P. R. J., Hovens, J. E., van Duijn, H., de Groen, J. H. M., et al. (2002). Alcohol use, cigarette consumption and chronic post-traumatic stress disorder. *Alcohol and Alcoholism, 37*(4), 355–361.

Parrott, A. C. (1998). Nesbitt's Paradox resolved? Stress and arousal modulation during cigarette smoking. *Addiction, 93*(1), 27–39.

Perkins, K. A., Giedgowd, G. E., Karelitz, J. L., Conklin, C. A., & Lerman, C. (2012). Smoking in response to negative mood in men versus women as a function of distress tolerance. *Nicotine & Tobacco Research, 14*(12), 1418–1425.

Pirkle, E. C., & Richter, L. (2006). Personality, attitudinal and behavioural risk profiles of young female binge-drinkers and smokers. *Journal of Adolescent Health, 38*(1), 44–54.

Prendergast, T. J., Preble, M. R., & Tennant, F. S. (1973). Drug use and its relation to alcohol and cigarette consumption in the military community of West Germany. *International Journal of the Addictions, 8*(5), 741–775.

Purnell, J. Q., Peppone, L. J., Alcaraz, K., McQueen, A., Guido, J. J., Carroll, J. K., Shacham, E., & Morrow, G. R. (2012). Perceived discrimination, psychological distress, and current smoking status: Results from the behavioral risk factor surveillance system reactions to race module, 2004–2008. *American Journal of Public Health, 102*(5), 844–851.

Richmond, R. L., Wodak, A., Kehoe, L., & Heather, N. (1998). How healthy are the police? A survey of life-style factors. *Addiction, 93*(11), 1729–1737.

Saladin, M. E., Gray, K. M., Carpenter, M. J., Larowe, S. D., DeSantis, S. M., & Upadhyaya, H. P. (2012). Gender differences in craving and cue reactivity to smoking and negative affect/stress cues. *American Journal of Addictions, 21*(3), 210–220.

Schachter, S., Silverstein, B., Kozlowski, L. T., Perlick, D., Herman, C. P., & Liebling, B. (1977). Studies of the interaction of psychological and pharmacological determinants of smoking. *Journal of Experimental Psychology. General, 106*(1), 3–4.

Simon, A. E., Wardle, J., Jarvis, M. J., Steggles, N., & Cartwright, M. (2003). Examining the relationship between pubertal stage, adolescent health behaviours and stress. *Psychological Medicine, 33*(8), 1369–1379.

Singleton, M. G., & Pope, M. (2000). A comparison of successful smoking cessation interventions for adults and adolescents. *Journal of Counseling and Development, 78*(4), 448–453.

Siqueira, L., Diab, M., Bodian, C., & Rolnitzky, L. (2000). Adolescents becoming smokers: The roles of stress and coping methods. *Journal of Adolescent Health, 27*(6), 399–408.

Slopen, N., Dutra, L. M., Williams, D. R., Muhahid, M. S., Lewis, T. T., Bennett, G. G., Ryff, D., & Albert, M. A. (2012). Psychosocial stressors and cigarette smoking among african american adults in midlife. *Nicotine & Tobacco Research, 14*(10), 1161–1169.

Slopen, N., Kontos, E. Z., Ryff, C. D., Ayanian, J. Z., Albert, M. A., & Williams, D. R. (2013). Psychosocial stress and cigarette smoking persistence, cessation, and relapse over 9-10 years: A prospective study of middle-aged adults in the United States. *Cancer Causes and Control*. doi:10.1007/s10552-013-0262-5.

Smith, D. R., Devine, S., Laggat, P. A., & Ishitake, T. (2005). Alcohol and tobacco consumption among police officers. *Kurume Medical Journal, 52*(1–2), 63–65.

Sperlich, S., Maina, M. N., & Noeres, D. (2013). The effect of psychosocial stress on single mothers' smoking. *BMC Public Health*. doi:10.1186/1471-2458-13-1125.

Spigner, C., Shigaki, A., & Tu, S.-P. (2005). Perceptions of Asian American men about tobacco cigarette consumption: A social learning theory framework. *Journal of Immigrant Health, 7*(4), 293–303.

Steuber, T., & Banner, F. (2006). Adolescent smoking and depression: Which comes first? *Addictive Behaviors, 31*(1), 133–136.

Straub, D. M., Hills, N. K., Thompson, P. J., & Moscicki, A. B. (2003). Effects of pro- and anti-tobacco advertising on nonsmoking adolescents' intentions to smoke. *Journal of Adolescent Health, 32*(1), 36–43.

Tanuseputro, P., Manuel, D. G., Leung, M., Nguyen, K., & Johansen, H. (2003). Risk factors for cardiovascular disease in Canada. *Canadian Journal of Cardiology, 19*(11), 1249–1259.

Tavolacci, M. P., Ladner, J., Grigioni, S., Richard, L., Villet, H., & Dechelotte, P. (2013). Prevalence and association of perceived stress, substance use and behavioral addictions: A cross-sectional study among university students in France, 2009–2011. *BMC Public Health, 13*, 724. doi:10.1186/1471-2458-13-724.

Taylor, G., McNeill, A., Girling, A., Farley, A., Lindson-Hawley, N., & Aveyard, P. (2014). Change in mental health after smoking cessation: Systematic review and meta-analysis. *British Medical Journal*. doi:10.1136/bmj.g1151.

Thorndike, F. P., Wernicke, R., Pearlman, M. Y., & Haaga, D. A. (2006). Nicotine dependence, PTSD symptoms, and depression proneness among male and female smokers. *Addictive Behaviors, 31*(2), 223–231.

Turner, L. R., Mermelstein, R., Berbaum, M. L., & Veldhuis, C. B. (2004). School-based smoking cessation programs for adolescents: What predicts attendance? *Nicotine & Tobacco Research, 6*(3), 559–568.

Tyas, S. L., & Pederson, L. L. (1998). Psychosocial factors related to adolescent smoking: A critical review of the literature. *Tobacco Control, 7*(4), 409–420.

Udry, J. R., Li, R. M., & Hendrickson-Smith, J. (2003). Health and behavior risks of adolescents with mixed-race identity. *American Journal of Public Health, 93*(11), 1865–1870.

Unger, J. B., Li, Y., Johnson, C. A., Gong, J., Chen, X., Li, C. Y., et al. (2001). Stressful life events among adolescents in Wuhan, China: Associations with smoking, alcohol use, and depressive symptoms. *International Journal of Behavioral Medicine, 8*(1), 1–18.

Van den Breen, M.B., Whitmer, M.D. and Pickworth, W.B. (2004). Preditors of smoking development in a population-based sample of adolescents: A prospective study. *Journal of Adolescent Health, 35*, 172–181.

Van der Deen, F. S., Carter, K. N., Wilson, N., & Collings, S. (2011). The association between failed quit attempts and increased levels of psychological distress in smokers in a large New Zealand cohort. *BMC Public Health*. doi:10.1186/1471-2458/11/598.

Van Jaarsveld, C. H. M., Fidler, J. A., Simon, A. E., & Wardle, J. (2007). Persistent impact of pubertal timing on trends in smoking, food choice activity and stress in adolescence. *Psychosomatic Medicine, 69*(8), 798–806.

Varescon, I., Leignel, S., Gérard, C., Auborg, F., & Detilleux, M. (2013). Self-esteem, psychological distress, and coping styles in pregnant smokers and non-smokers. *Psychological Reports, 113*(3), 935–947.

Vlahov, D., Galea, S., Resnick, H., Ahern, J., Boscarino, J. A., Bucuvalas, M., et al. (2002). Increased use of cigarettes, alcohol, and marijuana among Manhattan, New York, residents after the September 11th terrorist attacks. *American Journal of Epidemiology, 155*(11), 988–996.

Wannamethee, S. G., Lowe, G. D., Shaper, A. G., Rumley, A., Lennon, L., & Whincup, P. H. (2005). Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *European Health Journal, 26*, 1765–1773.

Whalen, C. K., Jamner, L. D., Henker, B., & Delfino, R. J. (2001). Smoking and moods in adolescents with depressive and aggressive dispositions: Evidence from surveys and electronic diaries. *Health Psychology, 20*(2), 99–111.

Whincup, P. J., Gilg, J. A., Emberson, J. R., Harvis, M. J., Feyerabend, C., Bryant, A., Walker, M., & Cook, D. G. (2004). Passive smoking and risk of coronary heart disease and stroke: Prospective study with cotinine measurement. *BMJ*. doi:10.1136/bmj.38146.427188.55.

Whitlock, E. P., Ferry, L. H., Burchette, R. J., & Abbey, D. (1995). Smoking characteristics of female veterans. *Addictive Behaviors, 20*(4), 409–426.

Wills, T. A., Sandy, J. M., & Yaeger, A. M. (2002). Stress and smoking in Adolescence: A test of directional hypotheses. *Health Psychology, 21*(2), 122–130.

Wynd, C. A., & Ryan-Wenger, N. A. (1998). The health and physical readiness of Army reservists: A current review of the literature and significant research questions. *Military Medicine, 163*(5), 283–287.

Yasin, S. M., Retneswari, M., Moy, F. M., Darus, A., & Koh, D. (2012). Job stressors and smoking cessation among Malaysian male employees. *Occupational Medicine, 62*(3), 174–181.

Smoking and Cardiovascular Risk: Role of Personality in Adolescent Smoking

Jason Mazanov and Don Byrne

Contents

J. Mazanov (✉)
School of Business, UNSW-Canberra, Canberra, ACT, Australia
e-mail: j.mazanov@adfa.edu.au

D. Byrne
ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia

ANU Medical School, Research School of Psychology, Australian National University, Canberra, ACT, Australia
e-mail: Don.Byrne@anu.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_67

Abstract

Work to mitigate the increased risk of cardiovascular disease (CVD) brought about by cigarette smoking compels primary and secondary prevention activity among adolescents. Personality plays a prominent role among the variables associated with adolescent onset and maintenance of smoking. The role of personality in adolescent smoking is examined by contrasting results from research exploring association versus causality and then evidence from studies examining onset versus maintenance in relation to models of personality, risk, smoking beliefs/knowledge, self-esteem/self-efficacy, locus of control, and religiosity. Analysis using the two comparisons demonstrates the need for research in the area to consider dynamical approaches to explain changes in adolescent smoking behavior more deeply. For example, advances in the mathematical sophistication of adolescent smoking research make it possible to understand how changes in knowledge about the health consequences of smoking influence the onset or maintenance of smoking among adolescents. The development of more dynamical explanations of adolescent behavior may prove valuable explanations of behavior among adults trying to quit smoking to reduce the risk of CVD.

Keywords

Adolescent • Smoking • Personality • Causation • Behavior Change

Introduction

The link between tobacco smoking and increased risk of cardiovascular disease (CVD) (among a plethora of other diseases) means primary and secondary prevention of adolescent smoking has a direct effect on primary and secondary prevention of CVD. Primary prevention seeks to preserve the naturally abstinent state of adolescents through to their adult life. Secondary prevention recognizes that adolescence is a time of experimentation with a range of behaviours including substance use, and therefore seeks to eliminate the behaviour before harms arising from an increased relative risk of CVD become established. The effort to develop intervention programs to promote the aims of primary and secondary prevention has therefore focused on smoking onset and maintenance among adolescents.

These efforts have demonstrated the determinants of adolescent smoking onset and maintenance to be both complex and diverse. Tyas and Pederson's (1998) four category typology of variables that influence onset of smoking (sociodemographic, environmental, behavioural and personal influences) can be usefully deployed to gain some insight into the complexity and diversity of adolescent smoking onset

and maintenance. Sociodemographic factors represent important control variables that can identify an adolescent "at risk" of increased vulnerability to CVD through smoking, such as the relationship between smoking and age and gender and socioeconomic status (e.g., disposable income). These represent variables of interest to public policy in terms of *who* needs prevention activity and *when* that activity needs to occur but provide little insight into *what* that activity needs to be.

Environmental factors suggest ways to influence adolescents by creating conditions that promote abstinence or rapid extinction of smoking behavior. The literature suggests that adolescent smoking is linked positively to parental smoking behaviors (e.g., Leonardi-Bee et al. 2011) and is negatively related to parental attitudes to smoking, although not in any simple manner (Huver et al. 2006). Smoking behavior in younger adolescents has a strong positive relationship with older sibling smoking behavior (e.g., Avenevoli and Merikangas 2003; Whiteman et al. 2013) and also to peer pressure in the same age group (Unger et al. 2001). A school culture of nonsmoking is associated with lower rates of adolescent smoking (Aveyard et al. 2004; Lovato et al. 2010).

Approaching the adolescent more directly indicates ways in which environmental variables might shape smoking behavior through the psychological processes underlying the decision to change from the natural nonsmoking state. Adolescents with poor self-esteem are more likely to smoke than those with strong self-esteem (Byrne and Mazanov 2001), and a propensity to risk taking appears to increase the likelihood of smoking (see below). Finally, there is a link between attitudes and adolescent smoking onset and maintenance, usually in the form of behavioral intention to smoke among those yet to adopt the stable form of the behavior (Kremers et al. 2001; Piko 2001; Markham et al. 2004; Mazanov and Byrne 2006a).

Variation both in the range and nature of variables, in the measures used to assess those variables, and in the ways in which those variables are combined mathematically has plagued comparative interpretations of the evidence on adolescent smoking. Published studies frequently mix and confuse outcome variables, which can include measures of current smoking behavior, expressed intention to smoke in the future, smoking onset over time in cohorts of current nonsmokers, and other indicators of actual or predicted tobacco consumption. The challenge of understanding the behavior has increased with advances in the emergence of different mathematical models used to explain changes in smoking behavior, arising from increasing mathematical sophistication among researchers and advances in computing power. These range from various forms of growth curve analysis (e.g., Brook et al. 2008; de Leeuw et al. 2010) to catastrophe theory (Byrne et al. 2001; Mazanov and Byrne 2006a; West and Sohal 2006) which offer powerful dynamical explanations of adolescent smoking behavior. This has created a new problem; while the variables that predict adolescent smoking appear appropriate, the ways in which they combine mathematically are yet to be determined (Mazanov and Byrne 2008). The lack of clarity in defining the range of variables important in understanding adolescent smoking onset and maintenance is not, therefore, surprising, but the importance of the search to primary and secondary prevention ensures that it continues.

While the complex explanations of smoking behavior are somewhat daunting, the consumption of tobacco must ultimately be considered to take the form of a

discretionary human behavior. The overwhelmingly dominant view in the literature is that the onset and maintenance of adolescent smoking behavior must be considered a psychological phenomenon and the prevention or cessation of smoking likewise may best be addressed using psychological strategies. Not too surprisingly then, research bearing on personality continually presents itself for attention. Examination of personality in relation to smoking onset and maintenance, from both theoretical and empirical perspectives, has a long history.

Personality and Adolescent Smoking

As noted above, the role of personality in adolescent smoking is both broad and complex. The volume of psychosocial variables associated with adolescent smoking behavior makes it impossible to include a comprehensive account of the entire spectrum (Mazanov and Byrne 2002). This makes the choice of variables for inclusion a difficult task, with some important variables necessarily omitted. This review examines some personality constructs more consistently related to adolescent smoking over time relative to others.

For this review, adolescence has been extended to include the teenage years and early twenties. From a sociological point of view, Western democratic societies tend to define adulthood as the voting age or the age at which a person can hold an elected seat in parliament, usually 18 years. However, experimentation with health risk behaviors characteristic of adolescence also occurs in the early twenties (when around 5 % of lifetime smokers initiate; Choi et al. 2001). This may be correlated with emerging evidence from neuroscience about the developing adolescent brain and the rapid evolution in how that developing brain interprets and understands risk-taking behavior (e.g., Pharo et al. 2011). For example, evidence suggests that there is a fundamental change in the way health risks are interpreted in the mid- to late 20s (Brook et al. 2008; Mahalik et al. 2013). The period of growth leading up to stabilization is characterized by a rapid evolution in both what is understood to be risky behavior and how often adolescents engage in risky behavior (Mazanov and Byrne 2006b; Morrell et al. 2010). For these reasons, results outside the traditional boundary of adolescence (18 years) are considered.

Each personality construct is considered two ways. The first is a contrast of factors influencing onset and those which influence maintenance. The second contrast of association versus causality is aimed at exploring how results from cross-sectional and longitudinal research vary and their implications for primary and secondary prevention.

Models

Personality research into adolescent smoking evolved from unidimensional (e.g., Coan 1973; Matarazzo and Saslow 1960) to model-based examinations (e.g., the five-factor model; McCrae and Costa 1996; and the biological theory of personality; Eysenck 1990). Research using instruments to operationalize these models

addresses the relationship of traditional personality constructs to adolescent smoking. This review was confined to the two models noted.

Association Versus Causality

The only "model" factor with no demonstrable association with adolescent smoking is openness to experience. Harakeh et al. (2005) demonstrate that agreeableness, conscientiousness, extraversion, and neuroticism have some correlation with adolescent smoking, with additional cross-sectional support for conscientiousness (negative; Kashdan et al. 2005) and extraversion (positive; Kikuchi et al. 1999). Cross-sectional (Munafo et al. 2007) and prospective longitudinal results (Presson et al. 2002) support the associative relationship of conscientiousness and extraversion. Growth curve analysis suggests a positive correlation with extraversion and a potentially curvilinear negative relationship with neuroticism (de Leeuw et al. 2010), although the causal effects of these constructs have only a small effect size in predicting smoking over the life course (Munafo and Black 2007). Psychoticism emerges as positively related to change in smoking behavior (Canals et al. 1997). Even this narrow range of results suggests theoretically or empirically demonstrated models of personality have a role to play in adolescent smoking.

Onset Versus Maintenance

The role of "model" personality variables changes from association to specific forms of causation with respect to onset and maintenance. Only extraversion and neuroticism appeared to consistently predict onset (Harakeh et al. 2005). However, this relationship is by no means established, with White et al. (1996) suggesting personality plays only a minor role in transitions between stages of smoking, at least in terms of effect size; extraversion had only a minor role to play and neuroticism became redundant. This is mirrored by work suggesting that extraversion and neuroticism emerge as risk factors only in the presence of sociodemographic and environmental variables and only for more severe forms of nicotine dependence (Kleinjan et al. 2012). However, there is some evidence neuroticism may play more of a role in the maintenance rather than onset of regular adolescent smoking (Vink et al. 2003).

The Role of Model Personality in Adolescent Smoking

This short review demonstrates the range of possible relationships that can emerge from models of personality and adolescent smoking. Any survey of the "model" literature is likely to find a mixture of results that declare ascendancy of one variable over another. Importantly, this discussion shows such variables need to

be included in any explanation of adolescent smoking as theoretically defined primary predictors, covariates, moderators, or mediators.

Risk

As a developmental stage, adolescence is conspicuous as a time for experimenting with "risky" behavior (Gonzalez et al. 1994). Many theories of health behavior incorporate risk as fundamental to describe adolescent commencement or continuation of health risk behaviors (Weinstein 1993). There are several ways of translating this into the context of personality (Gullone et al. 2000).

The first is to consider risk as an individual difference in terms of predisposition to engage with risky behavior. Behaviors which come with a certain health risk (e.g., smoking, condom use, or wearing seat belts) tend to cluster within individuals (comorbidity; Epstein et al. 2003). While helpful etiologically and epidemiologically, it gives little insight (beyond correlation) into why clustering occurs. Another way of approaching this issue is how adolescent perceives the risk of negative outcomes associated with a behavior. This has led to the investigation of how adolescents perceive and process risk in terms of the probability of events or fulfilling some psychologically relevant drive or predisposition. In this context, risk has been deconstructed to yield several factors that seem consistently related to adolescent smoking behavior, typically as some combination of rebelliousness, thrill seeking, or sensation seeking.

Association Versus Causality

There is a clear relationship between the way adolescents deal with "risk" in its many forms and smoking behavior. At a basic level, a number of studies correlate "risk" with smoking behavior (smoking status or number of cigarettes smoked) cross-sectionally (e.g., Doran et al. 2011) and longitudinally (Adalbjarnardottir and Rafnsson 2002; Brook et al. 2004; Malmberg et al. 2013). That is, there is an indication that "risk" and smoking behaviors have some kind of systematic relationship. Confirmation of the systematic relationship has come from studies specifically looking at what causes adolescents to start smoking. Some authors have found compelling statistical evidence risk as independently influential (Botvin et al. 2001), whereas others have found that risk influences smoking behavior in concert with other psychosocial variables (Wills et al. 2007).

Onset Versus Maintenance

The relationship between "risk" and onset of adolescent smoking is variable, with some research focusing on risk as the most central variable for prevention (Burt et al. 2000) and others finding no relationship (Mazanov and Byrne 2006a).

Audrain-McGovern et al. (2004) show that early onset is characteristic of those with a higher sensation seeking. White et al. (2002) analysis showed that disinhibition (part of the sensation-seeking domain) was the key for identifying different trajectories in onset. Rebelliousness appears to be correlated with transitions in adolescent smoking behavior in terms of onset and escalation from first cigarette to monthly and to daily smoking; by comparison, thrill seeking diminishes in the transition from monthly to daily smoking (Bricker et al. 2009). Other work on rebelliousness shows the construct has little influence at onset but predicts maintenance (Otten et al. 2011b). Importantly, these studies indicate risk as being equally important for maintenance as it is for onset.

Additional Thoughts on Adolescent Risk

One important aspect of research into adolescent smoking and risk is the way in which adolescents view the potentially negative impact smoking will have on their life. Arnett (2000) and Borland (1997) report an "optimistic bias," where adolescent consistently underestimates the consequences smoking may have for them (e.g., breaking addiction). This has a significant impact on their decision-making ability when it comes to making rational cost-benefit trade-offs described by theories of health decision-making. Halpern-Felsher et al. (2004) note that adolescents tend to minimize future risk, trading off future cost against immediate benefit. How this plays out in the context of onset or maintenance of adolescent smoking must be considered next to the result that perceptions of risk tend to evolve very rapidly as the adolescent progresses toward adulthood (presumably with age and experience) (see Mazanov and Byrne 2006b).

Smoking and the "Risky" Personality

Based on the reliability of the results over time and across studies, the way adolescents deal with risk clearly influences smoking onset and maintenance. This result has emerged from the application of more mathematically sophisticated models (e.g., analyzing growth trajectories) to understanding the role of risk in adolescent smoking. The next phase is disentangling the causal sequence to a finer level detail, perhaps through judicious application of neuroscience.

Smoking Beliefs/Knowledge

Individual variation in personal beliefs or knowledge of the health consequences of smoking represents an important component of the rational health decision-making theory cost-benefit analysis thought to drive adolescent smoking behavior (Weinstein 1993). This theoretically central individual difference has justified interventions to alter beliefs or knowledge by exposing adolescents to scientifically

demonstrated facts about the consequences of smoking (Glied 2003) with little success (Evans 2001). This failure brings into question whether beliefs or knowledge are associated with smoking behavior in the way theory suggests.

Association Versus Causality

There is evidence adolescents are very knowledgeable about the health consequences of smoking (Tilleczek and Hine 2006), smokers more than nonsmokers (Mazanov and Byrne 2007). What is less clear is whether this information influences beliefs or smoking behavior. There is some evidence that beliefs and knowledge predict smoking behavior cross-sectionally (Hines et al. 1999; Islam and Johnson 2005) and cross-culturally (Karimy et al. 2013; Steptoe et al. 2002; Yang et al. 2013). However, the association varies across gender, sometimes more important for boys than girls (Nebot et al. 2005) and vice versa (Epstein et al. 2003). Perceived health risk also appears to be more important to the intentions of adolescent smokers than never smokers (Brown et al. 2010). Some suggest that this variable association may be a function of interactions with other variables (e.g., mood, perceived social benefits, and avoidance self-efficacy; Ford et al. 2013) or psychometry (Panter and Reeve 2002). More importantly, there is evidence that beliefs and knowledge are causally irrelevant (Sperber et al. 2001), suggesting a more systematic examination of beliefs and knowledge is needed in terms of association and causality.

Onset Versus Maintenance

There is very little literature in relation to onset or maintenance. Mazanov and Byrne (2007) show that adolescent knowledge of the health consequences of smoking has no relationship with onset, maintenance, or cessation. Some evidence shows beliefs or knowledge relate to cessation, which implies beliefs and knowledge also influence maintenance (Etter et al. 2000b; Rose et al. 1996). The relationship between beliefs and knowledge and maintenance is also reflected in smokers tending to have more positive beliefs about smoking (Amos et al. 1997; Hines et al. 1999). It remains to be established whether this difference exists before onset or emerges as a post-decisional justification (e.g., avoiding cognitive dissonance).

The Role of Smoking Beliefs and Knowledge in Adolescent Smoking

Despite theoretical and intuitive importance, there is little evidence to support or refute a role for beliefs and knowledge in adolescent smoking. The role of variables in this domain warrants further attention. An essential first step in this process is to establish a psychometrically robust measure for beliefs and knowledge. Research

currently uses a range of single (e.g., Brown et al. 2010; Yang et al. 2013) and multiple item measures (e.g., Mazanov and Byrne 2007) unique to each study. Smoking expectancy scales that incorporate health consequences of smoking offer one way of achieving consistency across studies (e.g., Hine et al. 2007). With a robust and consistent measure in place, attention can refocus on the reliability of the relationship. If a reliable relationship is found, further work on the role beliefs and knowledge play in onset or maintenance is needed, especially for education-based intervention or prevention programs.

Self-Esteem/Self-Efficacy

The influences of self-esteem and self-efficacy on adolescent smoking have been intensively investigated. There is considerable theoretical support for self-esteem/self-efficacy as a key variable of interest to adolescent smoking; one of the eight variables declared central to understanding health behavior (Fishbein et al. 2001). The empirical literature supports the theoretical contention with esteem/efficacy established as both a main and sundry predictor of adolescent smoking.

There is an emerging literature that considers the problem of global versus specific esteem/efficacy (see below). Glendinning and Inglis (1999) suggest the relationship between self-esteem and adolescent smoking can be elaborated on the basis of rather blunt global measures, although contextually specific measures (e.g., peer or academic) are warranted. Glendinning (2004) reaffirms that more effort is needed to understand context-specific self-esteem, while maintaining global esteem still has an important role to play.

Association Versus Causality

The association of esteem/efficacy with adolescent smoking forms an established part of the literature (Byrne and Mazanov 2001, 2003), indicating that low esteem/efficacy is associated with both the smoking susceptibility (Ford et al. 2013; Kaai et al. 2014) and smoking behavior (e.g., Engels et al. 1999; Mazanov and Byrne 2002; Soldz and Cui 2001). Other work suggests that esteem/efficacy has indirect effects on adolescent smoking, either through social norms (Lazuras et al. 2009) or as part of an overarching well-being construct (Brook et al. 2011).

In terms of specific efficacy, social self-efficacy (Holm et al. 2003), physical self-concept (Thornton et al. 1999), and academic efficacy (Chung and Elias 1996) all have demonstrated associations with smoking behavior. In terms of specific esteem, Kawabata et al. (1999) report smokers have greater physical self-esteem and lower global, cognitive, and family esteem than nonsmokers. This result supports Glendinning and Inglis's (1999) assertion that global measures still have a role to play. Notably, some cross-sectional studies report the absence of an esteem/efficacy relationship with adolescent smoking (Moore et al. 1996; White et al. 1996).

While measures of association indicate a fairly reliable relationship, the longitudinal literature suggests the role of esteem/efficacy changes over time. There is an emerging set of evidence that suggests the predictive effectiveness of esteem/efficacy wanes over time (Hiemstra et al. 2011; Poikolainen et al. 2001; Wills et al. 2007). Engels et al. (2005) indicate that while low esteem/efficacy predicts cross-sectionally, the predictive effect only occurs for females longitudinally (see below). The evidence also suggests that the indirect effects observed cross-sectionally also emerge longitudinally for efficacy (Hiemstra et al. 2011). These results agree with Glendinning's (2004) assertion that the longitudinal evidence of a relationship between esteem/efficacy and adolescent smoking is less clear-cut than cross-sectional evidence.

Onset Versus Maintenance

Glendinning's (2004) assertion of ambiguity appears to hold in relation to onset (for example, Engels et al.'s (2005), result self-esteem has a role in onset for girls only). In terms of maintenance, O'Callaghan and Doyle (2002) show a potentially curvilinear relationship between self-esteem and ordinal smoking status, with occasional smokers demonstrating higher self-esteem than non- or regular smokers. The efficacy literature is more consistent with evidence that global self-efficacy influences onset (Otten et al. 2011a). Specifically, the protective effect of refusal self-efficacy interventions has been shown in studies of association (Islam and Johnson 2005; Nebot et al. 2005) and in retarding onset (Bruvold 1993; Byrne and Mazanov 2005). Self-efficacy also seems to influence the readiness to change smoking status (Stephens et al. 2004) perhaps as a function of cessation (increased self-efficacy and quitting; Etter et al. 2000a). However, Conner and Higgins (2010) report that a self-efficacy intervention had no impact on adolescent smoking onset measured over a 2-year window, suggesting that the role of efficacy in prevention is far from assured.

The Role of Self-Esteem/Self-Efficacy

The role of self-esteem/self-efficacy is tied to a broader philosophical debate about how much contextual detail is needed for a psychosocial construct to be useful. The answer is likely to be tied back to the utility of the results. For example, an excruciating level of detail on specific self-esteem/self-efficacy may be statistically or academically useful and meaningless for intervention. This is comparable to the debate on the inclusion of past behavior in models of health behavior (Conner and Armitage 1998), where the result provides no assistance for designing intervention programs.

Outside this debate, more work is needed on the role of esteem/efficacy in terms of how it changes over time. Researchers need to establish a compelling case for the

role of esteem/efficacy longitudinally, especially in relation to observed changes in behavior, relative to both onset and maintenance. For example, this might include whether esteem/efficacy influences onset or maintenance by provoking stability or instability in smoking behavior (Mazanov and Byrne 2006b).

Locus of Control

The belief that one has control over one's behavior is seen as central to health behavior (Steptoe and Wardle 2001), especially in the context of self-efficacy (refusal skills; Stuart et al. 1994). There has been a generally replicated result that adolescent smokers have an external locus of control (e.g., Abdollahia and Talib 2014; Ludtke and Schneider 1996). One significant study by Steptoe and Wardle (2001), involving 7115 university students (age range 18–30) across 18 - European countries, showed external locus of control was unrelated to smoking. Locus of control was found to be nonsignificant across adolescent nonsmokers, triers, and regular smokers (Tang and Loke 2013).

An important change in locus of control research has been the shift from Rotter's (1966) single internal-external continuum to facet locus of control (internality, chance, and powerful others). Some studies show all three influence for smoking behavior (Bennett et al. 1997) and others only for specific facets (e.g., extremely high chance orientation only; Steptoe and Wardle 2001). There has been little work on the role of locus of control in how smoking behavior changes. Stephens et al. (2004) suggest readiness to change smoking behavior is unrelated to locus of control. Presson et al. (2002) indicate an internal locus of control has some protective effect against uptake.

In terms of association, locus of control seems to have a relatively strong relationship with smoking behavior. Whether locus of control remains as a viable predictor in the context of onset or maintenance is something future research needs to address.

Religiosity

Religion has been used as the conduit for a range of substance use interventions, notably in relation to alcohol (e.g., Alcoholics Anonymous and Evangelical Protestantism; Sarafino 2006). This has seen research into the role religion might play in protecting adolescents from smoking. A review of the role of religiosity in substance abuse noted the dominance of research from the United States, problems with non-standardized measurement of religious engagement, and the need for more longitudinal research (Chitwood et al. 2008). Fortunately, these issues are being systematically addressed with respect to adolescent smoking.

Association Versus Causality

The established negative correlation between "religiosity" (church attendance, claimed faith, or self-report) and smoking has been replicated across cultural contexts, including Bangladesh (Kamal et al. 2010), Brazil (Gomes et al. 2013), Mexico (Marsiglia et al. 2012), and Slovakia (Pitel et al. 2012). However, this result is by no means universal, with no effect for religiosity emerging for adolescents coming from South African townships (Prinsloo et al. 2008). There is evidence to suggest that the effect for religiosity is driven by the strength of individual belief rather than simply associating with a religious community (Gmel et al. 2013; Marsiglia et al. 2012). This stands in contrast to research that argues that being part of a religious group provides the protection against smoking (e.g., social support; Metzger et al. 2011) rather than the psychological character of the individual (Chen et al. 2004; Wallace et al. 2003). There is also evidence that the protective effect of religiosity is more important for girls than boys (Kovacs et al. 2011; Pitel et al. 2012). Importantly, drifting away from religion over adolescence increased the likelihood of smoking behavior (Moscati and Mezuk 2014). This review found no concrete evidence of causality in terms of changes in smoking behavior being demonstrated by those "finding" or "losing" religion.

Onset Versus Maintenance

There was some evidence religion or personal morality was protective against onset (Amey et al. 1996). Timberlake et al. (2006) report religiosity was the only protective factor that overcame genetic effects. An interesting take on this relationship was that a strong "private" sense of religion protected adolescents from experimenting with cigarettes and the public demonstration of their religion protected them from regular smoking (Nonnemaker et al. 2003). That is, if religious adolescents take up smoking, their religion may retard progression to regular smoking. This contention is supported by religiosity mitigating the rate of growth in smoking over time (Mason and Spoth 2011; Spears et al. 2010; Wills et al. 2003) and possibly more so for boys (Van den Bree et al. 2004). This suggests differential processes are at work.

The Role of Religiosity

Religiosity has some role to play in adolescent smoking; exactly what that role may be is open to debate. More research is needed in a wider range of religious contexts; most research focuses on Judeo-Christian faiths with research in Islamic contexts a rare exception and other religions almost absent (e.g., Sikh). Such research needs designs that establish whether the correlation is psychological in nature or a spurious relationship. Establishing this result provides guidance on whether religion may be viable as a basis for prevention or intervention programs.

Conclusions

Given the central role of smoking increasing the relative risk of CVD, the ongoing interest in the role of personality in adolescent smoking is justifiably growing. The increasing mathematical sophistication of adolescent smoking research is demonstrating the importance of examining causality more thoroughly. While research examining differences provides descriptive evidence of *how* categories of smoking differ, it is the exploration of causality that enables an understanding of the processes that lead to those differences (e.g., Bricker et al. 2009); that is, an understanding of *why* those categories of smoking differ and an ability to predict the first tobacco smoking experience or accelerations in tobacco smoking. Researchers may find it valuable to consider the dynamical nature of both dependent and independent variables, that is, exploring how adolescent smoking behavior changes over time as a function of how personality changes over adolescence.

Methodological experimentation in adolescent smoking research may lead to the development of models and techniques that help combat CVD by promoting adult smoking cessation. For example, the mathematical models that describe onset and maintenance in adolescence may be directly applicable to explaining the psychosocial foundations of cessation among adults. With the potential to drive primary and secondary prevention among adolescents and adults, research examining change in behavior over time needs to accelerate to generate a new understanding of the role of personality in adolescent smoking onset and maintenance.

Acknowledgments Portions of this chapter are based on revisions of an earlier publication by the present authors (Personality, stress and the determination of smoking behaviour in adolescents, in G.J. Boyle, G. Matthews and D.H. Salkofske (Eds) (2008) *The Sage Handbook of Personality Theory and Assessment*. Los Angeles: Sage Publications Inc. (Chapter 34, pp 698-719). Used with the publisher's permission.

References

Abdollahia, A., & Talib, M. A. (2014). To examine the relationships between emotional intelligence, locus of control and smoking in adolescents. *The Social Sciences, 9*(3), 157–162.

Adalbjarnardottir, S., & Rafnsson, F. D. (2002). Adolescent anti-social behaviour and substance use: Longitudinal analyses. *Addictive Behaviours, 27*(2), 227–240.

Amey, C. H., Albrecht, S. L., & Miller, M. K. (1996). Racial differences in adolescent drug use: The impact of religion. *Substance Use and Misuse, 31*(10), 1311–1332.

Amos, A., Elton, R., Gray, D., & Currie, C. (1997). Healthy or druggy? Self-image, ideal image and smoking behaviour among young people. *Social Science and Medicine, 45*(6), 847–858.

Arnett, J. J. (2000). Optimistic bias in adolescent and adult smokers and nonsmokers. *Addictive behaviors, 25*(4), 625-632.

Audrain-McGovern, J., Cuevas, J., Rodgers, K., Rodriguez, D., Tercyak, K. P., & Patterson, F. (2004). Identifying and characterising adolescent smoking trajectories. *Cancer Epidemiology, Biomarkers and Prevention, 13*(12), 2023–2034.

Avenevoli, S., & Merikangas, K. R. (2003). Familial influences on adolescent smoking. *Addiction, 98*(Suppl 1), 1–20.

Aveyard, P., Markham, W. A., Lancashire, E., Bullock, A., Maca, C., Cheng, K. K., et al. (2004). The influence of school culture on smoking among pupils. *Social Science & Medicine, 58*(9), 1767–1780.

Bennett, P., Norman, P., Moore, L., Murphy, S., & Tudor-Smith, C. (1997). Health locus of control and value for health in smokers and non-smokers. *Health Psychology, 16*(2), 179–182.

Borland, R. (1997). What do people's estimates of smoking related risk mean? *Psychology and Health, 12*, 513-521.

Botvin, G. J., Griffin, J. W., Diaz, T., & Ifill-Williams, M. (2001). Drug abuse prevention among minority adolescents: Post-test and one-year follow-up of a school-based preventive intervention. *Prevention Science, 2*(1), 1–13.

Bricker, J. B., Rajan, K. B., Zalewski, M., Andersen, M. R., Ramey, M., & Peterson, A. V. (2009). Psychological and social risk factors in adolescent smoking transitions: A population-based longitudinal study. *Health Psychology, 28*(4), 439–447.

Brook, J. S., Pahl, T., Balka, E. B., & Fei, K. (2004). Smoking among New Yorican adolescents: Time 1 predictors of time 2 tobacco use. *Journal of Genetic Psychology, 165*(3), 324–340.

Brook, D. W., Brook, J. S., Zhang, C., Whiteman, M., Cohen, P., & Finch, S. J. (2008). Developmental trajectories of cigarette smoking from adolescence to the early thirties: Personality and behavioral risk factors. *Nicotine and Tobacco Research, 10*(8), 1283–1291.

Brook, D. W., Rubenstone, E., Zhang, C., Morojele, N. K., & Brook, J. S. (2011). Environmental stressors, low well-being, smoking, and alcohol use among South African adolescents. *Social Science and Medicine, 72*, 1447–1453.

Brown, A. K., Moodie, C., Hastings, G., Mackintosh, A.-M., Hassan, L., & Thrasher, J. (2010). The association of normative perceptions with adolescent smoking intentions. *Journal of Adolescence, 33*, 603–614.

Bruvold, W. H. (1993). A meta-analysis of adolescent smoking prevention programs. *American Journal of Public Health, 83*(6), 872–880.

Burt, R. D., Dinh, K. T., Peterson, A. V., & Sarason, I. G. (2000). Predicting adolescent smoking: A prospective study of personality smoking. *Preventive Medicine, 30*(2), 115–125.

Byrne, D. G., & Mazanov, J. (2001). Self-esteem, stress and cigarette smoking in adolescents. *Stress and Health, 17*(2), 105–110.

Byrne, D. G., & Mazanov, J. (2003). Adolescent stress and future smoking behaviour: A prospective investigation. *Journal of Psychosomatic Research, 54*(4), 313–321.

Byrne, D. G., & Mazanov, J. (2005). Prevention of adolescent smoking: A prospective test of three models of intervention. *Journal of Substance Use, 10*(6), 363–374.

Byrne, D. G., Mazanov, J., & Gregson, R. A. M. (2001). A cusp catastrophe model (CCM) analysis of changes to adolescent smoking behaviour in response to smoking prevention programs. *Nonlinear Dynamics, Psychology, and Life Sciences, 5*(2), 115–137.

Canals, J., Blade, J., & Domenech, E. (1997). Smoking and personality predictors among young Spanish people. *Personality and Individual Differences, 23*(5), 905–908.

Chen, C. Y., Dormitzer, C. M., Bejarano, J., & Anthony, J. C. (2004). Religiosity and the earliest stages of adolescent drug involvement in seven countries of Latin America. *American Journal of Epidemiology, 159*(12), 1180–1188.

Chitwood, D. D., Weiss, M. L., & Leukefeld, C. G. (2008). A systematic review of recent literature on religiosity and substance use. *Journal of Drug Issues, 38*(3), 653–688.

Choi, W. S., Gilpin, E. A., Farkas, A. J., & Pierce, J. P. (2001). Determining the probability of future smoking among adolescents. *Addiction, 96*(2), 313–323.

Chung, H., & Elias, M. (1996). Patterns of adolescent involvement in problem behaviours: Relationship to self-efficacy, social competence and life events. *American Journal of Community Psychology, 24*(6), 771–784.

Coan, R. W. (1973). Personality variables associated with cigarette smoking. *Journal of Personality and Social Psychology, 26*(1), 86–104.

Conner, M., & Armitage, C. J. (1998). Extending the theory of planned behaviour: A review and avenues for further research. *Journal of Applied Social Psychology, 28*(15), 1429–1464.

Conner, M., & Higgins, A. R. (2010). Long-term effects of implementation intentions on prevention of smoking uptake among adolescents: A cluster randomized controlled trial. *Health Psychology, 29*(5), 529–538.

de Leeuw, R. N., Scholte, R. H., Sargent, J. D., Vermulst, A. A., & Engels, R. C. (2010). Do interactions between personality and social-environmental factors explain smoking development in adolescence? *Journal of Family Psychology, 24*(1), 68–77.

Doran, N., Sanders, P. E., Bekman, N. M., Worley, M. J., Monreal, T. K., McGee, E., et al. (2011). Mediating influences of negative affect and risk perception on the relationship between sensation seeking and adolescent cigarette smoking. *Nicotine and Tobacco Research, 13*(6), 457–465.

Engels, R. C., Hale, W. W., Noom, M., & Vries, H. D. (2005). Self-efficacy and emotional adjustment as precursors of smoking in early adolescence. *Substance Use & Misuse, 40*(12), 1883-1893.

Engels, R. C. M. E., Knibbe, R. A., & Drop, M. J. (1999). Predictability of smoking in adolescence: Between optimism and pessimism. *Addiction, 94*(1), 115–124.

Epstein, J. A., Botvin, G. J., & Spoth, R. (2003). Predicting smoking among rural adolescents: Social and cognitive processes. *Nicotine and Tobacco Research, 5*(4), 485–491.

Etter, J. F., Perneger, T. V., Bergman, M. M., & Humair, J. P. (2000a). Development and validation of a scale measuring self-efficacy of current and former smokers. *Addiction, 95*(6), 901–913.

Etter, J. F., Perneger, T. V., Humair, J. P., & Bergman, M. M. (2000b). Development and validation of the Attitudes Towards Smoking Scale (ATS-18). *Addiction, 95*(4), 613–625.

Evans, R. I. (2001). Social influences in etiology and prevention of smoking and other health threatening behaviours in children and adolescents, Chapter 27. In A. Baum, T. A. Revenson, & J. E. Singer (Eds.), *Handbook of health psychology* (pp. 459–468). London: Lawrence Earlbaum Associates.

Eysenck, H. J. (1990). Biological dimensions of personality. In L. A. Pervin (Ed.), *Handbook of personality: Theory and research* (pp. 244–276). New York: Guilford.

Fishbein, M., Triandis, H. C., Kanfer, F. H., Becker, M., Middlestadt, S. E., & Eichler, A. (2001). Factors influencing behaviour and behaviour change, Chapter 1. In A. Baum, T. A. Revenson, & J. E. Singer (Eds.), *Handbook of health psychology* (pp. 3–17). London: Lawrence Earlbaum Associates.

Ford, K. H., Oladapo, A. O., Sterling, K. L., Diamond, P. M., Kelder, S. H., & McAlister, A. (2013). Assessing the psychometric properties of smoking related attitudes, self-efficacy, and intention among a diverse population of middle school students. *Addictive Behaviors, 38*, 2378–2383.

Glendinning, A. (2004). Self-esteem and smoking in youth – Muddying the waters? *Journal of Adolescence, 25*(4), 415–425.

Glendinning, A., & Inglis, D. (1999). Smoking behaviour in youth: The problem of low self-esteem? *Journal of Adolescence, 22*(5), 673–682.

Glied, S. (2003). Is smoking delayed or averted? *American Journal of Public Health, 93*(3), 412–416.

Gmel, G., Mohler-Kuo, M., Dermota, P., Gaume, J., Bertholet, N., Daeppen, J. B., & Studer, J. (2013). Religion is good, belief is better: Religion, religiosity, and substance use among young Swiss men. *Substance Use & Misuse, 48*(12), 1085–1098.

Gomes, F. C., Andrade, A. G. D., Izbicki, R., Moreira-Almeida, A., & Oliveira, L. G. D. (2013). Religion as a protective factor against drug use among Brazilian university students: A national survey. *Revista Brasileira de Psiquiatria, 35*(1), 29–37.

Gonzalez, J., Field, T., Yando, R., Gonzalez, K., Lasko, D., & Bendell, D. (1994). Adolescent perceptions of their risk-taking behaviour. *Adolescence, 29*(115), 701–709.

Gullone, E., Moore, S., Moss, S., & Boyd, C. (2000). The adolescent risk-taking questionnaire: Development and psychometric evaluation. *Journal of Adolescent Research, 15*(2), 231–250.

Halpern-Felsher, B. L., Biehl, M., Kropp, R. Y., & Rubinstein, M. L. (2004). Perceived risks and benefits of smoking: differences among adolescents with different smoking experiences and intentions. Preventive medicine, 39(3), 559-567.

Harakeh, Z., Engles, R. C. M. E., de Vries, J., & Scholte, R. H. J. (2005). Association between personality and adolescent smoking. *Addictive Behaviours, 31*(2), 232–245.

Hiemstra, M., Otten, R., de Leeuw, R. N. H., van Schayck, O. C. P., & Engels, R. C. (2011). The changing role of self-efficacy in adolescent smoking initiation. *Journal of Adolescent Health, 48*, 597–603.

Hine, D. W., Honan, C. A., Marks, A. D., & Brettschneider, K. (2007). Development and validation of the smoking expectancy scale for adolescents. *Psychological Assessment, 19* (3), 347–355.

Hines, D., Fretz, A. C., & Nollen, N. L. (1999). Regular and occasional smoking by college students: Personality attributions of smokers and non-smokers. *Psychological Reports, 83* (3Pt2), 1299–1306.

Holm, K., Kremers, S. P. J., & de Vries, H. (2003). Why do Danish adolescents take up smoking? *European Journal of Public Health, 13*(1), 67–74.

Huver, R. M. E., Engels, R. C. M. E., & de Vries, H. (2006). Are anti-smoking parenting practices related to adolescent smoking cognition and behavior? *Health Education Research, 21*(1), 66–77.

Islam, S. M. S., & Johnson, C. A. (2005). Influence of known psychosocial smoking risk factors of Egyptian adolescents' cigarette smoking behaviour. *Health Promotion International, 20*(2), 135–145.

Kaai, S. C., Brown, K. S., Leatherdale, S. T., Manske, S. R., & Murnaghan, D. (2014). We do not smoke but some of us are more susceptible than others: A multilevel analysis of a sample of Canadian youth in grades 9 to 12. *Addictive Behaviors, 39*, 1329–1336.

Kamal, S. M. M., Rahman, M. A., Uddin, M. K., & Islam, M. A. (2010). Smoking behavior of secondary school students in Kushtia district, Bangladesh: Prevalence and determinants. *Journal of Applied Science and Technology, 7*, 107–115.

Karimy, M., Niknami, S., Heidarnia, A. R., Hajizadeh, I., & Montazeri, A. (2013). Prevalence and determinants of male adolescents' smoking in Iran: An explanation based on the theory of planned behavior. *Iranian Red Crescent Medical Journal, 15*(3), 187.

Kashdan, T. B., Vetter, C. J., & Collins, R. L. (2005). Substance use in young adults: Associations with personality and gender. *Addictive Behaviours, 30*(2), 259–269.

Kawabata, T., Shimai, S., Cross, D., & Nishioka, N. (1999). Relationship between self-esteem and smoking behaviour among Japanese early adolescents: Initial results from a three-year study. *Journal of School Health, 69*(7), 280–284.

Kikuchi, Y., Masuda, M., Yoshimura, K., Inoue, T., Ito, M., & Watanabe, S. (1999). Health consciousness of young people in relation to their personality. *Journal of Epidemiology, 9*(2), 121–131.

Kleinjan, M., Vitaro, F., Wanner, B., Brug, J., van den Eijnden, R. J. J. M., & Engels, R. C. (2012). Predicting nicotine dependence profiles among adolescent smokers: The roles of personal and social-environmental factors in a longitudinal framework. *BMC Public Health, 12*, 196.

Kovacs, E., Piko, B. F., & Fitzpatrick, K. M. (2011). Religiosity as a protective factor against substance use among Hungarian high school students. *Substance Use and Misuse, 46*(10), 1346–1357.

Kremers, S. P. J., Mudde, A. N., & de Vries, H. (2001). Subtypes within the precontemplation stage of adolescent smoking acquisition. *Addictive Behaviors, 26*(2), 237–251.

Lazuras, L., Eiser, J. R., & Rodafinos, A. (2009). Predicting Greek adolescents' intentions to smoke: A focus on normative processes. *Health Psychology, 28*(6), 770–778.

Leonardi-Bee, J., Jere, M. L., & Britton, J. (2011). Exposure to parental and sibling smoking and the risk of smoking uptake in childhood and adolescence: A systematic review and meta-analysis. *Thorax, 66*, 847–855.

Lovato, C. Y., Zeisser, C., Campbell, H. S., Watts, A. W., Halpin, P., Thompson, M., Eyles, J., et al. (2010). Adolescent smoking: Effect of school and community characteristics. *American Journal of Preventive Medicine, 39*(6), 507–514.

Ludtke, H. A., & Schneider, H. G. (1996). Habit-specific locus of control scales for drinking, smoking and eating. *Psychological Reports, 78*(2), 363–369.

Mahalik, J. R., Levine Coley, R., McPherran Lombardi, C., Doyle Lynch, A., Markowitz, A. J., & Jaffee, S. R. (2013). Changes in health risk behaviors for males and females from early adolescence through early adulthood. *Health Psychology, 32*(6), 685–694.

Malmberg, M., Kleinjan, M., Overbeek, G., Vermulst, A. A., Lammers, J., & Engels, R. C. (2013). Are there reciprocal relationships between substance use risk personality profiles and alcohol or tobacco use in early adolescence? *Addictive Behaviors, 38*, 2851–2859.

Markham, W. A., Aveyard, P., Thomas, H., Charlton, A., Lopez, M. L., & de Vries, H. (2004). What determines future smoking intentions of 12- to 13-year-old UK African-Caribbean, Indian, Pakistani and white young people? *Health Education Research, 19*(1), 15–28.

Marsiglia, F. F., Ayers, S. L., & Hoffman, S. (2012). Religiosity and adolescent substance use in Central Mexico: Exploring the influence of internal and external religiosity on cigarette and alcohol use. *American Journal of Community Psychology, 49*(1–2), 87–97.

Mason, W. A., & Spoth, R. L. (2011). Thrill seeking and religiosity in relation to adolescent substance use: Tests of joint, interactive and indirect influences. *Psychology of Addictive Behaviors, 25*(4), 683–696.

Matarazzo, J. D., & Saslow, G. (1960). Psychological and related characteristics of smokers and non-smokers. *Psychological Bulletin, 57*(6), 493–513.

Mazanov, J., & Byrne, D. G. (2002). A comparison of predictors of the adolescent intention to smoke with adolescent current smoking using discriminant function analysis. *British Journal of Health Psychology, 7*(2), 185–201.

Mazanov, J., & Byrne, D. G. (2006a). A cusp catastrophe model analysis of changes in adolescent substance use: Assessment of behavioural intention as a bifurcation variable. *Nonlinear Dynamics, Psychology, and Life Sciences, 10*(4), 445–470.

Mazanov, J., & Byrne, D. G. (2006b). An evaluation of the stability of perceptions and frequency of adolescent risk taking over time and across samples. *Personality and Individual Differences, 40*(4), 725–735.

Mazanov, J., & Byrne, D. G. (2007). Changes in adolescent smoking behaviour and knowledge of health consequence of smoking. *Australian Journal of Psychology, 59*(3), 176–180.

Mazanov, J., & Byrne, D. G. (2008). Modelling change in adolescent smoking behaviour: Stability of predictors across analytic models. *British Journal of Health Psychology, 13*(3), 361–379.

McCrae, R. R., & Costa, P. T. (1996). Toward a new generation of personality theories: Theoretical contexts for the five-factor model. In J. S. Wiggins (Ed.), *The five-factor model of personality: Theoretical perspectives* (pp. 51–87). New York: Guilford.

Metzger, A., Dawes, N., Mermelstein, R., & Wakschlag, L. (2011). Longitudinal modeling of adolescents' activity involvement, problem peer associations, and youth smoking. *Journal of Applied Developmental Psychology, 32*, 1–9.

Moore, S., Laflin, M. T., & Weiss, D. L. (1996). The role of cultural norms in the self-esteem and drug use relationship. *Adolescence, 31*(123), 523–542.

Morrell, H. E. R., Song, A. V., & Halpern-Felsher, B. L. (2010). Predicting adolescent perceptions of the risks and benefits of cigarette smoking: A longitudinal investigation. *Health Psychology, 29*(6), 610–617.

Moscati, A., & Mezuk, B. (2014). Losing faith and finding religion: Religiosity over the life course and substance use and abuse. *Drug and Alcohol Dependence, 136*, 127–134.

Munafo, M. R., & Black, S. (2007). Personality and smoking status: A longitudinal analysis. *Nicotine and Tobacco Research, 9*(3), 397–404.

Munafo, M. R., Zetteler, J. I., & Clark, T. G. (2007). Personality and smoking status: A meta-analysis. *Nicotine and Tobacco Research, 9*(3), 405–413.

Nebot, M., Valmayor, S., Lopez, M. J., Tomas, Z., Arizen, C., & Juarez, O. (2005). Factors associated with smoking onset: 3-year cohort study of schoolchildren. *Archivos de Bronconeumología, 40*(11), 495–501.

Nonnemaker, J. M., McNeely, C. A., & Blum, R. W. (2003). Public and private domains of religiosity and adolescent health risk behaviours: Evidence from the National Longitudinal Study of Adolescent Health. *Social Science and Medicine, 57*(11), 2049–2054.

O'Callaghan, F., & Doyle, J. (2002). What is the role of impression management in adolescent cigarette smoking? *Journal of Substance Abuse, 13*(4), 459–470.

Otten, R., van Lier, P. A. C., & Engels, R. C. (2011a). Disentangling two underlying processes in the initial phase of substance use: Onset and frequency of use in adolescent smoking. *Addictive Behaviors, 36*, 237–240.

Otten, R., Bricker, J. B., Liu, J., Comstock, B. A., & Peterson, A. V. (2011b). Adolescent psychological and social predictors of young adult smoking acquisition and cessation: A 10-year longitudinal study. *Health Psychology, 30*(2), 163–170.

Panter, A. T., & Reeve, B. B. (2002). Assessing tobacco beliefs among youth using item response theory models. *Drug and Alcohol Dependence, 68*(Suppl1), S21–S39.

Pharo, H., Sim, C., Graham, M., Gross, J., & Hayne, H. (2011). Risky business: Executive function, personality, and reckless behavior during adolescence and emerging adulthood. *Behavioral Neuroscience, 125*(6), 970–978.

Piko, B. (2001). Smoking in adolescence. Do attitudes matter? *Addictive Behaviors, 26*(2), 201–217.

Pitel, L., Geckova, A. M., Kolarcik, P., Halama, P., Reijneveld, S. A., & Van Dijk, J. P. (2012). Gender differences in the relationship between religiosity and health-related behaviour among adolescents. *Journal of Epidemiology and Community Health, 66*(12), 1122–1128.

Poikolainen, K., Tuulio-Henriksson, A., Lonnqvist, J., Aalot-Setala, T., & Martunnen, M. (2001). Predictors of somatic symptoms: A five year follow-up of adolescents. *Archives of Disease in Childhood, 83*(5), 388–392.

Presson, C. C., Chassin, L., & Sherman, S. J. (2002). Psychosocial antecedents of tobacco chipping. *Health Psychology, 21*(4), 384–392.

Prinsloo, M., Tudhope, L., Pitt, L., & Campbell, C. (2008). Using demographics to predict smoking behavior: Large sample evidence from an emerging market. *Health Marketing Quarterly, 25*(3), 289–301.

Rose, J. S., Chassin, L., Presson, C. C., & Sherman, S. J. (1996). Prospective predictors of quit attempts and smoking cessation in young adults. *Health Psychology, 15*(4), 261–268.

Rotter, J. B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs, 80*(1), 1–28.

Sarafino, E. P. (2006). *Health psychology: Biopsychosocial interactions* (4th ed.). New York: Wiley.

Soldz, S., & Cui, X. (2001). A risk factor index predicting adolescent cigarettes smoking: A 7-year longitudinal study. *Psychology of Addictive Behaviours, 15*(1), 33–41.

Spears, G. V., Stein, J. A., & Koniak-Griffin, D. (2010). Latent growth trajectories of substance use among pregnant and parenting adolescents. *Psychology of Addictive Behaviors, 24*(2), 322–332.

Sperber, A. D., Schvartzman, P., Peleg, A., & Friger, M. (2001). Factors associated with daily smoking among Israeli adolescents: A prospective cohort study with a 3-year follow-up. *Preventive Medicine, 33*(2Pt1), 73–81.

Stephens, S., Cellucci, T., & Gregory, J. (2004). Comparing stage of change measures in adolescent smokers. *Addictive Behaviours, 29*(4), 759–764.

Steptoe, A., & Wardle, J. (2001). Locus of control and health behaviour revisited: A multivariate analysis of young adults from 18 countries. *British Journal of Psychology, 92*(Pt4), 659–672.

Steptoe, A., Wardle, J., Cui, W., Baban, A., Glass, K., Tsuda, A., & Vinck, J. (2002). An international comparison of tobacco smoking, beliefs and risk awareness in university students from 23 countries. *Addiction, 97*(12), 1561–1571.

Stuart, K., Borland, R., & McMurray, N. (1994). Self-efficacy, health locus of control and smoking cessation. *Addictive Behaviours, 19*(11), 1–12.

Tang, S. M., & Loke, A. Y. (2013). Smoking initiation and personal characteristics of secondary students in Hong Kong. *Journal of Advanced Nursing, 69*(7), 1595–1606.

Thornton, W., Douglas, G. A., & Houghton, S. J. (1999). Transition through stages of smoking: The effect of gender and self-concept on adolescent smoking behaviour. *Journal of Adolescent Health, 25*(4), 284–289.

Tilleczek, K. C., & Hine, D. W. (2006). The meaning of smoking as health and social risk in adolescence. *Journal of Adolescence, 29*(2), 273–287.

Timberlake, D. S., Rhee, S. H., Haberstick, B. C., Hopfer, C., Ehringer, M., Lessem, J. M., Smolen, A., & Hewitt, J. K. (2006). The moderating effects of religiosity on the genetic and environmental determinants of smoking initiation. *Nicotine and Tobacco Research, 8*(1), 123–133.

Tyas, S. L., & Pederson, L. L. (1998). Psychosocial factors related to adolescent smoking: A critical review of the literature. *Tobacco Control, 7*(4), 409–420.

Unger, J. B., Li, Y., Johnson, C. A., Gong, J., Chen, X., Li, C. Y., et al. (2001). Stressful life events among adolescents in Wuhan, China: Associations with smoking, alcohol use, and depressive symptoms. *International Journal of Behavioral Medicine, 8*(1), 1–18.

Van den Bree, M. B. M., Whitmer, M. D., & Pickworth, W. B. (2004). Predictors of smoking development in a population-based sample of adolescents: A prospective study. *Journal of Adolescent Health, 35*(3), 172–181.

Vink, J. M., Boomsma, D. I., Willemsen, G., & Engels, R. C. M. E. (2003). Smoking status of parents, siblings and friends: Predictors of regular smoking? Findings from a longitudinal twin-family study. *Twin Research, 6*(3), 209–217.

Wallace, J. M., Brown, T. N., Bachman, J. G., & La Veist, T. A. (2003). The influence of race and religion on abstinence from alcohol, cigarettes and marijuana among adolescents. *Journal of Studies on Alcohol, 64*(6), 843–848.

Weinstein, N. D. (1993). Testing four competing theories of health-protective behaviour. *Health Psychology, 12*(4), 324–333.

West, R., & Sohal, T. (2006). "Catastrophic" pathways to smoking cessation: Findings from national survey. *BMJ, 332*, 458–460.

White, V., Hill, D., & Hopper, J. (1996). The outgoing, the rebellious and the anxious: Are adolescent personality dimensions related to the uptake of smoking? *Psychology and Health, 12*(1), 73–85.

White, H. R., Pandina, R. J., & Chen, P.-H. (2002). Developmental trajectories of cigarettes use from early adolescent into young adulthood. *Drug and Alcohol Dependence, 65*(2), 167–178.

Whiteman, S. D., Jensen, A. C., & Maggs, J. L. (2013). Similarities in adolescent siblings' substance use: Testing competing pathways of influence. *Journal of Studies on Alcohol and Drugs, 74*(1), 104–113.

Wills, T. A., Yaegar, A. M., & Sandy, J. M. (2003). Buffering effect of religiosity for adolescent substance use. *Psychology of Addictive Behaviours, 17*(10), 24–31.

Wills, T. A., Sargent, J. D., Stoolmiller, M., Gibbons, F. X., Worth, K. A., & Cin, S. D. (2007). Movie exposure to smoking cues and adolescent smoking onset: A test for mediation through peer affiliations. *Health Psychology, 26*(6), 769–776.

Yang, F., Cheng, W. J. Y., Ho, M.-H. R., & Pooh, K. (2013). Psychosocial correlates of cigarette smoking among Asian American and Pacific Islander adolescents. *Addictive Behaviors, 38*, 1890–1893.

Alcohol and Cardiovascular Risk

Shalini Arunogiri and Dan Lubman

Contents

S. Arunogiri • D. Lubman (✉)
Turning Point, Fitzroy, VIC, Australia

Eastern Health Clinical School, Monash University, Box Hill, VIC, Australia
e-mail: shalinia@turningpoint.org.au; dan.lubman@monash.edu; danl@turningpoint.org.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_8

Abstract

Alcohol is a psychoactive substance that has a considerable impact on the physical and mental health of individuals. While there is clear evidence for a wide range of harms associated with alcohol consumption, research has also been conducted into the potential positive effects, including cardiovascular effects. The results of many of these studies are suggestive of a J-shaped association between low levels of regular alcohol intake and a reduction in cardiovascular risk – particularly coronary heart disease risk. This is an association that appears to be affected both by the level and the pattern of alcohol consumption. However, most of this research has consisted of observational and population-based studies, with inherent methodological limitations and difficulties controlling for confounding factors. Consequently, there is still insufficient evidence to suggest a causal relationship between alcohol consumption and a reduction in cardiovascular risk. On a population level, the putative benefits of alcohol intake are more salient for some individuals compared to others – such as older adults with other cardiovascular risk factors. On the other hand, negative health effects can arise from even low levels of alcohol intake. Thus, the provision of advice regarding alcohol consumption needs to be individualized and is best undertaken within a clinical context.

Keywords

Alcohol • Alcohol drinking • Cardiovascular • Cardiovascular risk • Coronary disease

Introduction

Alcohol is a psychoactive substance that has a significant impact on the health and well-being of individuals and communities. Alcohol consumption contributed to 5.1 % of the global burden of disease and injury and up to 3.3 million deaths worldwide in 2012 (WHO 2014). Alcohol is also a component cause of over 200 different types of disease and injury (WHO 2014). It has also been implicated as a source of far-reaching intangible and tangible harms to others. For instance, a recent Australian study estimated that heavy drinkers cost people around them more than $14 billion in out-of-pocket costs and up to an additional $6 billion in intangible costs (Laslett et al. 2010) – more than doubling previous estimates (Collins and Lapsley 2008). On the other hand, individuals often cite positive social and mental health benefits of alcohol, and moderate alcohol use is considered part of the social norm and lifestyle in many cultures and countries.

One potential benefit of alcohol that has been studied extensively is that of cardiovascular disease risk reduction. Substantial research has gone into understanding the association between cardiovascular disease and alcohol consumption, with such research focusing on a number of key areas. Investigators have sought to

clarify whether alcohol is cardioprotective on a population level. They have explored whether this protective association exists in both individuals without cardiovascular disease risk factors and those with preexisting disease. Studies have also attempted to identify underlying pathophysiological mechanisms to explain putative protective effects. However, considering alcohol as a "lifestyle" factor, there are many confounding factors that impact on this association and need to be taken into account by studies in this field. The complexity of the association between alcohol use and cardiovascular disease is best understood through the lens of both clinical and research practice.

The J-Shaped Curve: Is Alcohol Cardioprotective?

Epidemiological and observational studies over the past three decades have suggested that light to moderate alcohol consumption is associated with a reduced risk of cardiovascular disease (Corrao et al. 2000; Di Castelnuovo et al. 2010; Klatsky 2010; Marmot and Brunner 1991; Ronksley et al. 2011) (see Table 1). The majority of these studies have reported a J-shaped curve, with light to moderate drinking being associated with lower risk than complete abstinence and heavy drinking placing an individual at highest risk (O'Keefe et al. 2007; Rimm et al. 1999; Ronksley et al. 2011). Estimates of the cardiovascular mortality risk reduction conferred by light to moderate alcohol consumption range from 20 % to 30 % (Di Castelnuovo et al. 2006; Rimm et al. 1999; Ronksley et al. 2011).

The cardioprotective association of low to moderate alcohol consumption appears to be strongest for coronary artery disease (CAD), and it appears that the majority of cardiovascular mortality risk reduction is attributable to the effect of alcohol on CAD (Mukamal et al. 2010; Ronksley et al. 2011). Ronksley and colleagues' recent systematic review and meta-analysis included 84 studies of the impact of alcohol on cardiovascular risk (Ronksley et al. 2011) and is the most complete meta-analysis of this subject to date, sampling over one million people. They found a pooled estimate of relative risk for all-cause mortality in all drinkers compared to nondrinkers of 0.87 (95 % CI of 0.83–0.92); for cardiovascular mortality, alcohol consumption was associated with a relative risk of about 0.75 (95 % CI 0.70–0.80 (Ronksley et al. 2011). This association was similar for incident coronary artery disease (RR 0.71 (0.66–0.77)) and coronary artery disease mortality (RR 0.75 (0.68–0.81)) (Ronksley et al. 2011). When dose relationships were analyzed, they confirmed a J-shaped relationship between alcohol intake and cardiovascular intake (Ronksley et al. 2011), which was later graphically represented in Thompson's discussion of the topic (Thompson 2013) as below (see Figure 1). A dose-response analysis suggested that the lowest risk of CAD mortality occurred with one to two drinks per day (Ronksley et al. 2011).

Another meta-analysis of 44 studies looked at the relationship between alcohol consumption and ischemic heart disease (IHD) and attempted to quantify a dose-response relationship stratified by sex and by IHD outcome

Table 1 Summary of levels of alcohol consumption associated with cardiovascular benefit/risk

Study	Study population	Outcome(s) of interest	Level of consumption
Ronksley et al. 2011	No pre-existing cardiovascular disease	Cardiovascular disease mortality	2.5–14.9 g alcohol per day for *all* outcomes (approx. <1 standard drink per day[a])
	Drinkers versus nondrinkers	Coronary heart disease mortality	Coronary heart disease: >2.5 g/day was protective
		Stroke mortality	Incident stroke: >6 g per day increased risk of stroke
		Incident coronary heart disease events	
		Incident stroke events	
Roerecke and Rehm 2012	No pre-existing cardiovascular disease	Ischemic heart disease mortality	Men: lowest IHD risk at 31 g/day of alcohol, protective effect up to 63 g/day
	Drinkers versus lifetime abstainers		Women: lowest IHD risk at 11 g/day of alcohol
	Separate analyses based on gender		
Costanzo et al. (2010a)	History of cardiovascular events	Cardiovascular mortality	Maximal cardioprotective effect between 5 and 10 g of alcohol per day, up to 26 g/day
Mukamal et al. 2005	Men with no preexisting cardiovascular disease	Ischemic stroke	Increased risk of stroke at >2 standard drinks per day (>30 g of alcohol)

[a]American guidelines define one standard drink as 14 g of alcohol; Australian and UK guidelines define one standard drink as 10 g of alcohol

(Roerecke and Rehm 2012). This meta-analysis provided useful information as the authors completely excluded any studies that included former drinkers and only included lifetime abstainers (Roerecke and Rehm 2012). They found an overall cardioprotective effect of alcohol on IHD risk and found a J-shaped curve relationship between alcohol intake and IHD morbidity and mortality in men, with reduced morbidity in women (Roerecke and Rehm 2012). In their dose-response analysis, the lowest point of the J-curve (the point at which there was lowest IHD risk) was at an alcohol intake of 31 g/day for men and 11 g/day for women (Roerecke and Rehm 2012). Thompson's recent review reconstructed these findings from Roerecke and Rehm, as demonstrated below (Thompson 2013, see Fig. 1) and summarized in Table 1.

In conclusion, there is strong evidence for a J-shaped relationship between alcohol intake and a number of cardiovascular outcomes. Whether this association is a causal relationship, however, remains to be proven.

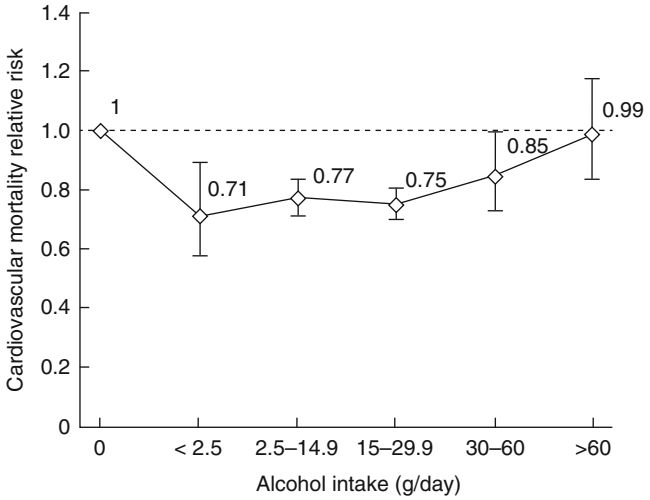


Fig. 1 Meta-analysis showing the J-shaped relationship between alcohol intake and cardiovascular mortality (Redrawn from data in Ronksley et al. 2011, Thompson 2013)

Risk of Hypertension

Both experimental and observational studies show that the more people drink, the higher their risk of hypertension (Parry et al. 2011; Patra et al. 2010; Taylor et al. 2009). A meta-analysis of 12 cohort studies found a linear dose-response relationship between alcohol consumption and hypertension, particularly in men (Taylor et al. 2009). Adopting the Heart and Stroke Foundation definition of hypertension as a blood pressure of over 140/90 mmHg, men who drank 50 g or more of alcohol daily (>5 standard drinks) had a relative risk of 1.57 for hypertension, rising to a relative risk of 2.47 at 100 g per day (ten standard drinks) (Taylor et al. 2009). For women, there was a modest protective effect for consumption levels of less than 5 g per day (<0.5 standard drinks); however, above this level, there was a linear relationship of alcohol intake with hypertension risk, to a relative risk of 1.81 at 50 g per day and 2.81 at 100 g per day (Taylor et al. 2009). These estimates are summarized in Table 1.

Risk of Stroke

Stroke can be classified as ischemic stroke or hemorrhagic stroke. Alcohol has been demonstrated to elevate the risk of hemorrhagic stroke by contributing to hypertension (Ohsawa and Tanno 2013). Some studies have suggested an almost linear relationship between increasing doses of alcohol consumption and increasing risk of hemorrhagic stroke, particularly in men (Patra et al. 2010). Hypertension also

contributes to increased arteriocapillary sclerosis (Ohsawa and Tanno 2013), and thus alcohol consumption is thought to contribute to an elevated risk of lacunar or small-vessel ischemic stroke (Ohsawa and Tanno 2013).

Large-vessel ischemic stroke is mainly attributable to atherosclerosis, which is accelerated by dyslipidemia. Alcohol appears to decrease the risk of large-vessel stroke (Ohsawa and Tanno 2013) in a curvilinear or J-shaped manner, similar to that observed with CAD – with alcohol consumption of up to three standard drinks a day being associated with a decreased risk of ischemic stroke and drinking at higher levels associated with increased risk (Patra et al. 2010). Some evidence suggests that this protective effect may be moderated by age, with older individuals appearing to derive a greater reduction in risk for ischemic stroke with low levels of alcohol consumption (Djoussé et al. 2002).

There is clear evidence that heavy drinking, over and above about three standard drinks per day, raises the risk of all types of stroke mortality and morbidity (Mukamal et al. 2005; Parry et al. 2011; Patra et al. 2010).

Risk of Arrhythmias

Acute alcohol consumption has been associated with an increased risk of paroxysmal atrial arrhythmias such as atrial fibrillation via a number of pathophysiological pathways (Sheikh et al. 2014). So-called holiday heart syndrome was described in the 1970s as a consequence of excessive alcohol consumption during a vacation resulting in presentations with atrial fibrillation (Fauchier 2003; Sheikh et al. 2014). It is unclear what level of consumption results in the development of these arrhythmias.

Heavy drinking occasions have also been associated with a lower threshold for ventricular fibrillation (Costanzo et al. 2010b; Rehm et al. 2003) and have been associated with other ventricular arrhythmias (Fauchier 2003).

Risk of Cardiomyopathy

Alcohol has been shown to have a detrimental effect on cardiac muscle structure and function (Goncalves et al. 2014), and long-term alcohol consumption can lead to a recognized and specific form of cardiomyopathy known as alcoholic cardiomyopathy. This is a non-ischemic form of dilated cardiomyopathy, characterized by an increase in myocardial mass, dilatation of the ventricles, and wall thinning (Piano 2002). While the exact amount and duration of consumption leading to cardiomyopathy has been hard to determine, data appear to suggest that levels of alcohol consumption of greater than 7–15 standard drinks per day for more than 5–15 years are associated with cardiomyopathy (Piano and Phillips 2014). The interaction between alcohol and myocardial injury is moderated by a range of

pathophysiological mechanisms, including genetic susceptibility, nutritional factors, and oxidative stress (Piano and Phillips 2014). Individuals with this form of cardiomyopathy demonstrate improved ventricular function with abstinence from alcohol, with a direct relationship between ongoing intake and deterioration in clinical state (Piano 2002).

Individuals with Preexisting Cardiovascular Disease

While the initial studies of the impact of alcohol on cardiovascular risk focused on healthy individuals with no baseline disease, evidence has since begun to emerge showing that alcohol may have a cardioprotective role even in individuals with cardiovascular disease.

A 2010 meta-analysis by Costanzo and colleagues examined eight published prospective observational studies of 16, 351 patients with a history of cardiovascular disease (specifically, a history of coronary heart disease, acute myocardial infarction, or stroke) (Costanzo et al. 2010a). The relationship between cardiovascular mortality and alcohol consumption in this cohort found a J-shaped curve, with maximal effects in the range of 5–10 g/day of alcohol; this effect held even when former drinkers were excluded from the reference category (Costanzo et al. 2010a). Most studies included in this meta-analysis only administered alcohol intake questionnaires late (over 2 months) after the index cardiovascular event, as authors sought to get an accurate representation of individuals' real intake of alcohol prior to the event (Costanzo et al. 2010a). The authors also conducted a second meta-analysis on this cohort for all-cause mortality and found a J-shaped relationship between alcohol consumption and all-cause mortality in individuals with preexisting cardiovascular disease – maximal protective effects were, again, in the range of 5–10 g/day of alcohol (Costanzo et al. 2010a). In both analyses, the protective effect held for levels of alcohol consumption up to 25 g/day. It is worth noting that the greatest benefit derived was thus at a level of less than one standard drink of alcohol per day, with some benefit up to 2.5 standard drinks per day (Costanzo et al. 2010a).

One consideration in individuals with preexisting cardiovascular disease is the risk of interactions between alcohol and cardiac medications. Alcohol may potentially interact with antiplatelet and oral anticoagulant drugs. For instance, alcohol consumption in combination with aspirin can raise the risk of gastrointestinal bleeding in an additive fashion (Costanzo et al. 2010b). The effect of alcohol on the induction of the cytochrome P-450 enzyme system in the liver can result in the breakdown of particular medications being sped up, thereby decreasing the concentration of these medications – this may play some role in the metabolism of anticoagulant drugs such as warfarin and clopidogrel (Costanzo et al. 2010b).

Choice of Alcoholic Beverage

It was once believed that red wine was responsible for many of the cardioprotective effects of alcohol (Grønbæk et al. 2000). This assumption arose from the concept of the "French paradox" – the low cardiovascular disease and ischemic heart disease mortality rate observed in French men, despite a diet high in saturated fat, was attributed to the consumption of red wine (Renaud and de Lorgeril 1992). Compounds in red wine, including polyphenols (such as resveratrol) and flavonoids, were found to have a protective effect on endothelial function, platelet aggregation, and low-density lipoprotein oxidation (Di Castelnuovo et al. 2010; Karatzi et al. 2004).

However, large prospective studies have since found that the beneficial effects of low to moderate alcohol consumption are not dependent on the type of alcoholic beverage consumed or properties of the beverage but, rather, due to alcohol itself (Mukamal et al. 2003; Rimm et al. 1996). Some studies have also demonstrated that moderate-consumption wine drinkers may have healthier diets in comparison to nondrinkers and heavy drinkers, which may further contribute to lowered cardiovascular risk (Hansel et al. 2012).

Pattern of Consumption

While much of the evidence focuses on the cardioprotective effect of light to moderate alcohol consumption, this evidence has generally been for regular drinking rather than binge pattern or infrequent consumption (Bagnardi et al. 2008; Ellison 2005; O'Keefe et al. 2007; Roerecke and Rehm 2010).

Some studies have attempted to investigate the impact of irregular heavy drinking occasions on cardiovascular risk. Roerecke and Rehm's review and meta-analysis of 14 studies defined irregular heavy drinking occasions as 60 g or more per day at least 12 times per year, but not more than 5 days per week (Roerecke and Rehm 2010). They found that irregular heavy drinking occasions, in comparison to regular moderate consumption, resulted in a 45 % increase in the risk of ischemic heart disease (Roerecke and Rehm 2010). The results of this meta-analysis showed that the cardioprotective effect of low to moderate alcohol consumption disappeared when this pattern was mixed with irregular heavy drinking occasions (Roerecke and Rehm 2010).

Ruidavets and colleagues used data from the Prospective Epidemiological Study of Myocardial Infarction (PRIME) to perform a cross-cultural comparison of alcohol consumption in middle-aged men in Northern Ireland versus France, comparing binge pattern alcohol consumption in the former and regular moderate consumption in the latter (Ruidavets et al. 2010). A total of 9,778 men aged between 50 and 59, free of ischemic heart disease at baseline, were followed up over 10 years for ischemic heart disease outcomes (including incident myocardial infarction and coronary death (hard coronary events) and incident angina pectoris) (Ruidavets et al. 2010). Among regular drinkers in the study, the total volume of

alcohol consumed over a week was almost the same in both countries (281.7 g in Ireland, 254.6 g in France), but when the pattern of consumption was compared between countries, 9.4 % of the Belfast cohort reported binge drinking compared to 0.5 % in the French sample – men in Belfast appeared to consume the total volume over 1–2 days, whereas men in France reported consumption over the course of the week (Ruidavets et al. 2010). The prevalence of binge drinking was thus almost 20 times higher in Ireland than in France, and this was associated with a doubling of risk of ischemic heart disease for binge drinkers (hazard ratio of 1.97, 95 % CI 1.21–3.22) compared to regular drinkers (Ruidavets et al. 2010).

Other earlier studies that have found a protective effect for daily light to moderate drinking have found no such protective effect, or even detrimental effects, for individuals who report occasional heavy drinking even if their usual pattern was moderate consumption (Rehm et al. 2003). In addition, evidence is emerging linking infrequent consumption with high-volume drinking occasions (Naimi et al. 2013). A recent study showed that of a group of individuals who reported low average consumption overall, those who drank less frequently were more likely to drink at higher levels associated with increased risk (Naimi et al. 2013). Thus, any protective effects of low average consumption may be reversed or nullified by this pattern of binge drinking (Naimi et al. 2013).

There are some problems with the literature in this area. Variability in the definition of irregular heavy drinking occasions, and in the methods used to identify or report relative risk estimates, results in significant levels of heterogeneity in meta-analyses of existing studies (Roerecke and Rehm 2010). However, on balance, the overall consensus from the literature is that any putative cardioprotective effect of alcohol consumption is strongly influenced by the pattern and volume of consumption.

Risks Associated with Excessive Alcohol Consumption, Drinking to Intoxication, and Alcohol Dependence

There is overwhelming evidence that excessive alcohol consumption results in an increased risk of a range of cardiovascular outcomes. Alcohol abuse is associated with hyperlipidemia, vasoconstriction, increased clotting activity, and cardiomyopathy; it has also been shown to be associated with weight gain and metabolic syndrome (Costanzo et al. 2010b). Binge or heavy consumption has been linked to excess coronary heart disease risk (Bagnardi et al. 2008), and a study of binge pattern consumption in a Russian population found that heavy drinkers (consuming >10 standard drinks more than three times per week) were twice as likely to die from cardiovascular causes (Malyutina et al. 2002). Among individuals with baseline cardiovascular disease, binge drinkers were found to have double the total cardiovascular mortality risk of regular drinkers (Mukamal et al. 2005). As outlined above, there are also concerns about an elevated risk of arrhythmias such as atrial fibrillation, and a lowered threshold for ventricular fibrillation, in those who drink excessively (Costanzo et al. 2010b).

This evidence for increased cardiovascular risk with heavy alcohol consumption needs to be taken in the context of the significant burden of morbidity and mortality from other causes arising from binge drinking and from long-term heavy consumption. A thorough discussion of such harms falls beyond the scope of this chapter. Briefly, short-term harms from drinking to intoxication include intentional and unintentional injury (such as road traffic accidents, falls, or drowning), violence, and elevated risk of suicide (WHO 2011). Long-term harms include the risk of a number of cancers, pancreatitis, liver cirrhosis, fetal alcohol syndrome, alcohol-related brain injury, and alcohol dependence (Corrao et al. 2000; Costanzo et al. 2010a; Parry et al. 2011; Rehm et al. 2009).

Confounding Factors and the Limitations of Evidence from Observational Studies

All studies investigating the relationship between alcohol and cardiovascular risk are observational in nature, and thus subject to a number of limitations. Firstly, they are unable to prove direct causation between variables of interest. Secondly, such studies need to adequately account for a range of confounding factors that may play a role in the association being investigated. In the case of alcohol and cardiovascular risk, there are myriad confounding factors that may not be able to be adequately assessed and controlled for, including social, cultural, and economic variables. Finally, the literature in this field has often come under criticism for the heterogeneity prevalent in the definitions used and the measurement of variables in different studies. This leads to inherent difficulties in consolidating evidence for meta-analyses.

In this section, some of the limitations of this evidence and proposed challenges to the classical "J-shaped" relationship between alcohol consumption and cardiovascular risk will be examined.

The "Sick Quitter" Hypothesis: The Misclassification of Ex-Drinkers as Abstainers

Many of the prospective studies in this field classify "former drinkers," who have decreased or terminated their drinking, as abstainers. However, many individuals may decrease or terminate their alcohol consumption as they age due to illness or increasing medication use – that is, they would be considered "sick quitters" (Shaper et al. 1988). These individuals may thus be at increased risk of developing cardiovascular disease by virtue of their ill health rather than their reduction in alcohol use. Shaper and colleagues suggested that including these people in the "abstainer" comparison group resulted in a systematic misclassification error in studies, which would bias findings toward an overestimation of protective effects and an underestimation of detrimental effects of alcohol consumption (Roerecke and Rehm 2011; Shaper et al. 1988). This misclassification can arise from a range of

errors in studies, from the actual inclusion of former drinkers in the abstainer category to inconsistencies in the assessment and measurement of alcohol intake (Fillmore et al. 2007).

The impact of this misclassification has been tested in a number of meta-analyses that sought to remove former drinkers and "sick quitters" from the reference group. Fillmore and colleagues' meta-analysis was rigorous and attempted to address a number of errors in classification, which resulted in only a small number of studies for analysis (Fillmore et al. 2006). In the final seven studies analyzed, the evidence failed to confirm a J-shaped relationship between alcohol consumption and cardiovascular events (Fillmore et al. 2006).

A more recent meta-analysis compared differences in ischemic heart disease morbidity and mortality risk between former drinkers and long-term abstainers and found that former drinkers had a significantly elevated risk of ischemic heart disease mortality compared to long-term abstainers (Roerecke and Rehm 2011). These authors went on to conduct a meta-analysis excluding former drinkers from the reference category. While they found a trend to cardioprotective association between low to moderate alcohol consumption and a number of ischemic heart disease outcomes for both sexes, they stated that all models of the analysis showed a significant level of unexplained heterogeneity (Roerecke and Rehm 2012). Thus, while their results supported a cardioprotective effect of moderate alcohol consumption, the authors highlighted that these findings were subject to inconsistencies in the studies themselves, including lack of control for a variety of confounding factors (Roerecke and Rehm 2012).

Finally, Ronksley and colleagues attempted to analyze the relationship between alcohol intake and a number of cardiovascular outcomes (Ronksley et al. 2011). Their results suggested that "former drinkers" had a significantly higher risk of cardiovascular mortality in comparison to "current drinkers" (Ronksley et al. 2011). However, they found that removing "former drinkers" from the reference category did not make a "substantive difference" to the risk reduction estimates for mortality or incident disease. Other authors have criticized these findings, feeling that studies of inadequate rigor or statistical quality were included in the analysis (Stockwell et al. 2012).

In summary, a number of meta-analyses have tried to study the impact of the "sick quitter" effect, but their endeavors have been limited by the quantity and quality of the studies conducted to date.

Lifetime Abstainers May Differ from Drinkers in Ways Other than Just Alcohol Consumption: Moderate Alcohol Consumption as a Marker of Optimal Social Status

When studying an association between a risk factor and an outcome, the only difference between the two groups being examined should ideally be the presence or absence of the risk factor. Therefore, in this field, comparison and reference groups should only differ in their level of alcohol consumption, with adjustments

made to account for all other variables. In particular, it is crucial that confounding factors that may play a role in the outcome of interest are adjusted for.

However, there is growing evidence that there are a range of lifestyle factors that are independently associated with an elevated risk of cardiovascular disease that may occur more frequently in nondrinkers or lifetime abstainers; that is, light and moderate drinkers have healthier lifestyles (Fekjaer 2013). For instance, Hansel and colleagues found that moderate male drinkers were more likely than lifetime abstainers to have characteristics associated with lower cardiovascular risk – including lower BMI, heart rate, pulse pressure, fasting glucose, fasting triglycerides, stress, and depression scores and better subjective health status, respiratory function, social status, and physical activity (Hansel et al. 2010). Many of these factors are not causally associated with alcohol consumption. The authors' analysis suggested that moderate and low drinkers had better health status than never-drinkers (Hansel et al. 2010).

Other studies support these conclusions (Hansel et al. 2012). Naimi and colleagues conducted a US-based telephone survey to assess the prevalence of a range of cardiovascular risk factors in moderate drinkers versus never-drinkers (Naimi et al. 2005). These included factors such as health access, behavioral factors, social factors, comorbid health conditions, and demographic factors (Naimi et al. 2005). They found that 90 % of the risk factors they assessed were significantly more prevalent among nondrinkers (Naimi et al. 2005).

Of note, many studies do not comprehensively or adequately account for these factors. Many studies adjust for one or two factors, such as age or "socioeconomic status"; however, residual confounding can still occur in such studies (Hansel et al. 2012). Indeed, in one of the few studies to assess the impact of alcohol consumption in tandem with physical activity, it was found that low physical activity played a greater role in increasing cardiovascular risk than heavy drinking (Soedamah-Muthu et al. 2013).

Thus, it may be possible that moderate alcohol consumption does not cause cardioprotection but rather occurs in tandem with other healthy behaviors within healthy individuals. While moderate drinkers may have a lower risk of cardiovascular disease, whether this lowering of risk is due to alcohol remains to be seen. Studies that demonstrate a peak cardioprotective effect at one to two standard drinks per day may actually reflect that other beneficial factors possibly peak at or around these levels of alcohol consumption (Fekjaer 2013). As some authors have suggested, "moderate alcohol consumption may represent a marker of higher socioeconomic status, superior health status and lower cardiovascular risk" (Hansel et al. 2010).

Limitations of Methodology: Measuring and Classifying Alcohol Consumption in Observational Studies

A common limitation of the majority of the existing literature in this field is the use of self-report measures of alcohol consumption. While self-report drinking measures

have been shown to have reasonable reliability for most research purposes (Del Boca and Darkes 2003), there are particular aspects of research in this area that may impact on their validity, for example, the role of social context (Del Boca and Darkes 2003). This includes factors such as the assessment setting (a treatment facility, versus a household survey) and the immediate interpersonal situation – research or treatment staff, other staff, family members, and bystanders (Del Boca and Darkes 2003) – as well as the perceived social or cultural norms within the population. This is particularly salient in this area of research – for instance, a measure of consumption within a treatment setting, shortly after an individual has suffered a cardiac event, may result in a response influenced by the social desirability and expectation, leading to a level of response bias (Del Boca and Darkes 2003).

In addition, most of the epidemiological studies in this field have only collected measures of alcohol at baseline. For example, none of the cohort studies included in one large systematic review of binge consumption assessed alcohol more than once at baseline (Roerecke and Rehm 2010). This can lead to a fundamental misclassification of the status of individuals (as drinkers versus nondrinkers) when considering exposure to alcohol and not accounting for changes in the level of consumption over time (Hansel et al. 2012). Furthermore, few studies incorporate an assessment of instances of heavier consumption or a measure of patterns of consumption, and may thus be misclassifying individuals who usually drink at low to moderate levels but also have frequent binge or heavier alcohol intake (Hall 2012; Roerecke and Rehm 2012). Finally, substantial variability in both the measures used, and in the reporting of relative risk estimates, also contributes to heterogeneity between studies in this area and limits the ability to consolidate data for meta-analysis (Roerecke and Rehm 2010) (Figs. 1 and 2).

Pathophysiological Mechanisms

Alcohol and Lipoproteins

Alcohol appears to have a favorable effect on the lipid profile, believed to be mediated largely by its effects on high-density lipoprotein cholesterol (HDL-C) (Fig. 3). HDL-C has been shown to protect against the development of atherosclerosis by a number of mechanisms in the initiation and development of disease, including the inhibition of low-density lipoprotein cholesterol (LDL-C) oxidation. Several studies have shown that alcohol consumption increases HDL-C (Brien et al. 2011; Kloner and Rezkalla 2007; Rimm et al. 1999). A number of these studies have demonstrated a dose-dependent relationship between these variables (Freiberg and Samet 2005; Mukamal et al. 2003, 2007; O'Keefe et al. 2007; Rimm et al. 1999).

A meta-analysis of 42 studies of biological markers of cardiovascular risk found that alcohol caused an overall increase in HDL-C of about 0.1 mmol/L, with this increase being dose-dependent – 0.072 mmol/L for 1–2 drinks a day, 0.10 mmol/L

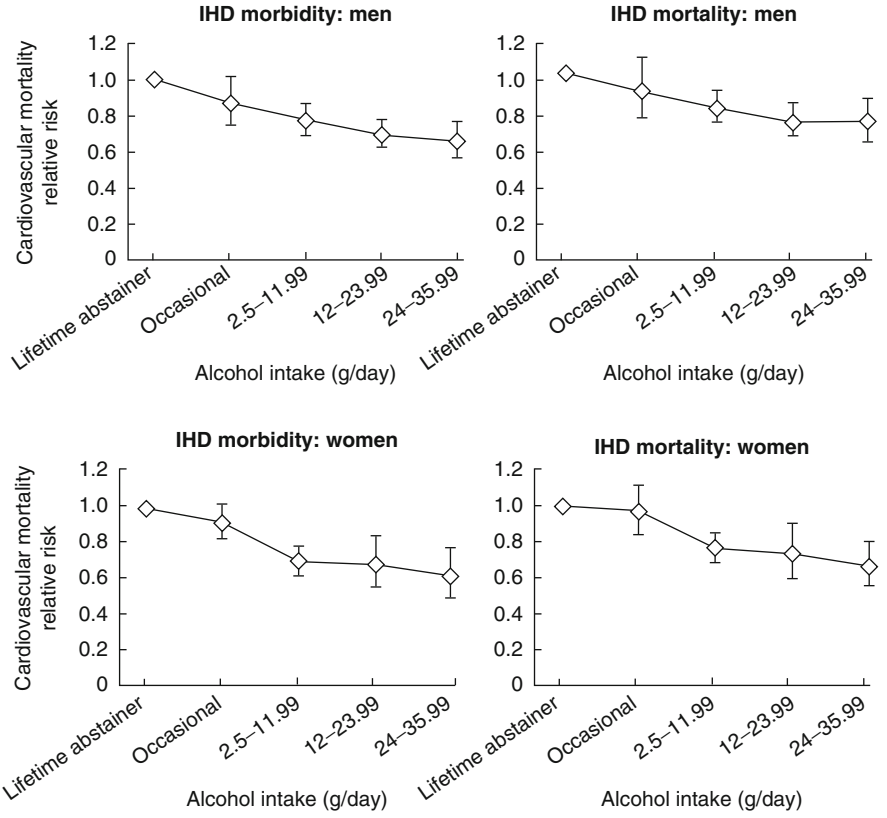


Fig. 2 Relationship between alcohol intake and IHD morbidity and mortality, stratified by gender (Redrawn from Roerecke and Rehm 2012, Thompson 2013)

for 2–4 drinks a day, and 0.14 mmol/L for ≥4 drinks a day (Brien et al. 2011). This study concluded that consumption of 30 g of alcohol per day (three standard drinks) would increase HDL-C by about 8.3 % (Brien et al. 2011). This effect appeared to be particularly strong in men, in sedentary patients, or in individuals with a low baseline HDL-C (Brien et al. 2011; Rimm et al. 1999).

While there is strong evidence for this relationship between changes in alcohol consumption and HDL-C concentration, it remains unclear whether this translates into a direct reduction in cardiovascular risk. For instance, the Russian population has an average high consumption of alcohol and also has a higher average HDL-C compared to other countries, but has higher age-adjusted rates of cardiovascular disease (O'Keefe et al. 2007). Other studies have also found that the impact of alcohol on the risk of mortality from coronary heart disease is not affected by adjusting for HDL-C (Magnus et al. 2011). Conversely, some studies suggest that pharmacologically increasing HDL-C does not affect vascular risk in patients at high risk for coronary events (Costanzo et al. 2010b).

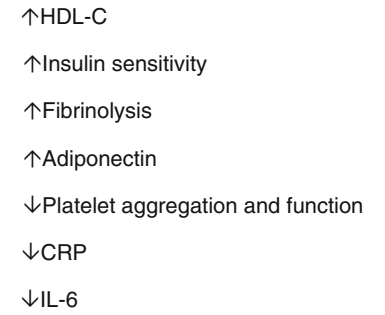


Fig. 3 Suggested mechanism for beneficial effects of alcohol on the cardiovascular system (Albert et al. 2003; Brien et al. 2011; Costanzo et al. 2010b; Lucas et al. 2005)

Thus the direct effect of alcohol on increasing HDL-C should not be considered to entirely account for any cardioprotective role of alcohol – this effect is believed to account for approximately 50 % of the reduced CHD risk (Criqui and Ringel 1994; Gaziano et al. 1993).

Other Mechanisms

Any additional cardioprotective effect of alcohol may be attributable to a range of other mechanisms (Fig. 3). Firstly, regular light to moderate alcohol consumption has a favorable effect on coagulation profiles (Brien et al. 2011; Rimm et al. 1999). There is meta-analytic evidence that fibrinogen levels significantly decrease after alcohol consumption by up to 20 % (Brien et al. 2011). Secondly, alcohol also appears to affect a number of steps in inflammatory pathways implicated in cardiovascular disease (Lucas et al. 2005; Ohsawa and Tanno 2013). Studies have found that moderate alcohol consumption may have some impact on a variety of inflammatory markers, including interleukin (IL)-6, C-reactive protein (CRP) (Albert et al. 2003), and tumor necrosis factor-alpha (TNF-α) (Brien et al. 2011; Lucas et al. 2005), and alcohol also plays a role in regulating endothelial cell genes involved in inflammation, cell adhesion, and the patency of vessels (Lucas et al. 2005). Finally, there is some evidence suggesting that alcohol may increase insulin sensitivity and decrease insulin resistance (Brien et al. 2011; Rimm et al. 1999).

Public Health Implications: Should Safer Drinking Guidelines Be Altered?

Alcohol is the third largest risk factor for disease and disability worldwide (WHO 2014). In 2012, about 3.3 million deaths (or 5.9 % of all global deaths) were attributable to alcohol consumption, with alcohol contributing to 5.1 % of the global burden of disease and injury (WHO 2014). Globally, alcohol contributes to 14 % of all cardiovascular and diabetes-related deaths (WHO 2011). Analyses in

2010 suggest that alcohol use contributes to 33 % of disability-adjusted life years (DALYs) related to ischemic heart disease – a greater proportion than tobacco smoking and greater than the independent risk asserted by physiological risk factors such as high body mass index, high fasting plasma glucose, or high cholesterol (Lim et al. 2013). In some higher-income countries, alcohol is consumed in a regular pattern at low to moderate levels without binge drinking, and this may contribute to a net protective effect in terms of reducing cardiovascular disease burden. However, even in these high-income countries, while the net effect on cardiovascular disease is protective, the overall impact of alcohol consumption on burden of disease is harmful (WHO 2009).

Thus, the risks of recommendations favoring moderate alcohol consumption need to be weighed against the clear evidence for the burden of morbidity and mortality that is associated with excessive consumption and binge drinking. Some authors have argued that levels of consumption that may be safe or recommended for the health of an individual drinker may be detrimental on a population health basis (Hall 2012; Skog 1996). Others have highlighted that moderate daily drinking "is a slippery slope that many individuals cannot safely navigate" (O'Keefe et al. 2007). A universal limit may also not take into account significant public health consequences that may arise from even moderate consumption in vulnerable individuals, such as an increased risk of female breast cancer in susceptible people (Klatsky 2010). In addition, the acute risks such as injury risk disproportionately affect younger people, whereas cardiovascular disease risk reduction is predominantly seen in middle-aged to older individuals (Hall 2012; Ronksley et al. 2011).

Current safe drinking guidelines vary from population to population – the latest American Heart Association Guidelines suggest that those who do not already drink alcohol should be cautioned against doing so, on the basis that it is impossible to predict who may develop problematic or excessive consumption as a result (Pearson 1996). Australia's National Health and Medical Research Council's 2009 Guidelines outline safe drinking limits, but do not recommend low levels of consumption (NHMRC 2009). On the other hand, Canada's Low-Risk Alcohol Drinking Guidelines currently include the comment "While drinking may provide health benefits for certain groups of people, do not start to drink, or increase your drinking, for health benefits" (Butt et al. 2011). These recommendations reflect the uncertainty that continues to exist around alcohol having a causal role in cardiovascular risk reduction and the lack of tools for predicting which subpopulations may be susceptible to alcohol-related risks.

Clinical Implications and Recommendations

While universal population-level guidelines may not comment on any benefits associated with alcohol, it may be useful for health professionals to consider the delivery of individualized and targeted advice within a clinical context. Any advice that is provided needs to take into account the conditionality of benefits that may result from alcohol consumption (Fig. 4), that is, that these benefits occur with

Clinical Considerations for Providing Advice on Alcohol Consumption

Individuals who are likely to attain cardiovascular benefits from alcohol consumption

- Middle aged and older adults
- Those who drink at low to moderate levels, within safe drinking limits, regularly and do not drink to intoxication

Precautions regarding alcohol consumption in older adults

- Alcohol may cause interactions with medication
- Older adults may be more sensitive to the biological adverse effects of alcohol (e.g., risk of falls, sedation)
- Even moderate consumption may be associated with some health risks (e.g.breast cancer risk)
- Excessive consumption is clearly associated with both acute and longer term health risks

Fig. 4 Clinical considerations for providing advice on alcohol consumption

regular moderate consumption in individuals who avoid drinking to intoxication (Rehm et al. 2003) and only occur in middle-aged to older drinkers in whom alcohol may not be contraindicated for other health reasons (for instance, cancer risk or other health risks) (Hall 2012). The complex interaction between alcohol and the individual's current physical and mental health comorbidities also needs to be considered, such as the potential for worsening depressive disorders or the risk of falls. Information also needs to be provided about the risk of adverse interactions between alcohol and current medication use. It is also useful to emphasize that cardiovascular health benefits can be attained in other ways, such as diet modification and physical exercise. Indeed, there is clear evidence that excessive alcohol consumption confers cardiovascular risk, in addition to other significant health risks. Thus, it is imperative that individuals also receive advice on the detrimental effects of binge drinking and drinking to intoxication. Given the complexities inherent in such a risk-benefit analysis, it is a discussion that is best undertaken by clinicians, using a balanced and objective consideration of the individual's holistic health status.

Conclusions

Decades of research have been conducted on the links between alcohol consumption and the risk of cardiovascular disease. The literature contributes to our understanding in a number of key areas. Firstly, there appears to be an association between low to moderate levels of alcohol consumption and lower levels of cardiovascular disease. This is particularly true of risk reduction for ischemic heart disease. However, there are a wide range of confounding factors and methodological limitations that apply to the existing literature, which means that this association cannot be considered to be causal in nature. Secondly, excessive alcohol

consumption has been overwhelmingly proven to be associated with an increased burden of disease, both in terms of an increased risk of cardiovascular disease and a component cause of a wide range of medical and psychiatric illnesses. This burden of disease sees alcohol contributing up to 5.9 % of all deaths worldwide (WHO 2014), and resulting in considerable harm both to the individual and to others.

The answer to one question remains elusive; as a clinician, should one recommend alcohol consumption to individuals who do not already drink alcohol, as a means of primary or secondary prevention? A conclusive answer to this question would need to come from a prospective study that addresses the broad range of methodological limitations pertinent to the existing evidence, such as randomizing levels of alcohol consumption across a cohort. These studies would be problematic and ethically questionable. In the absence of such studies, the existing literature does not currently support a causal relationship between alcohol intake and cardiovascular disease (Hansel et al. 2012). Until such evidence exists, it is unadvisable to recommend that nondrinkers take up drinking to reduce their coronary heart disease risk (Hall 2012).

In conclusion, the evidence for alcohol preventing cardiovascular disease is substantially weaker than that for alcohol causing a range of harms. Any advice regarding alcohol consumption needs to take this into account. On a population level, current safe drinking guidelines reflect this message. On an individual level, patients presenting to clinicians need to receive advice that involves a risk-benefit analysis of the impact of alcohol consumption on an individualized case-by-case basis. Any putative benefits disproportionately apply to middle-aged and older drinkers who have an elevated risk of cardiovascular disease overall. Much of the evidence for deriving benefits from alcohol consumption lie within levels of intake of less than two standard drinks per day, with clear evidence for increased risk associated with consumption above this level. This is a key issue that needs to be considered when discussing alcohol intake with individuals, highlighting the caveat that any putative benefits associated with low to moderate alcohol intake will be significantly outweighed by instances of heavier consumption. Given such a potential low therapeutic window, it is imperative that individuals receive a clear message that excessive alcohol consumption is hazardous to both physical and mental health.

References

Albert, M. A., Glynn, R. J., & Ridker, P. M. (2003). Alcohol consumption and plasma concentration of C-reactive protein. *Circulation, 107*(3), 443–447.

Bagnardi, V., Zatonski, W., Scotti, L., La Vecchia, C., & Corrao, G. (2008). Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis. *Journal of Epidemiology and Community Health, 62*(7), 615–619.

Brien, S. E., Ronksley, P. E., Turner, B. J., Mukamal, K. J., & Ghali, W. A. (2011). Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: Systematic review and meta-analysis of interventional studies. *BMJ [British Medical Journal], 342*, d636.

Butt, P., Beirness, D., Cesa, F., Gliksman, L., Paradis, C., & Stockwell, T. (2011). Alcohol and health in Canada: A summary of evidence and guidelines for low-risk drinking. Ottawa, ON: Canadian Centre on Substance Abuse.

Collins, D. J., & Lapsley, H. M. (2008). *The costs of tobacco, alcohol and illicit drug abuse to Australian society in 2004/05*. Canberra: Department of Health and Ageing.

Corrao, G., Rubbiati, L., Bagnardi, V., Zambon, A., & Poikolainen, K. (2000). Alcohol and coronary heart disease: A meta-analysis. *Addiction, 95*(10), 1505–1523.

Costanzo, S., Di Castelnuovo, A., Donati, M. B., Iacoviello, L., & de Gaetano, G. (2010a). Alcohol consumption and mortality in patients with cardiovascular disease: A meta-analysis. *Journal of the American College of Cardiology, 55*(13), 1339–1347. doi:10.1016/j.jacc.2010.01.006.

Costanzo, S., Di Castelnuovo, A., Donati, M. B., Iacoviello, L., & de Gaetano, G. (2010b). Cardiovascular and overall mortality risk in relation to alcohol consumption in patients with cardiovascular disease. *Circulation, 121*(17), 1951–1959. doi:10.1161/CIRCULATIONAHA.109.865840.

Criqui, M. H., & Ringel, B. L. (1994). Does diet or alcohol explain the French paradox? *The Lancet, 344*(8939), 1719–1723.

Del Boca, F. K., & Darkes, J. (2003). The validity of self-reports of alcohol consumption: state of the science and challenges for research. *Addiction, 98*(s2), 1–12.

Di Castelnuovo, A., Costanzo, S., Bagnardi, V., Donati, M. B., Iacoviello, L., & de Gaetano, G. (2006). Alcohol dosing and total mortality in men and women: An updated meta-analysis of 34 prospective studies. *Archives of Internal Medicine, 166*(22), 2437–2445.

Di Castelnuovo, A., Costanzo, S., Donati, M. B., Iacoviello, L., & de Gaetano, G. (2010). Prevention of cardiovascular risk by moderate alcohol consumption: Epidemiologic evidence and plausible mechanisms. *Internal and Emergency Medicine, 5*(4), 291–297.

Djoussé, L., Ellison, R. C., Beiser, A., Scaramucci, A., D'Agostino, R. B., & Wolf, P. A. (2002). Alcohol consumption and risk of ischemic stroke the Framingham Study. *Stroke, 33*(4), 907–912.

Ellison, R. C. (2005). Importance of pattern of alcohol consumption. *Circulation, 112*(25), 3818–3819.

Fauchier, L. (2003). Alcoholic cardiomyopathy and ventricular arrhythmias. *CHEST Journal, 123*(4), 1320–1320.

Fekjaer, H. O. (2013). Alcohol-a universal preventive agent? A critical analysis. *Addiction, 108*(12), 2051–2057. doi:10.1111/add.12104.

Fillmore, K. M., Kerr, W. C., Stockwell, T., Chikritzhs, T., & Bostrom, A. (2006). Moderate alcohol use and reduced mortality risk: Systematic error in prospective studies. *Addiction Research & Theory, 14*(2), 101–132.

Fillmore, K. M., Stockwell, T., Chikritzhs, T., Bostrom, A., & Kerr, W. (2007). Moderate alcohol use and reduced mortality risk: Systematic error in prospective studies and new hypotheses. *Annals of Epidemiology, 17*(5 Suppl), S16–S23. doi:10.1016/j.annepidem.2007.01.005.

Freiberg, M. S., & Samet, J. H. (2005). Alcohol and coronary heart disease the answer awaits a randomized controlled trial. *Circulation, 112*(10), 1379–1381.

Gaziano, J. M., Buring, J. E., Breslow, J. L., Goldhaber, S. Z., Rosner, B., VanDenburgh, M.,... Hennekens, C. H. (1993). Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *New England Journal of Medicine, 329*(25), 1829–1834.

Goncalves, A., Jhund, P., Claggett, B., Shah, A., Konety, S., Butler, K.,... Solomon, S. (2014). Increasing alcohol consumption is related to detrimental changes in cardiac structure and function. *Journal of the American College of Cardiology, 63*(12_S).

Grønbæk, M., Becker, U., Johansen, D., Gottschau, A., Schnohr, P., Hein, H. O.,... Sørensen, T. I. (2000). Type of alcohol consumed and mortality from all causes, coronary heart disease, and cancer. *Annals of Internal Medicine, 133*(6), 411–419.

Hall, W. (2012). What place, if any, does information on putative cardioprotective effects of moderate alcohol use have in safer drinking guidelines? *Drug and Alcohol Review, 31*(2), 194–197.

Hansel, B., Thomas, F., Pannier, B., Bean, K., Kontush, A., Chapman, M.,... Bruckert, E. (2010). Relationship between alcohol intake, health and social status and cardiovascular risk factors in the urban Paris-Ile-De-France Cohort: Is the cardioprotective action of alcohol a myth & quest. *European Journal of Clinical Nutrition, 64*(6), 561–568.

Hansel, B., Kontush, A., & Bruckert, E. (2012). Is a cardioprotective action of alcohol a myth? *Current Opinion in Cardiology, 27*(5), 550–555. doi:10.1097/HCO.0b013e328356dc30.

Karatzi, K., Papamichael, C., Aznaouridis, K., Karatzis, E., Lekakis, J., Matsouka, C.,... Feliou, G. (2004). Constituents of red wine other than alcohol improve endothelial function in patients with coronary artery disease. *Coronary Artery Disease, 15*(8), 485–490.

Klatsky, A. L. (2010). Alcohol and cardiovascular mortality: Common sense and scientific truth. *Journal of the American College of Cardiology, 55*(13), 1336–1338. doi:10.1016/j.jacc.2009.10.057.

Kloner, R. A., & Rezkalla, S. H. (2007). To drink or not to drink? That is the question. *Circulation, 116*(11), 1306–1317.

Laslett, A.-M., Catalano, P., Chikritzhs, Y., Dale, C., Doran, C., Ferris, J., Jainullabudeen, T., Livingston, M., Matthews, S., Mugavin, J., Room, R., Schlotterlein, M., & Wilkinson, C. (2010). *The range and magnitude of alcohol's harm to others*. Fitzroy: AER Centre for Alcohol Policy Research, Turning Point Alcohol and Drug Centre, Eastern Health.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., Andrews, K. G. (2013). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet, 380*(9859), 2224–2260.

Lucas, D. L., Brown, R. A., Wassef, M., & Giles, T. D. (2005). Alcohol and the cardiovascular system: Research challenges and opportunities. *Journal of the American College of Cardiology, 45*(12), 1916–1924. doi:10.1016/j.jacc.2005.02.075.

Magnus, P., Bakke, E., Hoff, D. A., Høiseth, G., Graff-Iversen, S., Knudsen, G. P.,... Tambs, K. (2011). Controlling for high-density lipoprotein cholesterol does not affect the magnitude of the relationship between alcohol and coronary heart disease. *Circulation, 124*(21), 2296–2302.

Malyutina, S., Bobak, M., Kurilovitch, S., Gafarov, V., Simonova, G., Nikitin, Y., & Marmot, M. (2002). Relation between heavy and binge drinking and all-cause and cardiovascular mortality in Novosibirsk, Russia: A prospective cohort study. *The Lancet, 360*(9344), 1448–1454.

Marmot, M., & Brunner, E. (1991). Alcohol and cardiovascular disease: The status of the U shaped curve. *BMJ [British Medical Journal], 303*(6802), 565.

Mukamal, K. J., Conigrave, K. M., Mittleman, M. A., Camargo, C. A., Jr., Stampfer, M. J., Willett, W. C., & Rimm, E. B. (2003). Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *New England Journal of Medicine, 348*(2), 109–118.

Mukamal, K. J., Ascherio, A., Mittleman, M. A., Conigrave, K. M., Camargo, C. A., Kawachi, I.,... Rimm, E. B. (2005). Alcohol and risk for ischemic stroke in men: The role of drinking patterns and usual beverage. *Annals of Internal Medicine, 142*(1), 11–19.

Mukamal, K. J., Mackey, R. H., Kuller, L. H., Tracy, R. P., Kronmal, R. A., Mittleman, M. A., & Siscovick, D. S. (2007). Alcohol consumption and lipoprotein subclasses in older adults. *Journal of Clinical Endocrinology & Metabolism, 92*(7), 2559–2566.

Mukamal, K. J., Chen, C. M., Rao, S. R., & Breslow, R. A. (2010). Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002. *Journal of the American College of Cardiology, 55*(13), 1328–1335. doi:10.1016/j.jacc.2009.10.056.

Naimi, T. S., Brown, D. W., Brewer, R. D., Giles, W. H., Mensah, G., Serdula, M. K.,... Naimi, S. (2005). Cardiovascular risk factors and confounders among nondrinking and moderate-drinking US adults. *American Journal of Preventive Medicine, 28*(4), 369–373.

Naimi, T. S., Xuan, Z., Brown, D. W., & Saitz, R. (2013). Confounding and studies of 'moderate' alcohol consumption: The case of drinking frequency and implications for low-risk drinking guidelines. *Addiction, 108*(9), 1534–1543. doi:10.1111/j.1360-0443.2012.04074.x.

NHMRC. (2009). *Australian guidelines to reduce health risks from drinking alcohol*. Canberra: Commonwealth Government of Australia.

O'Keefe, J. H., Bybee, K. A., & Lavie, C. J. (2007). Alcohol and cardiovascular health: The razor-sharp double-edged sword. *Journal of the American College of Cardiology, 50*(11), 1009–1014. doi:10.1016/j.jacc.2007.04.089.

Ohsawa, M., & Tanno, K. (2013). Conflicting effect of alcohol on cardiovascular risk: A clue to understand the different etiologies of coronary artery disease, stroke and peripheral artery disease. *Hypertension Research, 36*(1), 16–18. doi:10.1038/hr.2012.152.

Parry, C. D., Patra, J., & Rehm, J. (2011). Alcohol consumption and non-communicable diseases: Epidemiology and policy implications. *Addiction, 106*(10), 1718–1724. doi:10.1111/j.1360-0443.2011.03605.x.

Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types-a systematic review and meta-analysis. *BMC Public Health, 10*(1), 258.

Pearson, T. A. (1996). Alcohol and heart disease. *Circulation, 94*(11), 3023–3025.

Piano, M. R. (2002). Alcoholic cardiomyopathy Incidence, clinical characteristics, and pathophysiology. *CHEST Journal, 121*(5), 1638–1650.

Piano, M. R., & Phillips, S. A. (2014). Alcoholic cardiomyopathy: Pathophysiologic insights. *Cardiovascular Toxicology, 14*(4), 291–308.

Rehm, J., Room, R., Graham, K., Monteiro, M., Gmel, G., & Sempos, C. T. (2003). The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: An overview. *Addiction, 98*(9), 1209–1228. doi:10.1046/j.1360-0443.2003.00467.x.

Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y., & Patra, J. (2009). Alcohol and global health 1. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet, 373*, 2223–2233. doi:10.1016/S0140-6736(12)61766-8.

Renaud, S. d., & de Lorgeril, M. (1992). Wine, alcohol, platelets, and the French paradox for coronary heart disease. *The Lancet, 339*(8808), 1523–1526.

Rimm, E. B., Klatsky, A., Grobbee, D., & Stampfer, M. J. (1996). Review of moderate alcohol consumption and reduced risk of coronary heart disease: Is the effect due to beer, wine, or spirits? *BMJ, 312*(7033), 731–736.

Rimm, E. B., Williams, P., Fosher, K., Criqui, M., & Stampfer, M. J. (1999). Moderate alcohol intake and lower risk of coronary heart disease: Meta-analysis of effects on lipids and haemostatic factors. *BMJ, 319*(7224), 1523–1528.

Roerecke, M., & Rehm, J. (2010). Irregular heavy drinking occasions and risk of ischemic heart disease: A systematic review and meta-analysis. *American Journal of Epidemiology, 171*(6), 633–644. doi:10.1093/aje/kwp451.

Roerecke, M., & Rehm, J. (2011). Ischemic heart disease mortality and morbidity rates in former drinkers: A meta-analysis. *American Journal of Epidemiology, 173*(3), 245–258.

Roerecke, M., & Rehm, J. (2012). The cardioprotective association of average alcohol consumption and ischaemic heart disease: A systematic review and meta-analysis. *Addiction, 107*(7), 1246–1260.

Ronksley, P. E., Brien, S. E., Turner, B. J., Mukamal, K. J., & Ghali, W. A. (2011). Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. *BMJ, 342*, d671. doi:10.1136/bmj.d671.

Ruidavets, J.-B., Ducimetière, P., Evans, A., Montaye, M., Haas, B., Bingham, A.,... Kee, F. (2010). Patterns of alcohol consumption and ischaemic heart disease in culturally divergent countries: The Prospective Epidemiological Study of Myocardial Infarction (PRIME). *BMJ: British Medical Journal, 341*.

Shaper, A. G., Wannamethee, G., & Walker, M. (1988). Alcohol and mortality in British men: Explaining the U-shaped curve. *The Lancet, 332*(8623), 1267–1273.

Sheikh, A. I., Khalif, M. O., & Houmsse, M. (2014). Alcohol consumption and atrial fibrillation: Leisure or suffering? *Ibnosina Journal of Medicine and Biomedical Sciences, 6*(2), 110–113.

Skog, O.-J. (1996). Public health consequences of the J-curve hypothesis of alcohol problems. *Addiction, 91*(3), 325–337.

Soedamah-Muthu, S. S., De Neve, M., Shelton, N. J., Tielemans, S. M., & Stamatakis, E. (2013). Joint associations of alcohol consumption and physical activity with all-cause and cardiovascular mortality. *American Journal of Cardiology, 112*(3), 380–386. doi:10.1016/j.amjcard.2013.03.040.

Stockwell, T., Greer, A., Fillmore, K., Chikritzhs, T., & Zeisser, C. (2012). How good is the science. *BMJ, 344*, e2276.

Taylor, B., Irving, H. M., Baliunas, D., Roerecke, M., Patra, J., Mohapatra, S., & Rehm, J. (2009). Alcohol and hypertension: Gender differences in dose–response relationships determined through systematic review and meta-analysis. *Addiction, 104*(12), 1981–1990.

Thompson, P. L. (2013). J-curve revisited: Cardiovascular benefits of moderate alcohol use cannot be dismissed. *Medical Journal of Australia, 198*(8), 419–422.

WHO. (2009). *Global health risks: Mortality and burden of disease attributable to selected major risks*. Geneva: WHO.

WHO. (2011). *Global status report on alcohol and health*. Geneva: WHO.

WHO. (2014). *Global status report on alcohol and health 2014*. Geneva: WHO.

Part II

Stress, Psychopathology, and Cardiovascular Disease

Stress: Concepts, Models, and Measures

Unni Karin Moksnes and Geir Arild Espnes

Contents

U.K. Moksnes (✉)
Center for Health Promotion Research, Norwegian University of Science and Technology, Trondheim, Norway
e-mail: unni.k.moksnes@ntnu.no

G.A. Espnes
Center for Health Promotion Research, Department of Social Work and Health Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Australian National University, Canberra, ACT, Australia
e-mail: geirae@svt.ntnu.no; geir.arild.espnes@svt.ntnu.no

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_11

Abstract

Most people harbor some perception of the word "stress." When one hears someone mention that they are "under a lot of stress," one has a certain idea of what they mean and experience. Indeed, the word "stress" infuses everyday conversations, providing a term with rich subtexts that explain innumerable problems, ailments, and illnesses of unknown origins. Links between hypertension and stress have for many years constituted the archetypical example of the causal relation between physiological (or clinical) and psychological phenomena. Stressors, both mental and environmental, are today readily identified and reproduced, and one of the most active areas in psychosomatic research has been the investigation of cardiovascular reactivity to mental stress. This chapter addresses the development of various concepts of stress ranging from those of the ancient Greeks to today, as well as how to operationalize and measure stress. Furthermore, the chapter describes models of stress development and how to understand the role of stress in association with health. In this regard, the chapter also focuses on the role of coping and coping resources that influence the stress-health relationship. At the end of the chapter, stress is demonstrably linked to the development of coronary heart disease (CHD).

Keywords

Cannon, Walter • Conservation of Resources (COR) model • Coronary heart disease (CHD) • Diathesis-stress model • Family Heart Study • Galenus, Claudius • General adaptation syndrome (GAS) • Hardiness • Hassles Scale • Hypothalamic-pituitary-adrenal (HPA) cortical axis • Osler, William • Perceived Stress Scale (PSS) • Psychological stress • Resilience • Schedule of Recent Experiences (SRE) • Self-esteem • Selye • Sense of coherence (SOC) • Social Readjustment Rating Scale (SRRS) • Social support • Stockholm Female Coronary Risk Study • Stress • Cannon-Selye tradition • Coping resources • Definition • Perception, cognition, and psychological appraisal • Physiological measures • Psychobiology of stress • Risk factors • Self-report life event scales • Stress-exposure model • Stress-generation model • Tend-and-befriend • Tend-and-befriend • Uplifts Scale

Introduction Theories, Definitions, and Concepts of Stress

Stress is a physical or emotional response to strain, and the human behavior it gives rise to has puzzled researchers for more than a thousand years. The first extant reports of stress's behavioral impact are most commonly traced to the Roman medical doctor Claudius Galenus (129–200AD) (often referred to as Galen in modern texts). A young woman experiencing various inexplicable physical disease symptoms made an appointment with Galen, who examined the woman and found no physical cause for the symptoms she described. During this examination, a person standing nearby began to talk about a young and stunning dancer named Phylades that he had seen dancing on one of the city's stages. At the mention of this dancer's name, the young woman's pulse suddenly became rapid and uneven. Galen uttered

the name of several other dancers, without any observable effect. From this, Galen surmised that the young woman's unease was directly attributable to her unconscious love for the dancer Phylades. Though earlier descriptions exist of both the psychological implications for physical conditions, and the physical impact on psychological states, Galen's observation represents the first known observation of a stressful emotional state's impact on and cause of alternations in physical health.

In modern times, some of the earliest and best descriptions of the same stem from Sir William Osler's studies on the impact of psychological strains on the human heart, and as we will soon see, from Walter Cannon's well-known studies of psychological and physiological disequilibrium.

But what then is stress? How is it defined? What is the uniquely modern concept of stress, and how did we get there? How is the phenomenon best described? And, importantly, how can it be measured?

The Stress Concept and the Development of Understanding

Stress is often defined as the physical and psychological result of internal or external pressures. Research has linked stress to more diseases than any other biopsychological factor. In particular, stress has been connected to the development of CHD. Researchers have been studying stress and its impact on psychological and physical health for several decades. Contributions to the understanding of stress have come from basic neuroscience and biology, as well as from psychology, epidemiology, sociology, and anthropology (Monroe 2008). This broad and multilevel mandate for stress research has given rise to diverse approaches and much debate over the most appropriate ways to define, conceptualize, and measure life stress. Separate research traditions have emphasized different facets of the general topic of stress. One common characteristic of all such definitions is the focus on environmental circumstances and on conditions that threaten, challenge, exceed, or harm the psychological or biological capacities of the individual (Grant et al. 2004). In this sense, all definitions of stress include an environmental component. These definitions differ, however, in the degree to which they emphasize physiological and psychological processes that occur in response to the environmental stressors (Grant et al. 2003).

Research has identified stress as a precursor for the development of other risk factors, particularly hypertension and lipid levels. In recent years, researchers have questioned whether stress is caused by a uniform kind of strain, whether stressors are all the same, and finally, whether stress has the same consequences for both sexes (Weidner et al. 1997, 2001; Taylor et al. 2000).

The Cannon-Selye Tradition

The term "stress" is loosely borrowed from the field of physics. Humans, it is thought, are in some ways analogous to physical objects like metals that resist moderate outside forces but lose their resiliency at a certain point of greater pressure.

Cannon (1932) was likely the first modern stress researcher to apply the concept of stress to humans in these physical terms, and he was principally concerned with the effects on organisms of cold temperatures, a lack of oxygen, and other environmental stressors. Cannon proposed that when an organism perceives a threatening stimulus, the organism's emotional and physiological homeostasis is rapidly aroused and motivated via the sympathetic nervous and endocrine systems (Fleming et al. 1984). This physiological activation results in a fight-or-flight response, which means that the organism either mobilizes to attack the threat or, alternatively, to flee. In this view, stress is a threat response directly related to survival and adaptation. Cannon concluded that while organisms might be capable of withstanding initial and low levels of stressors, prolonged exposure to severe stressors leads to the breakdown of biological systems (Fleming et al. 1984; Taylor et al. 2000).

Alongside Cannon whose work he followed, Selye (1974) is also a prominent person in stress research. Like Cannon, Selye's basic understanding of stress was oriented toward the threat to an organism's homeostasis, but focused to a greater degree than Cannon on a person's emotional and physiological response to *stressors*, which refer to the environmental conditions that elicit stress. Selye also employed the word *strain* to describe the individual's emotional and physiological reactions to stress. Significantly, he also suggested that stress is not necessarily a negative factor to be avoided; in fact, a distinction can be made between positive stress (eustress) and negative stress (distress). In either case, the demand for coping resources is the same (Selye 1974, 1979).

Selye's contributions to stress research included a concept of stress and a model for how the body defends itself in stressful situations. According to Selye (1982, p. 22), stress represents *the nonspecific result of any demand upon the body.* The notion of a "nonspecific" response derives from the claim that all stressors, regardless of type, produce essentially the same pattern of physiological responses, namely, an enlarged adrenal cortex, shrinking of the thymus and lymph glands, and ulceration of the stomach and duodenum. Over time, with repeated or prolonged exposure to stress, the system experiences wear and tear. Based on these observations, Selye (1956) developed his concept of the general adaptation syndrome (GAS).

The GAS consists of three stages: the alarm stage, the resistance stage, and the exhaustion stage (Selye 1956, 1974, 1979, 1982). The *alarm* reaction refers to the fight-or-flight response, in which case the organism is mobilized to meet the threat. During the alarm stage, the body's defenses against a stressor are mobilized through activation of the sympathetic nervous system. In the second, *resistance* stage, the physiological reactions of the alarm stage mobilize energy in order to adapt to or overcome the stressor and obtain homeostasis. The length of this stage depends on the severity of the stressor and the adaptive capacity of the organism. If the organism can adapt, the resistance stage will continue for a long time. However, continuous stress will cause neurological and hormonal changes, which pose risks for the development of various diseases including peptide ulcers, ulcerative colitis, hypertension, and cardiovascular disease. The third stage, that of *exhaustion*, is the result of long-lasting resistance that has sapped the body's energy reservoir, resulting in breakdown. This collapse often results in death. Presumably, this only occurs when the threats persist or are repeated often enough to overwhelm the organism's ability to resist.

This theory implies, first of all, the cumulative nature of the effects of stress. That is, damage produced by stressors accumulates over time. Secondly, these effects are involved in serious pathology when they overwhelm one's ability to cope. Finally, stress may be additive – because the body responds similarly to different threats, an individual's reaction to a threat will be augmented by his or her exposure to previous threats.

Selye has been criticized on two levels. Firstly, a wealth of data challenge the notion that humans react uniformly to stress. The manner in which individuals respond to challenges in their environment can be understood as a function of their personality, constitution, perceptions, and the context in which stressors occur. Secondly, Selye has been criticized for employing somewhat illogical deductive reasoning; he depicted stress in terms of outcome, such that an organism could be seen as under stress only during a phase of the general adaptation sequence (Brannon and Feist 2007).

Perception, Cognition, and Psychological Appraisal

A third view of stress emphasizes the cognitive appraisal of a stressful situation and deems the mediating role of psychological processes between environmental events and the organism's response more important than the stressful event itself (Fleming et al. 1984; Monroe 2008). Implied here is the view that stress is not the product of an imbalance between objective demands and response capacity, but rather of the *perception* of these factors. In addition, the consequences of failing to cope are perceived by the individual as important. Thus, stress is here described as the subjective experience of pressure, implying an evaluation of the outcome of a cognitive process. This view focuses on the degree and type of the challenge, threat, harm, or loss, as well as on the individual's perceived abilities to cope with such stressors (Lazarus and Folkman 1984). The most widely accepted definition of stress, the transactional definition offered by Lazarus and Folkman (1984), accords with this focus on subjective experience: "Psychological stress involves a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" (p. 19). Accordingly, stress is subjective by nature, as it involves an appraisal of individual experiences.

Lazarus and Folkman (1984) recognized that people use different types of appraisal in their assessments of a situation. The individual initially appraises the event itself – this is the primary appraisal – and identifies the event as (1) irrelevant, (2) benign positive, or (3) stressful. In the course of a primary appraisal of stressful circumstances, a secondary appraisal is initiated whereby an individual assesses their own coping abilities and resources, i.e., whether they will be sufficient to meet the harm, threat, or challenge of an event. Ultimately, the subjective experience of stress is a balance between primary and secondary appraisals. The third type of appraisal is reappraisal, which is necessitated by the fact that appraisals change constantly as new information becomes available. Reappraisal does not always result in more

stress; indeed sometimes it decreases stress (Caltabiano et al. 2008). Whether an individual perceives an event as stressful is influenced by two types of factors – those that relate to the person and those that relate to the situation. According to Lazarus (1999), the more confident we are of our capacity to overcome obstacles and dangers, the more likely we are to be challenged rather than threatened and vice versa. An important component of Lazarus' theory of stress is thus the ability or inability to cope with a stressful situation, and one's coping capacity is interwoven with the appraisal process. Whereas at any point in time secondary appraisal is influenced by an individual's perceived ability to cope with the event, over time the actual coping activities and their efficacy contribute significantly to the appraisal process. Theoretically, however, it is important to keep separate the concepts of coping and appraisal (Monroe and Kelly 1995).

People differ with respect to the degree of strain they experience in response to the same stressor, and much of this difference is attributable to individual variations in the cognitive interpretation of stressors (Caltabiano et al. 2008). When we consider stress as a dynamic interaction between the individual and his or her environment, the condition of stress comes into focus as the result of person-environment transactions that lead the individual to perceive a discrepancy between the demands of a situation and the resources available (Caltabiano et al. 2008). The perception, cognition, and psychological appraisal model is important because it nicely integrates the body and the mind and brings together sensory experience with the cognitive processing that follows. The diagram below (adopted from Caltabiano et al. 2008) is a theoretical model describing the linear flow of the transactional process. Upon encountering a stressor, one cognitively interprets the aspects of the current situation alongside evaluations of prior experiences. The possible threat or unpleasantness expected to arise from the encountered situation is thus evaluated. If the situation is threatening to a degree beyond the capacities of the resources easily available, a perceived discrepancy exists (whether the situation is real or not), which results in a stress response. Based on the cognitive evaluation of the possible threat and unpleasantness, the body raises its level of alert and readiness (see the psychobiology of stress later in the chapter). The first reaction is accomplished in an autonomic manner, but the individual also feels distress, the level of which reflects the level of the threat or the expected unpleasantness caused by the situation (Fig. 1).

Tend-and-Befriend

In spite of the fact that the human stress response has often been characterized as one of fight-or-flight, Taylor et al. (2000) have proposed a theory that constitutes a biobehavioral alternative to the fight-or-flight response. Taylor et al. (2000) maintain that as a result of gender differences in the stress response, human female responses are better characterized by a pattern termed "tend-and-befriend." Tending involves nurturing activities designed to protect the self and offspring that promote safety and reduce distress, and befriending is the creation and maintenance of social networks.

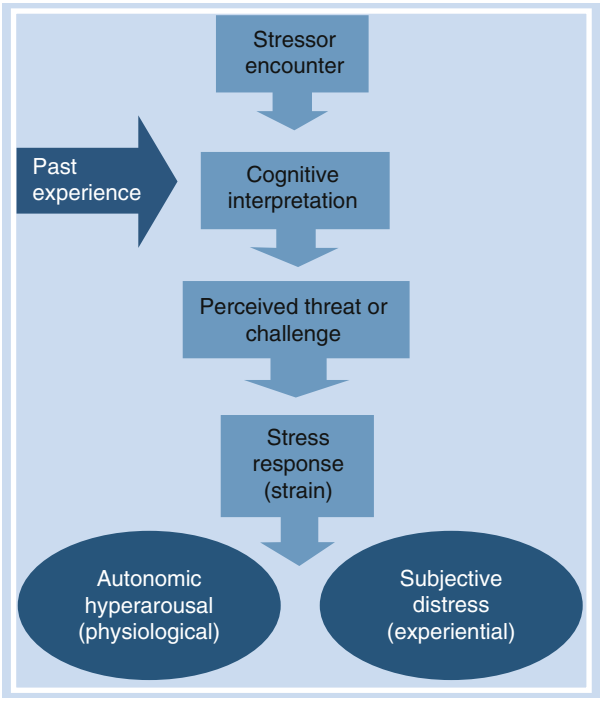


Fig. 1 A simple model to understand the nature of stress (Adopted from Caltabiano et al. (2008) with permission to use the model from author Don G. Byrne)

The biobehavioral mechanism that underlies the tend-and-befriend pattern appears to draw on the attachment-caregiving system and contributes to the development of social groupings, especially those involving female networks, for the further exchange of resources and responsibilities.

The Conservation of Resources

Many of the prominent stress theories have been criticized for not addressing the positive aspects of stress. One exception is the Conservation of Resources (COR) model introduced by Hobfoll (1989), which encompasses several theories of stress, but also extends these theories by employing a resource perspective. Hobfoll (1989) presented this stress model as an attempt to bridge the gap between environmental and cognitive viewpoints. The model's basic tenet is that individuals strive to retain, protect, and build valued resources, the potential or actual loss of which is threatening. These resources are those objects, personal characteristics, conditions, or energies that are valued by the individual or that serve as the means for attaining these objects, personal characteristics, conditions, or energies (Hobfoll 1989). According to this model, stress occurs when resources are lost or threatened. Therefore, when confronted with stressors, individuals will strive to minimize net loss of these resources, and when not stressed, individuals will develop resource surpluses in

order to offset the possibility of future loss. The COR model expands upon previous stress models by not only describing what individuals do when confronted with stress but in the absence of threats, as well.

The Psychobiology of Stress

The model of stress and strain is derived from material technology. Though these phenomena have been recognized for more than two millennia, we have developed the theoretical concepts from the description of what goes on when a metal bar gives in under the weight of heavy strain. As shown earlier in the chapter, this strain/stress concept was eagerly adopted in the early twentieth century by physiological and psychological researchers who focused on what happens when straining situations like diseases or other damages are imposed on the body. Therefore, the signs of stress that we have thus far demonstrated are a mixture of physiological (biological) and psychological symptoms. But the term stress is now more often employed to describe situations on an individual level, or even on the social level, rather than to merely describe challenging situations to the body (Caltabiano et al. 2008).

Everyone experiences stressful situations in their day-to-day lives. Examples might include an exam, a near accident, an actual accident, etc. What is clear in the experience of stress is the fact that it is not only a psychological experience; rather, in stressful situations, one's whole system (all the component physiological and psychological systems) is activated in order to alert the whole organism and allow for the allocation of resources to the part of the organism most capable of addressing the situation. A stressful situation activates the whole range of our biological systems and prepares the body for problem solving, a process often referred to as the physiological arousal. The table below describes the most evident physiological symptoms of bodily arousal that prepare the body and allocate resources during a stressful situation (Table 1).

Table 1 Showing the most evident physiological stress responses

Phenomenon	Action
Heart rate	Raises to accommodate for larger blood flow to areas that need activation
Muscles	Muscle tone is increasing
Blood flow	Less blood directed to the inner organs – more to muscles and skin causes higher skin temperatures and sweating (and rubor)
Urine	In stressful situations, the body sends signals to get rid of what is in the bladder, constrictions, urge to urinate
Cortisol	Level rises. Cortisol is a hormone often called the stress hormone. Is it emitted to help the body cope with damage
Catecholamines	Sets the whole system in an alert situation

Measuring Stress

Given the breadth of the concept of stress and the differing views as to its nature, it is no surprise that a variety of measurement approaches exist. Methodology surrounding the measurement of stress has long been controversial, and this applies just as strongly to the case of adolescent studies as it does to the more widely researched area of adult stress. There are some basic ways to assess stress: one can assess physical arousal, survey or interview individuals as to their life events, or assess the daily hassles that people experience (Monroe 2008).

Physiological Measures

Since the emergence of interest in stressful phenomena, biological factors have provided a strong focal theme. Stress produces physiological arousal, which is reflected in the functioning of many of our body systems. Animal laboratory and human experimental stress studies commonly incorporate biological indicators of stress responses, which have been far less frequent in human field studies regarding life stress. Furthermore, the past decade has witnessed increased interest in the psychobiology of stress and resilience (Caltabiano et al. 2008; Monroe 2008). One way to assess arousal is to measure blood pressure, heart rate, galvanic skin response, and respiration rate. Alternatively, arousal can also be measured by the biomedical analyses of blood, urine, or saliva samples that reveal the level of hormones the adrenal glands secrete profusely during stress. This approach allows for the assessment of two classes of hormones: corticosteroids, the most important of which is cortisol, and catecholamines, which include epinephrine and norepinephrine. In particular, the developmental neurobiology of the hypothalamic-pituitary-adrenal (HPA) cortical axis and the regulation of cortisol have become a major focus of interest among those attempting to understand individual differences with respect to stress reactivity (Brannon and Feist 2008; Monroe 2008).

Findings across the animal, experimental human, and clinical human literatures suggest that early adversity contributes to alterations in the neurobiological systems that regulate stress and in particular to HPA axis functioning. Such alterations have been hypothesized to lead to greater sensitivity in the face of environmental stress, as well as to the development of psychopathology and other disorders (Caltabiano et al. 2008; Monroe 2008; Taylor 2009).

Self-Report Life Event Scales

The vast majority of human life stress studies have assessed recent major events in the lives of individuals. Since the late 1950s and early 1960s, researchers have developed a number of self-report instruments to measure stress. Though the relative merits of interview versus inventory (self-report) approaches have been debated in the case of both adult and adolescent groups, the use of inventories clearly saves both

time and labor and increases the respondents' anonymity (Byrne et al. 2007; Grant et al. 2004). A further strength of the life event inventories as measures of stressor load is illustrated by the fact that the items included on the instruments represent a fairly wide range of stressful events. Such scales assign to each event a value that reflects its stressor intensity (Monroe 2008). The earliest and best known of these self-report procedures is the Schedule of Recent Experiences (SRE) developed by Hawkins, Davies, and Holmes (1957) and the Social Readjustment Rating Scale (SRRS) by Thomas H. Holmes and Richard Rahe (1967; Dohrenwend 2006). These and other derivative self-report checklists include a range of relatively common life experiences that assumedly assess varying degrees of adjustment or implicit life stress. The SRRS, for instance, consists of a list of 43 life events arranged in rank order from the most to the least stressful. The SRRS does not assess whether the changes have been positive or negative, welcomed or unwelcomed, expected or unexpected. Vague or ambiguous items reduce the precision of an instrument and the likelihood of its correlation with other variables (Monroe 2008). As presented by Byrne et al. (2007), the self-report debate also raises the issue of whether to focus on stimulus versus process or response approaches to the measurement of stress. In line with such a debate, the SRRS and other life event inventories have been criticized for their inclusion of life events that may be confounded with measures of illness.

Alternative checklists for the assessment of life events have also been developed. The Perceived Stress Scale (PSS) (Cohen et al. 1983) emphasizes an individual's perception of events. The PSS is a 14-item scale that assesses three components of stress – daily hassles, major events, and changes in coping resources – and attempts to measure the degree to which individuals appraise situations as "unpredictable, uncontrollable, and overloading."

A considerable body of research has directly compared life event checklist measures with interview-based measures. Although the procedures across different studies vary with regard to the specific life event checklist and interview method used, findings consistently point to significant differences in the respective information obtained by the two methods. Interviews are designed to elicit details of what actually happened in order to furnish narratives that can be then rated by trained investigators according to severity and other important characteristics. More generally, reviews of the life event literature nearly unanimously conclude that interview-based measures represent the current gold standard for assessing life stress (Dohrenwend 2006; Gorman 1993; Hammen 2005; Kessler 1997; Mazure 1998; Paykel 2001).

Checklist measures of life events are, by contrast, the traditional and dominant procedure for collecting data and are also the method most frequently employed for assessing stressors affecting children and adolescents. Though the checklists vary with regard to their respective width and depth, the general checklists are all similar, as they present respondents with a sample of negative and, in some cases, positive events that are representative of stressful experiences in childhood and adolescence. Researchers have made some advances in the development and refinement of general stressor checklists for adolescents (Bagley 1993; Cheng 1997; Compas et al. 1987; Masten et al. 1994; Newcomb et al. 1981; Swearingen and Cohen 1985; Yeaworth,

York, Hussey, Ingle, and Goodwin 1980), but less progress in the development of checklists for children (for a review, see Grant et al. 2004). Measures for adolescents have ranged from 39 to more than 200 items, the latter of only limited use in large sample studies of adolescent stress and health. Other stressor checklists used for stress measurement in younger age groups have been derived from existing inventories of adult stressors. However, this approach is unsuccessful because it indirectly equates stressors common in adult life with those central to adolescence, leaving unmeasured certain important areas of adolescent stress.

Researchers typically develop specialized stressor checklists with two related issues in mind: the need for measures specific to particular populations and the need for measures specific to certain types of events. With some notable exceptions, measures of cumulative life stressors have been hitherto largely based on European and American middle-class samples. These measures have drawn criticism for ignoring items pertinent to individuals of other ethnic and social groups, particularly those living in disadvantaged urban communities (Grant et al. 2004).

Daily Hassles

Many of the life events assessed by psychological instruments are rare in occurrence and spread out over the life span. Most inventories attempt to assess stressful life events with traditional checklists that consist of relatively broad life event categories, such as those in the SRRS. However, some more recent investigators have employed checklists that assess "daily hassles" or those stresses that result from minor incidents in everyday life (Caltabiano et al. 2008; Monroe 2008). These ongoing stressors that are a constant feature of our lives may be just as – if not more – damaging to our health than those major life events that occur with less frequency. As a consequence, Richard Lazarus and his associates developed the original Hassles Scale, which consists of 117 items ranging from the merely annoying, irritating, or frustrating ways in which people feel hassled to more major problems and difficulties (Kanner et al. 1981). The subjects indicate which hassles occurred in the past month and identify each event as "somewhat," "moderately," or "extremely" severe. A companion inventory called the Uplifts Scale was designed on the basis that desirable experiences make hassles more bearable and thereby reduce their impact on health (Brannon and Feist 2007; Monroe 2008). Administered along with the Hassles Scale, the Uplifts Scale provides a list of events that might make a person feel good. In addition to checking hassles or uplifts from the past month, respondents also rate the degree of each on a three-point scale. This second assessment is consistent with Lazarus' view that an individual's perception of their stress is more crucial than the objective event itself.

Three common aspects arise in the debate regarding the appropriate methods for life stress measurement. The first concerns memory and the ability of individuals to recall life events (Grant et al. 2004). Somewhat surprisingly, with the proper structuring of questioning, individuals can remember reasonably well. The second

issue of debate relates to the formal definition of a life event. Monroe (2008) suggests that individuals quite often interpret life event descriptors in highly personal ways and that this is a major problem of self-report checklists. Thirdly, research participants draw upon a number of additional sources of background and contextual information when recalling and evaluating stressors. Recognition of these aspects brings into focus just how readily stress measures are influenced by extraneous information or confounded by subjective bias.

Theoretical Models for How Stress Affects Health

It is a widely held notion that stressful and negative life events play an important role in the development of many psychological and physical problems. Researchers have proposed various models to explain how stress may lead to negative health outcomes in the lives of all people, including adolescents.

The stress-exposure model conceptualizes stress as causing maladaptive behavior and negative health outcomes by arguing that a preponderance of stressful life events or perhaps one major stressful life event (e.g., death of a family member) could precede and contribute to an individual becoming depressed or exhibiting maladaptive behavior (Hankin Mermelstein and Roesch 2007). In this regard, stress-exposure models highlight the environmental context of an individual's life and more specifically the effects that stressful environments can have on the lives of young people and adults. Coping resources may be overwhelmed by the experience of multiple changes in close proximity, thus causing the internalization of symptoms or the maladaptation of behavior (Graber and Sontag 2009; Rudolph 2002). In essence, the experience of stressful events and their timing, as well as the increased likelihood that certain events will occur, are the critical factors predicting negative health outcomes in this model.

The stress-generation model focuses on a greater awareness of the complex and reciprocal relation between stress and maladaptive behavior and emotions (Cole et al. 2006). Influenced by the salience of interpersonal vulnerabilities and precipitants in depression, it is employed specifically in relation to depression. That is, while the traditional stress-exposure model very much remains an important focus of research, increasing consideration has also been given to a complimentary and similarly important process, whereby depression-prone individuals are not simply passive respondents to stressful events in their lives, but active agents in the creation of depressogenic life stressors (Hammen 2006).

The diathesis-stress model postulates that major transitions or negative events interact with prior vulnerabilities to psychopathology and result in increased problems or poor outcomes in the face of stressors (Graber and Sontag 2009). According to this model, individuals with certain negative prior vulnerabilities (e.g., poor emotion regulation skills, depressogenic cognitive styles, genetic markers) are disproportionately – or even exclusively – likely to be affected when they experience stressful life events (Hankin and Abrahamson 2001).

Coping with Stress

The manner in which individuals respond to and deal with stress contributes crucially to stress' impact on their physical, emotional, and psychological well-being. Lazarus and Folkman (1984) provide an oft-used definition of coping as "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person" (1984, p. 141). Coping is thus understood as an ongoing process that responds dynamically to the changing demands of a stressful encounter or event. These efforts can be both action oriented and intrapsychic; they seek to manage, tolerate, reduce, or minimize the demands of a stressful situation (Lazarus and Launier 1978, see Taylor and Stanton 2007). As a dynamic transactional process with the environment, the coping process is therefore substantially influenced by an individual's subjective appraisal of the stressful situation.

According to Lazarus and Folkman (1984), coping can serve two main functions: coping can change or alienate the problem that has given rise to the experience of stress or it can regulate the emotional response to that problem. Problem-focused coping aims to reduce the demands of a stressful situation by recourse to action, e.g., to quit one's job, learn new skills, or seek help from a professional. Individuals tend to employ problem-focused approaches when they believe the necessary resources are available. Emotional-focused coping focuses on changing one's own emotional response to a stressful situation, either emotionally or cognitively, and is often used in situations in which individuals believe they do not possess the adequate resources to meet the demands of the stressor. Examples of emotional-focused coping strategies include seeking emotional support from friends and family and engaging in activities that distract or suppress/refuse one's attention, e.g., drinking alcohol, being physically active, or watching a movie. Cognitive approaches emphasize and involve redefinition of the manner in which individuals think about stressful situations. Examples are illustrated by such statements as: "now that I've got this chronic disease, I must try to think positively" or "now that I've lost my job, I realize that I can find one that I really like" (Lazarus 1999; Lazarus and Folkman 1984; Taylor and Stanton 2007).

Coping Resources

As described above, stress alone is insufficient for accurately explaining individual differences in people's health. Even in the face of the very same stressor(s), individuals' stress processes and the impacts of this stress vary substantially and lead to different health outcomes. One's unique response depends on individual and environmental vulnerabilities, as well as on the available coping resources, which themselves affect the coping process and thereby the stress-health relationship (Compas and Reeslund 2009; Grant et al. 2006).

Social support can be defined as the perception or experience that one is loved and cared for by others, esteemed, and valued and part of a social network of mutual

assistance and obligations. Research has demonstrated that during periods of stress, social support can reduce the likelihood of psychological problems like depression or anxiety and promote psychological adjustment to a broad array of chronically stressful conditions (Taylor and Stanton 2007). Social support can influence the stress response in several different ways. In one broad type of instance, a social support network might allow a stressed individual to gain confidence in his or her ability to handle stressful situations; thus, when experiencing stress in the future, this individual might appraise the stressor as less threatening than one would who possessed fewer coping resources.

Resilience is defined as the achievement of a relatively good outcome despite the experience of situations known to carry significant risks for the development of psychopathology (Luthar et al. 2000). Resilience is thus not the mere absence of risk, but rather the presence of protective factors or processes that buffer the effects of adversity. This protection may be the result of individual factors, environmental factors, or interplay between the two. Much of the interest in resilience research is related to the potentially modifiable nature of resilience factors. Studies have found that resilience is a significant predictor of mental health and an effective stress buffer in relation to psychiatric symptoms (Friborg et al. 2006; Hjemdal et al. 2006).

Self-esteem encompasses an individual's set of thoughts and feelings about his or her own worth and importance (Rosenberg 1965), referring to one's "global" or "general" self-worth. Decades of theory and research have underscored the importance of self-esteem by demonstrably linking its positive role in relation to psychological health and well-being. Furthermore, many consider low self-esteem an important factor in relation to symptoms of depression (Orth et al. 2009; Sowislo and Orth 2013). Particularly, when faced with stressful events, individuals with low self-esteem are seen to possess fewer coping resources and are therefore more vulnerable to the development of psychological symptoms, whereas those with high self-esteem are buffered against this effect. According to Orth et al. (2009), "following stressful events, protective factors such as high self-esteem may prevent the outcome of depressive symptoms by decreasing the negative impact of depressogenic thoughts on the affective, cognitive, behavioural, and physiological symptoms of depression" (p. 308). However, previous research that has tested the moderating effect of self-esteem has yielded inconsistent results, highlighting the urgent need for further investigation on this issue (Abela et al. 2006; Orth et al. 2009).

Sense of coherence (SOC) is a concept introduced by Aaron Antonovsky (1987) and denotes the tendency of individuals to see their world as comprehensible, manageable, and meaningful. A strong SOC has been related to the possession of internal resources like optimism and self-efficacy (Lindström and Eriksson 2010). Moreover, a strong SOC is found to be associated with positive perceived health (Eriksson and Lindström 2006; Honkinen et al. 2005), and strongly negatively related to psychological symptoms (Buddeberg-Fischer et al. 2001; Skirka 2000). In stressful situations, researchers have identified SOC's moderating role with respect to negative health outcomes. For individuals with a strong SOC, it is postulated that they will harbor a general confidence in the availability of resources

to meet the demands posed by stressful situations and will thus consider a stressor as more a challenge than a threat. Such confidence increases the likelihood of positive coping expectancies, which consequently prevent stress from turning into potentially harmful tension (Antonovsky 1987). Adults with high SOC appear to cope better under stress than people with a low SOC (Eriksson and Lindström 2006; Gana 2001; Jorgensen et al. 1999; Richardson and Ratner 2005). However, few and inconsistent findings of the stress-moderating role of SOC have been located in the case of adolescent populations (Nielsen and Hansson 2007; Torsheim et al. 2001).

Hardiness, a concept introduced by Kobasa (1979), represents a personality characteristic that significantly affects the relationship between stress and health. Hardiness is characterized by three interrelated attitudes: (1) *Control* refers to an individual's belief that they can influence events in their lives – that is, a sense of personal control. (2) *Commitment* designates an individual's sense of purpose or involvement in the events, activities, and social relationships in their lives. (3) *Challenge* refers to an individual's tendency to view changes as incentives or opportunities for growth, rather than as threats to security. Thus, hardy people believe they exercise control over their experiences, are committed, and perceive changing environments as challenging opportunities for growth. Studies have shown that hardy individuals remain healthier in the face of stress (Delahaij et al. 2010).

Stress and its Linkage to CHD

Though stress and coronary heart diseases will be given more attention in a subsequent chapter, we will nevertheless conclude this discussion by addressing the link between stress and CHD development. The Stockholm Female Coronary Risk Study demonstrated that women who had suffered an episode of CHD exhibited lower heart rate responses to mental stress than their male counterparts (Weidner et al. 2001). In summation of another Swedish study, stress is the main risk factor for the development of CHD in women, and women suffer more problems with home-based stress – that is, stress from within the family – than do men (Balog et al. 2003). These results are supported by the findings of the Family Heart Study (USA), which demonstrated that females experience less job strain from working outside the house than do homemakers and men (Weidner et al. 1997; Ferris et al. 2005) and from studies on burnout (Kinnunen et al. 2006).

A variety of strain situations appear to contribute to stress's role in the production of CHD, including factors marked by membership in a disadvantaged social class, socioeconomic status, or low occupational class. It was suggested above that such stressors may exercise the same effect on CHD development in both males and females (Brezinka and Kittel 1995; Wamela et al. 2001), but more recently there have been indications of differences, as well (e.g., Mobley et al. 2004). Lawlor et al. (2005), in their examination of socioeconomic position through the life course and its association with CHD development in women, illustrate that neither cigarette smoking nor other adult risk factors can fully explain the elevated CHD risk in females from adverse socioeconomic positions. Indeed, it is important to note, as one

study reminds us (Wamala et al. 2001), the cumulative effect of socioeconomic disadvantage. Several other studies are similarly oriented (Gliksman et al. 1995; Galobardes et al. 2006). However, certain results also indicate that adult socioeconomic status may be a more important predictor of morbidity attributable to coronary disease than measures of social status earlier in life (Marmot et al. 2001). In the NHANES III study, for instance, an overrepresentation of CHD development was found among lone mothers (Young et al. 2005) as compared to partnered mothers.

It would seem that psychological stress is caused by various strain situations in the case of both sexes, thereby suggesting quite different CHD pathological outcomes, as well.

Conclusions

This chapter has demonstrated the wide range of studies on stress and stress development and on the health consequences of stress. Investigators continue to research better ways of tuning the definition and operationalization of stress in order to more accurately measure stress levels and its impact on human health. Though the stress concept is understood as one of the most potent pathogenic neurobiopsychological conditions – certainly, it is the most researched – there still exist several mysteries related to its impact on health development. One such mystery concerns the different ways that stress develops and variously impacts health across the two sexes. Though we have noticed differences in stress' paths, processes, and impacts, these are far from thoroughly mapped. The clear differences in the manner in which males and females develop and cope with stress may have a large influence on our understanding of stress, its pathogenic character, and its operationalization and measurement. At the moment, it seems stress research must address a number of new complex research questions in order to more fully understand stress's impact on human health.

References

Abela, J. R. Z., Webb, C. A., Wagner, C., Ho, M. R., & Adams, P. (2006). The role of self-criticism, dependency, and hassles in the course of depressive illness: A multiwave longitudinal study. *Personality and Social Psychology Bulletin, 32*, 328–338.

Antonovsky, A. (1987). *Unraveling the mystery of health. How people manage stress and stay well*. San Francisco: Jossey-Bass.

Bagley, C. (1993). Development of an adolescent stress scale for use by school counsellors. *School Psychology International, 13*, 31–49.

Balog, P., Janszky, I., Leineweber, C., Blom, M., Wamala, S. P., & Orth-Gomer, K. (2003). Depressive symptoms in relation to marital and work stress in women with and without coronary heart disease. The Stockholm Female Coronary Risk Study. *Journal of Psychosomatic Research, 54*, 113–119.

Brannon, L., & Feist, J. (2008). *Health psychology. An introduction to behavior and health*. San Fransisco: Wadsworth.

Brannon, L., & Feist, J. (2007). *Health psychology. An introduction to behavior and health* (6th ed.). Belmont: Wadsworth.

Brezinka, V., & Kittel, F. (1995). Psychological factors of coronary heart disease in women: A review. *Social Science and Medicine, 42*, 1351–1365.

Buddeberg-Fischer, B., Klaghofer, R., & Schnyder, U. (2001). Sense of coherence in adolescents. *Sozial – und Präventivmedizin, 46*, 404–410.

Byrne, D. G., Davenport, S. C., & Mazanov, J. (2007). Profiles of adolescent stress: The development of the adolescent stress questionnaire. *Journal of Adolescence, 30*, 393–416.

Caltabiano, M. L., Sarafino, E. P., & Byrne, D. (2008). *Health psychology. Biopsychosocial interactions*. Singapore: Wiley.

Cannon, W. (1932). The Wisdom of the Body. New York: Norton.

Cheng, C. (1997). Assessment of major life events for Hong Kong adolescents: The Chinese Adolescent Life Event Scale. *American Journal of Community Psychology, 25*, 17–33.

Cohen, S., Kamarack, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24*, 385–396.

Cole, D. A., Nolen-Hoeksema, S., Girgus, J., & Paul, G. (2006). Stress exposure and stress generation in child and adolescent depression: A latent trait-state-error approach to longitudinal analyses. *Journal of Abnormal Psychology, 115*, 40–51.

Compas, B. E., Davis, G. E., Forsythe, C. J., & Wagner, B. M. (1987). Assessment of major and daily stressful events during adolescence: The Adolescent Perceived Event Scale. *Journal of Consulting and Clinical Psychology, 55*, 534–541.

Compas, B. E., & Reeslund, K. L. (2009). Processes of risk and resilience during adolescence. In R. M. Lerner & L. Steinberg (Eds.), *Handbook of adolescent psychology* (3rd ed., pp. 561–588). New Jersey: Wiley.

Delahaij, R., Gaillard, A. W. K., & Dam, K. (2010). Hardiness and the response to stressful situations: Investigating mediating processes. *Personality and Individual Differences, 49*, 386–390.

Dohrenwend, B. P. (2006). Inventory stressful life events as risk factors for psychopathology: Toward resolution of the problem of intracategory variability. *Psychological Bulletin, 132*, 477–495.

Eriksson, M., & Lindström, B. (2006). Antonovsky's sense of coherence scale and the relation with health: A systematic review. *Journal of Epidemiology and Community Health, 60*, 376–381.

Ferris, P. A., Sinclair, C., & Kline, T. J. (2005). It takes two to tango: Personal and organizational resilience as predictors of strain and cardiovascular disease risk in a work sample. *Journal of Occupational Health Psychology, 10*, 225–238.

Fleming, R., Baum, A., & Singer, J. E. (1984). Toward an integrative approach to the study of stress. *Journal of Personality & Social Psychology, 46*, 939–949.

Friborg, O., Hjemdal, O., Rosenvinge, J. H., Martinussen, M., Aslaksen, P. M., & Flaten, M. A. (2006). Resilience as a moderator of pain and stress. *Journal of Psychosomatic Research, 61*, 213–219.

Gana, K. (2001). Is sense of coherence a mediator between adversity and psychological well-being in adults? *Stress and Health, 17*, 77–83.

Galobardes, B., Smith, G. D., & Lynch, J. W. (2006). Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. *Annals of Epidemiology, 16*, 91–104.

Gliksman, M. D., Kawach, I., Hunter, D., Colditz, G. A., Manson, J. E., Stampfer, M. J., Speizer, F. E., Willett, W. C., & Hennekens, C. H. (1995). Childhood socioeconomic status and risk of cardiovascular disease in middle aged US women: A prospective study. *Journal of Epidemiological Community Health, 49*, 10–15.

Gorman, D. M. (1993). A review of studies comparing checklist and interview methods of data collection in life event research. *Behavioral Medicine, 19*, 66–73.

Graber, J. A., & Sontag, L. M. (2009). Internalizing problems during adolescence. In R. M. Lerner & L. Steinberg (Eds.), *Handbook of adolescent psychology.* New Jersey: Wiley.

Grant, K. E., Compas, B. E., Stuhlmacher, A. F., Thurm, A. E., McMahon, S. D., & Halpert, J. A. (2003). Stressors and child and adolescent psychopathology: Moving from markers to mechanisms of risk. *Psychological Bulletin, 129*, 447-466.

Grant, K. E., Compas, B. E., Thurm, A. E., McMahon, S. D., & Gipson, P. Y. (2004). Stressors and child and adolescent psychopathology: Measurement issues and prospective effects. *Journal of Clinical Child and Adolescent Psychology, 33*, 412–425.

Grant, K. E., Compas, B. E., Thurm, A. E., McMahon, S. D., Gipson, P. Y., Campbell, A. J., Krochock, K., & Westerholm, R. I. (2006). Stressors and child and adolescent psychopathology: Evidence of moderating and mediating effects. *Clinical Psychology Review, 26*, 257–283.

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology, 1*, 293–319.

Hammen, C. (2006). Stress generation in depression: Reflections on origins, research, and future directions. *Journal of Clinical Psychology, 62*, 1065–1082.

Hankin, B. L., & Abrahamson, L. Y. (2001). Development of gender differences in depression: An elaborated cognitive vulnerability-transactional stress theory. *Psychological Bulletin, 127*, 773–796.

Hankin, B. L., Mermelstein, R., & Roesch, L. (2007). Sex differences in adolescent depression: Stress exposure and reactivity models. *Child Development, 78*, 279–295.

Hawkins, N. G., Davies, R., & Homes, T. H. (1957). Evidence of psychosocial factors in the development of pulmonary tuberculosis. *American Review of Tuberculosis, 75*, 768–780.

Hjemdal, O., Friborg, O., Stiles, T. C., Martinussen, M., & Rosenvinge, J. H. (2006). A new rating scale for adolescent resilience: Grasping the central protective resources behind healthy development. *Measurement and Evaluation in Counseling and Development, 39*, 84–96.

Hobföll, S. E. (1989). Conservation of resources. A new attempt at conceptualizing stress. *American Psychologist, 44*, 513–524.

Holmes, T. H., & Rahe, R. H. (1967). The social readjustment scale. *Journal of Psychosomatic Research, 11*, 213–218.

Honkinen, P. L. K., Suominen, S. B., Välimaa, R. S., Helenius, H. Y., & Rautava, P. T. (2005). Factors associated with perceived health among 12-year-old school children. Relevance of physical exercise and sense of coherence. *Scandinavian Journal of Public Health, 33*, 35–41.

Jorgensen, R. S., Frankowski, J. J., & Carey, M. P. (1999). Sense of coherence, negative life events and appraisal of physical health among university students. *Personality and Individual Differences, 27*, 1079–1089.

Kanner, A. D., Coyne, J. C., Schaefer, C., & Lazarus, R. S. (1981). Comparison of two modes of stress measurement: Daily hassles and uplifts versus major life events. *Journal of Behavioral Medicine, 4*, 1–39.

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology, 48*, 191–214.

Kinnunen, U., Feldt, T., Geurts, S., & Pulkkinen, L. (2006). Types of work-family interface: Well-being correlates of negative and positive spill over between work and family. *Scandinavian Journal of Psychology, 47*, 149–162.

Kobasa, S. C. (1979). Stressful life events, personality, and health: An inquiry into hardiness. *Journal of Personality and Social Psychology, 37*, 1–11.

Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and coping*. New York: Springer.

Lazarus, R. S. (1999). *Stress and emotion: A new synthesis*. New York: Springer.

Lazarus, R. S., & Launier, R. (1978). Stress-related transactions between person and environment. In L. A. Pervin & M. Lewis (Eds.), *Perspectives in Interactional Psychology* (pp. 87–327). New York: Plenum.

Lindström, B., & Eriksson, M. (2010). *The Hithchiker's guide to salutogenesis*. Helsinki: Folkhalsen Research Centre.

Lawlor, D. A., Ebrahim, S., & Smith, G. D. (2005). Adverse socioeconomic position across the lifecourse increases coronary heart disease risk cumulatively: Findings from the British women's heat and health study. *Journal of Epidemiological Community Health, 59*, 785–793.

Luthar, S. S., Cicchetti, D., & Becker, B. (2000). The construct of resilience: A critical evaluation and guidelines for future work. *Child Development, 71*, 543–562.

Marmot, M., Shipley, M., Brunner, E., & Hemingway, H. (2001). Relative contribution of early life and adult socioeconomic factors to adult morbidity in the Whitehall II study. *Journal of Epidemiology and Community Health, 55*, 301–307.

Masten, A. S., Neeman, J., & Andenas, S. (1994). Life events and adjustment in adolescents: The significance of event independence, desirability, and chronicity. *Journal of Research on Adolescence, 4*, 71–97.

Mazure, C. M. (1998). Life stressors as risk factors in depression. *Clinical Psychology in Science & Practice, 5*, 291–313.

Mobley, L. R., Finkelstein, E. A., Khavjou, O. A., & Will, J. C. (2004). Spatial analysis of Body Mass Index and smoking behavior among WISEWOMAN participants. *Journal of Women's Health, 13*, 519–528.

Monroe, S. M., & Kelly, J. M. (1995). Measurement of stress appraisal. In S. Cohen, R. C. Kessler, & L. U. Gordon (Eds.), *Measuring stress: A guide for health and social sciences* (pp. 122–147). New York: Oxford University Press.

Monroe, S. M. (2008). Modern approaches to conceptualizing and measuring human life stress. *Annual Review of Clinical Psychology, 4*, 33–52.

Newcomb, M. D., Huba, G. J., & Bentler, P. M. (1981). A multidimensional assessment of stressful life events among adolescents: Derivation and correlates. *Journal of Health and Social Behaviour, 22*, 400–415.

Nielsen, A. M., & Hansson, K. (2007). Associations between adolescents' health, stress and sense of coherence. *Stress and Health, 23*, 331–341.

Orth, U., Robins, R. W., & Meier, L. L. (2009). Disentangling the effects of low self-esteem and stressful events on depression: Findings from three longitudinal studies. *Journal of Personality and Social Psychology, 97*, 307–321.

Paykel, E. S. (2001). The evolution of life events research in psychiatry. *Journal of Affective Disorders, 62*, 141–149.

Richardson, C. G., & Ratner, P. (2005). Sense of coherence as a moderator of the effects of stressful life events on health. *Journal of Epidemiology and Community Health, 59*, 979–984.

Rosenberg, M. (1965). *Society and the adolescent self-image*. Princeton: Princeton University Press.

Rudolph, K. D. (2002). Gender differences in emotional responses to interpersonal stress during adolescence. *Journal of Adolescent Health, 30*, 3–13.

Selye, H. (1956). *The stress of life*. New York: McGraw-Hill.

Selye, H. (1974). *Stress without distress*. New York: New American Library.

Selye, H. (1979). The stress concept and some of its implications. In V. Hamilton & D. M. Warburton (Eds.), *Human Stress and Cognition: An Information Processing Approach*. New York: Wiley.

Selye, H. (1982). History and present status of the stress concept. In A. Monat, R. Lazarus (1991) (Eds.). *Stress and coping, an anthology* (3rd ed.). New York: Columbia University Press.

Skirka, N. (2000). The relationship of hardiness, sense of coherence, sport participation, and gender to perceived stress and psychological symptoms among college students. *Journal of Sports Medicine and Physical Fitness, 40*, 63–70.

Sowislo, J., & Orth, U. (2013). Does low self-esteem predict depression and anxiety? A meta-analysis of longitudinal studies. *Psychological Bulletin, 139*, 213–240.

Swearingen, E. M., & Cohen, L. H. (1985). Measurement of adolescents` life events: The junior high life experiences survey. *American Journal of Community Psychology, 13*, 69–85.

Taylor, S. E. (2009). *Health psychology* (7th ed.). New York: McGraw-Hill.

Taylor, S. E., Klein, L., Lewis, B. P., Gruenwald, T. L., Gurung, R. A. R., & Updegraff, J. A. (2000). Biobehavioral responses to stress in females: Tend-and-befriend, not fight-or-flight. *Psychological Review, 107*, 411–429.

Taylor, S. E., & Stanton, A. L. (2007). Coping resources, coping processes, and mental health. *Annual Review of Clinical Psychology, 3*, 377–401.

Torsheim, T., Aaroe, L. E., & Wold, B. (2001). Sense of coherence and school-related stress as predictors of subjective health complaints in early adolescence: Interactive, indirect or direct relationships? *Social Science and Medicine, 53*, 603–614.

Wamela, S. P., Lynch, J., & Kaplan, G. A. (2001). Women's exposure to early and later life socioeconomic disadvantage and coronary heart disease risk: The Stockholm Female Coronary Risk Study. *International Journal of Epidemiology, 30*, 275–284.

Weidner, G., Boughal, T., Connor, S. L., Pieper, C., & Mendell, N. R. (1997). Relationship of job strain to standard coronary risk factors and psychological characteristics in women and men of the Family Heart Study. *Health Psychology, 16*, 239–247.

Weidner, G., Kohlmann, C. W., Horsten, M., Wamala, S. P., Schenck-Gustafsson, K., Hogbom, M., & Orth-Gomer, K. (2001). Cardiovascular reactivity to mental stress in the Stockholm Female Coronary Risk. *Psychosomatic Medicine, 63*(6), 917–924.

Yeaworth, R. C., York, J., Hussey, M. A., Ingle, M. E., & Goodwin, T. (1980). The development of an adolescent life change event scale. *Adolescence, 15*, 91–97.

Young, L. E., Cunningham, S. L., & Buist, D. S. M. (2005). Lone mothers are at higher risk for cardiovascular disease compared with partnered mothers. Data from the National Health and Nutrition Examination Survey III (NHANES III). *Health Care for Women International, 26*, 604–621.

Stress and Cardiovascular Reactivity

Anna C. Phillips

Contents

Abstract

The response of the cardiovascular system to stressful situations has long been considered to have implications for health outcomes. Both exaggerated and diminished cardiovascular reactivity to acute psychological stressors have serious consequences for health. This chapter will compare and discuss research on both high and low cardiovascular responses to psychological stress. Exaggerated reactions are associated with the development of hypertension, markers of systemic atherosclerosis, and cardiovascular disease. Blunted or low reactivity is related to depression, obesity, and a range of addictions. It has been proposed that an interaction between genetics and the environment contributes to individ-

A.C. Phillips (✉)
Health Psychologist and Reader in Behavioural Medicine, School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK
e-mail: A.C.Phillips@bham.ac.uk

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_16

uals' reactivity to stress. The objective of this chapter is to explore cutting-edge research on the pathways to the development of disease via alterations in stress reactivity. It will also highlight some of the key environmental, social, and mechanistic pathways from high and low cardiovascular reactivity to health and ill health in later life and potential research and clinical implications.

Keywords
Acute stress • Blood pressure • Cardiovascular disease • Heart rate • Life events • Stress • Reactivity

Introduction

Individual differences in emotional and physical responses to psychological stress and the consequences of these responses for health have been of interest for some time. One hypothesis which encapsulates how our bodies respond to stress is the "reactivity hypothesis," which has attracted substantial scientific research over the past 30 years. It proposed that large-magnitude cardiovascular reactions to acute psychological stress exposures increased the risk of developing high blood pressure or hypertension (Obrist 1981). It has been expanded subsequently to link high cardiovascular reactivity with other related cardiovascular disease outcomes and even cardiovascular mortality. An implication of this hypothesis is that small or low physiological reactivity to stress would be protective. However, research across the past few years has shown that this is not necessarily the case but that low or blunted cardiovascular responses to stress also have a range of negative health correlates and consequences.

Evidence Linking Stress Reactivity to Cardiovascular Pathology

Cardiovascular reactions to psychological stress are most commonly studied in response to a variety of acute laboratory-based stress tasks such as mental arithmetic under time pressure, cold pressor, memory tasks, mirror tracing, and others. All of these tasks have been shown to elicit considerable heart rate and/or blood pressure reactions via beta- and/or alpha-adrenergic stimulation. Collectively, such studies indicate that high-magnitude hemodynamic reactions to stress confer a modest but reasonably consistent risk for developing high blood pressure, carotid atherosclerosis, and increasing left ventricular mass or hypertrophy of the heart (see, e.g., Lovallo and Wilson 1992; Treiber et al. 2003 for reviews). The most compelling evidence emerges from prospective studies. For example, in the Twenty-07 study in the West of Scotland, large-magnitude cardiovascular reactions to stress predicted an upward drift in blood pressure 5 (Carroll et al. 2003) and 12 years later (Carroll et al. 2011). This has been confirmed in a number of large-scale studies, and both qualitative reviews and meta-analyses of this evidence

confirm the contention that exaggerated stress reactions signal poor future cardiovascular health (see, e.g., Chida and Steptoe 2010; Treiber et al. 2003). More recently, exaggerated cardiovascular responses to acute stress have also been shown to relate to an increased risk of 16-year cardiovascular disease mortality (Carroll et al. 2012).

Stress Exposures and Acute Cardiovascular Events: The Triggering Hypothesis

The associations described above have emerged implicating high reactivity in the etiology of cardiovascular disease. However, acute stress and how we react to it may trigger acute cardiovascular events. A number of epidemiological studies indicate that environmental stressors such as earthquakes, terror attacks, and even the stress associated with watching key soccer matches are associated with increased hospital admissions and mortality from acute cardiovascular events (Carroll et al. 2002). The physiological mechanisms that may account for this link are poorly understood. However, it is likely that elevated levels of hematocrit (the percentage volume of blood that is occupied by red blood cells) and blood viscosity would increase the shear stress on vulnerable atherosclerotic plaques, thereby increasing the likelihood of rupture; acute cardiovascular events, particularly heart attacks, are often the result of plaque rupture and coagulation. Increases in hematocrit or decreases in its converse, plasma volume, have frequently been found with acute psychological stress exposure (see, e.g., de Boer et al. 2006). This suggests that acute psychological stress provokes a "prothrombotic" state and increases the risk of a clot forming in vulnerable individuals precipitating a heart attack or stroke. What is missing is concerted evidence that those who show higher-magnitude reactions in these prothrombotic markers are at particular risk of suffering a cardiovascular event. Thus, there are indications that greater reactivity may constitute a risk for both the development and aggravation of inflammatory disease.

Mediators of Cardiovascular Reactivity and Health Outcomes

High cardiovascular reactivity has also been suggested as a mediator between a wide variety of psychosocial and behavioral risk factors and cardiovascular disease (Chida and Hamer 2008). Further, the scope of the reactivity hypothesis has been expanded to embrace the notion that excessive reactivity may be implicated in non-cardiovascular health outcomes. It is from research examining aspects of this expanded role for reactivity that a number of seemingly paradoxical findings have emerged. Consideration of these areas may point the way for an expanded view of altered stress reactivity and its role in predicting health outcomes.

Cardiovascular Reactivity and Psychological Stress

Given that exaggerated hemodynamic reactivity to acute stress is implicated in the development and expression of cardiovascular disease, as detailed above, it is important to take into account variations in the frequency and/or severity of stress exposures (Carroll and Sheffield 1998; Lynch et al. 1998). The simple assumption here is that it is the product of exposure history and reactivity that confers risk. However, although such a proposition seems reasonable, it does presume that reactivity levels are independent of individuals' histories of exposure to stressful life events. It has been hypothesized, however, that high levels of background stress may be sensitizing, serving to increase hemodynamic reactions to acute stress (Roy et al. 1998). If this were the case, it is possible that variations in stress exposure have already, to an extent, been accounted for in individual differences in acute reactivity. In contrast, a larger number of studies examining the effects of differences in exposure to life events on acute stress reactivity have found a negative relationship, i.e., that high life event exposure is associated with blunting of cardiovascular reactivity. If the stressful experiences serve to blunt reactivity, then a simple multiplicative, stress exposure history x reactivity model would again be problematic. Life event stress (Boyce and Chesterman 1990; Carroll et al. 2005; Musante et al. 2000; Phillips et al. 2005) has been shown to negatively relate to hemodynamic responses to acute stress tasks. Further, among a student sample, individuals with a higher differential between their perceived stress scores relative to their actual stressful life event occurrence scores showed lower pulse rate reactivity to mental arithmetic stress (Ginty and Conklin 2011). There are also a number of studies that have found no relationship between chronic stress and reactivity (see, e.g., Cacioppo et al. 2000). However, many tested small sample sizes, and of the four sizable population studies (Carroll, et al. 2005; Matthews et al. 1997; Musante et al. 2000; Phillips et al. 2005), three showed life event stress to be associated with blunted responses to acute stress. Another issue is that most studies have included fairly minor, and sometimes positive, events in their assessment. However, this would suggest that although exposure to major negative events can induce blunting of acute stress reactivity, the phenomenon is not necessarily restricted to particularly negative stressful experiences.

An explanation for the blunting of responses described above is that of physiological adaptation. The assumption here is that exposure to high-impact life events desensitizes the hemodynamic system, such that when confronted by a further challenge, an acute stress task, individuals experiencing such events will show diminished reactivity. There is certainly evidence that recurrent exposure to acute stress tasks is associated with a habituation of hemodynamic reactivity (see, e.g., Hughes 2007). As individual differences in reactivity to laboratory stress tasks have been shown to be related to variations in reaction in naturalistic settings (Johnston et al. 2008), similar habituation would be expected with "real-life" stressful events. This adaptation or habituation is also evident as blunted stress reactivity among individuals who have experienced stressful events in early life (see, e.g., Lovallo et al. 2012; Trickett et al. 2014). This suggests that stress itself in earlier life can

mold our stress response systems to respond in a certain way later in life, which may have long-term implications for health.

Depression

Depression has been linked prospectively with mortality from cardiovascular disease (Wulsin et al. 1999). The mechanisms underlying this association have yet to be established but might include factors such as socioeconomic position, ill health and disability, and unhealthy behaviors (Wulsin et al. 1999). Exaggerated cardiovascular reactions to psychological stress exposure have also been suggested as a mechanism (Kibler and Ma 2004). With regard to this latter possibility, depression has been associated with a variety of physiological adaptations that suggest altered autonomic function, such as an enhancement of cardiac sympathetic activity relative to vagal tone (Carney et al. 1988). Thus, the hypothesis that such autonomic dysregulation in depression may also be manifest as exaggerated cardiovascular reactivity, which in turn increases the risk of cardiovascular pathology, is intuitively appealing. A meta-analysis of 11 relevant studies found small to moderate effect sizes indicative of a positive relationship between depressive symptomatology and cardiovascular reactions to acute psychology stress (Kibler and Ma 2004). Unfortunately, none of the aggregate effects were statistically significant at conventional levels. Studies generally tested fairly small samples and few adjusted for potential confounding variables such as demographic factors and medication status. In contrast, in a larger sample, higher depressive symptom scores were associated with lower, not higher, cardiovascular reactions to acute psychological stress, even after controlling for a number of likely confounders (York et al. 2007). Similarly, in the West of Scotland Twenty-07 study (Carroll et al. 2007), significant negative associations were observed between depression and reactivity for both SBP and HR. As depressive symptoms were also assessed 5 years later, a prospective analysis was run in which the associations between reactivity and change in depression score over time were assessed. In these analyses, HR reactivity was again negatively associated with depression symptomatology, such that those with lower reactivity were more likely to display an increased depression score 5 years later (Phillips et al. 2011). A similar cross-sectional analysis was conducted in the Dutch Famine Birth Cohort study where SBP, DBP, HR, and cortisol reactivity were all lower in those with mild to severe depression or anxiety symptoms and those who had ever been diagnosed with depression or anxiety (de Rooij et al. 2010).

Thus, it would appear that as putative risk factors for cardiovascular pathology, high levels of depressive symptomatology and exaggerated cardiovascular reactions to stress may operate independently of one another. More recently, it has also been shown that individuals with subclinical depression levels displayed blunted cardiovascular responses to tasks associated with the consequences of punishment and reward in comparison to those with higher depression scores (Brinkmann

et al. 2009). Similarly, depression is also characterized by diminished emotional responsiveness to pleasant stimuli and reward (Bylsma et al. 2008; McFarland and Klein 2009).

Obesity

The reactivity hypothesis has also been considered in the context of physical health problems such as obesity. Obesity is a fast-growing epidemic in Western countries (WHO 1997) with adverse health consequences. Abdominal adiposity has also been linked with psychological distress, and it has been argued that an increased vulnerability to stress in the abdominally obese may be manifest as physiological hyperreactivity. The impact of stress on the neuroendocrine system is thought to promote abdominal fat deposition (Bjorntorp 1996), and it has been suggested that obesity, and especially central adiposity, will be associated with exaggerated cardiovascular reactions to stress (Waldstein et al. 1999). The question arises as to whether obesity and exaggerated cardiovascular reactivity to acute stress are positively related or whether they are independent risk factors for cardiovascular pathology. A few mainly small-scale studies have attempted to address this issue with mixed results (see, e.g., Davis et al. 1999; Waldstein et al. 1999). In the largest study to date, body mass index was not significantly related to cardiovascular reactivity in 225 middle-aged public servants, although waist-hip ratio, a measure of abdominal adiposity, was positively associated with diastolic reactivity (Steptoe and Wardle 2005). In contrast, greater fatness was related to a blunted vasodilatation response to mental stress in 48 healthy young men (Hamer et al. 2007). Further, recently, adiposity was unrelated to cardiovascular or neuroendocrine stress reactivity in a sample of 67 women, although those with larger waists had a greater increase in plasma leptin to stress (Brydon 2011).

It is difficult to draw firm, confident conclusions from the results of these studies, particularly given that most samples were small and poorly representative of the general population and few adjusted for potential confounding variables, including baseline cardiovascular levels. The most consistent result appears to be a positive association between systemic resistance reactivity, as reflected by DBP and/or total peripheral resistance, and abdominal adiposity, although not all studies report this. The West of Scotland Twenty-07 dataset was exploited to explore the association between cardiovascular reactivity and adiposity, both cross-sectionally and prospectively (Carroll et al. 2008). In this study, there was a significant negative association between body mass index and HR reactivity. Obese participants also exhibited much smaller HR reactions to stress than their non-obese counterparts. These associations were independent of age cohort, sex, occupational group, smoking, antihypertensive medication status, baseline cardiovascular levels, and depression. BMI was measured again 5 years later and, as might be expected, had significantly increased. In fully adjusted analyses with obesity at the fourth follow-up as the dependent variable and obesity at the third follow-up as a covariate, lower HR reactivity was associated with an increased risk of becoming obese over the 5 years between follow-ups. More recently, these cross-sectional findings have been

replicated in the Dutch Famine Birth Cohort study and also emerged for cortisol (Phillips et al. 2012). The findings across these two studies seem to mainly hold for HR stress reactivity and not so much for BP stress reactivity. Sympathetic nervous system blockade studies indicate that cardiac reactivity in the context of mental stress reflects β-adrenergic activation (Sherwood et al. 1986; Winzer et al. 1999). Indeed, indices of cardiac reactivity seem to be more sensitive than blood pressure reactivity to β-adrenergic blockade (Sherwood et al. 1986; Winzer et al. 1999), suggesting that cardiac reactivity reflects β-adrenergic activation to a greater extent than blood pressure reactivity. This could explain why the present associations mainly obtain for HR reactivity and hardly for blood pressure reactivity.

There is some other evidence that whereas the obese have elevated sympathetic tone in the resting state, their sympathetic nervous system may be less responsive to stimulation. For example, after ingestion of a meal, there is a postprandial sympathetic nervous system response as reflected by higher plasma norepinephrine concentrations and an increased low- to high-frequency ratio in the heart rate variability spectrum (Tentolouris et al. 2003; Welle et al. 1981). However, this effect has been observed to be much smaller in obese as opposed to lean individuals (Tentolouris et al. 2003). Further, obesity is associated with a state of leptin resistance in humans, and hyperleptinemia is related to lower sympathetic nervous system activity in obese individuals (Quilliot et al. 2008), whereas circulating leptin has been shown to relate to acute stress-induced increases in heart rate in non-obese humans (Brydon et al. 2008). Thus, it is possible that obese individuals become resistant to the sympatho-activating effects of leptin, resulting in blunted reactivity. In sum, these studies suggest that it is low not high cardiac and cortisol reactivity that is related to adiposity. Indeed, low reactivity, possibly by reflecting generally blunted sympathetic nervous system response to acute challenge, may even be a risk marker for developing obesity.

Self-Reported Health

The impact of cardiovascular reactivity on non-cardiovascular health has attracted little research attention. However, if reactivity has wider implications for health, it is likely that it might also be associated with self-reported health. Numerous large-scale prospective epidemiological studies testify that self-reported health predicts various health outcomes including mortality in a dose-response fashion, independently of traditional risk factors and medical status (see, e.g., Idler and Benyamini 1997). If self-reported health is affected by cardiovascular morbidity and its precursory processes, it might be expected to be inversely related to reactivity. It is perhaps curious then that so few studies have examined whether exaggerated cardiovascular reactions to acute stress are associated with poor self-reported health. The exceptions to this rule again are the West of Scotland Twenty-07 study (Phillips et al. 2009) and the Dutch Famine Birth Cohort study (De Rooij and Roseboom 2010). To assess self-reported health, the question presented is generally, “Would you say that for someone your age your own health is. . .” and

given four response options: excellent, good, fair, and poor. Self-reported health at the time of stress reactivity measurement was positively associated with blood pressure reactions to the acute stress task such that participants who reported relatively excellent or good health had larger SBP and DBP reactions than those who reported poor or only fair health (Phillips et al. 2009). Prospective analyses showed that cardiovascular reactivity also predicted the change in health status 5 years later for DBP and HR reactivity. These positive associations indicate that participants exhibiting relatively higher cardiovascular reactivity had better self-reported health 5 years later, independent of their earlier self-reported health. Thus, as with obesity, it was low reactivity that was associated with the poorer health outcomes, even following adjustment for a range of confounders. Supporting cross-sectional data has also been provided from the Dutch Famine Birth Cohort study. Those with large cardiovascular reactions to acute psychological stress reported better health than those with small reactions; the same held true for cortisol reactivity (De Rooij and Roseboom 2010).

Self-reported health is likely to be a function of numerous factors and to depend on the integrity of multiple biological systems, not simply the subjective impact of occult or manifest cardiovascular disease. One system that would appear to be critical in this context is the immune system. Indeed, it has been proposed that what we experience as illness, sickness, and pain is, at least in part, determined by feedback from the immune system to the central nervous system (Maier and Watkins 1998). Further, the acute stress-induced immuno-enhancement hypothesis proposes that acute stress upregulates various aspects of immunity and that this has functional implications for host defense (Dhabhar 2002). However, what about individual differences in reactivity to acute stress? The acute stress-induced immuno-enhancement hypothesis would imply that it would be the most reactive that would reap the greatest immunological dividend. We now have provisional evidence that this might be the case; greater blood pressure reactions toward the end of an acute stress task were characteristic of individuals who mounted a better antibody response to two influenza strains (Phillips et al. 2009). In sum, it would appear that whereas high reactivity contributes to and exacerbates inflammatory cardiovascular disease, low reactivity may compromise immunity and our ability to fight infectious disease and as such be the maladaptive response.

Addictions

Finally, a further focus of research into the health implications of cardiovascular reactivity has been that of substance abuse and addictions. While it may seem intuitive that physiological reactions to psychological stress might have relevance for the onset or progression of cardiovascular disease, it is perhaps less obvious that stress reactivity may similarly be a signal of risk for behavioral disorders, including addictions (Lovallo 2006). A useful starting point for considering this possibility is to restate the observation that behavioral and psychological tendencies are also physiological response characteristics (Lovallo 2005). Therefore, emotional reactions to the environment,

their impact on physiological reactivity, and their health consequences are part of the expanded sense of reactivity and health discussed in this chapter.

There is emerging evidence that low or blunted cortisol and cardiovascular reactivity is characteristic of those with substance dependencies and may indeed be a general marker for risk of addiction (Lovallo 2006). For example, although the act of smoking per se is associated with increases in cardiovascular activity (Pomerleau et al. 1983), habitual smokers have been found to show diminished cardiovascular (Girdler et al. 1997; Phillips et al. 2009; Roy et al. 1994; Sheffield et al. 1997; Straneva et al. 2000) reactions to acute psychological stress. It is unlikely that these effects reflect temporary abstinence during stress testing and its effects on stress task engagement (Girdler et al. 1997). In addition, cardiovascular and cortisol hypo-responsiveness has been found to predict relapse among smokers who have recently quit smoking (al'Absi 2006; al'Absi et al. 2005). Thus, low reactivity not only characterizes those addicted to smoking; it may also be a risk marker of some prognostic significance (Glahn et al. 2007; Lovallo 2006).

Those addicted to alcohol have also been found to exhibit blunted cardiovascular and cortisol stress reactivity (Lovallo et al. 2000; Panknin et al. 2002). In addition, relatively low reactivity would appear to be a characteristic of nonalcoholics with a family history of alcoholism (Sorocco et al. 2006), and offspring of parents addicted to alcohol or drugs showed a blunted cortisol response to stress and were more likely to experiment with cigarettes and marijuana (Moss et al. 1999). The data suggest that blunted reactivity may not only be a characteristic of those with a dependency but it may actually predate the addiction and signal risk of future addiction. Accordingly, in low reactivity, we may have a marker of motivational dysregulation linked to inherited risk of a wide range of addictions (Lovallo 2006). Thus, it is not only high physiological reactivity that can be a risk marker for poor health outcomes; low reactivity would also seem to be implicated.

Further, it is not only substance addictions which appear to correlate with blunted cardiovascular reactivity. Exercise-dependent women, identified through a questionnaire regarding exercise behaviors, showed blunted cardiac and cortisol reactions to a mental arithmetic stress task (Heaney et al. 2011). In a similar study in our laboratory, we also showed that young women with symptoms of bulimia in the disordered eating group showed blunted cortisol, cardiac output, heart rate, and stroke volume reactions to the acute stress compared to controls (Ginty et al. 2011). These effects could not be accounted for in terms of group differences in stress task performance or cardiorespiratory fitness nor comorbid bulimia or exercise dependence, respectively. These results offer further support for the hypothesis that blunted stress reactivity may be a peripheral marker of a central motivational dysregulation in the brain.

Clinical Implications

The prevailing evidence testifies that large-magnitude cardiovascular reactions to acute psychological stress place individuals at risk for the upward drift of resting blood pressure and hypertension. There are also indications that high reactivity

might pose a risk for other manifestations of cardiovascular disease, such as atherosclerosis and increased left ventricular mass. In addition, although there have been no direct tests to date, the pattern of cardiovascular, rheological, and inflammatory changes with psychological stress exposure suggests that they may constitute a prothrombotic state, increasing the likelihood of acute cardiovascular events, such as heart attacks and stroke. However, from tests of the association between reactivity and other health outcomes, a very different picture is starting to emerge. It is low, not high, reactivity that appears to be associated with depression, predicts the development of obesity, and is implicated in poor self-reported health. Further, acute stress exposure, although an issue for inflammatory disease, would appear to enhance other aspects of immunity in a way that may benefit our ability to ward off infection. There is preliminary evidence that those who respond best to a vaccination challenge are also those who show greater cardiovascular and cortisol reactions to stress. Finally, an increasing body of research indicates that low cardiovascular and cortisol reactivity is a characteristic of individuals with an alcohol or tobacco and non-substance dependencies and, indeed, may predict risk of addiction, as well as signaling the likelihood of relapse following abstinence. It would appear that depending on the outcomes in question, departures from the norm in either direction may pose problems, suggesting that in both instances the system is operating in a biased state. The clinical implications of these findings are that both high and low reactivity are detrimental to health, and individuals in either category may be at risk of a range of different but severe health outcomes. While high reactivity should be considered a strong marker of cardiovascular risk, blunted or low reactivity could be indicative of a range of other future negative health outcomes, some of which may also have implications for cardiovascular health, such as smoking, obesity, and depression. Indeed, blunted reactivity may also be of use in clinical settings as a marker of individuals most likely to relapse and thus in need of greater support in addiction cessation or rehabilitation programs.

Conclusion

We have seen that both high and low reactivity are bad for the health depending on the health outcome in question. This could be conceptualized as either an inverted U model of cardiovascular reactivity to stress or a model of continuous positive associations between reactivity and some health outcomes and continuous negative associations between reactivity and other health outcomes. These two models are shown in Fig. 1. The data presented also suggest that the original cardiovascular reactivity hypothesis might be revised to include prediction of pathology from both ends of the continuum of cardiovascular response. This new perspective on reactivity may allow us to expand our conceptual model of how departures from normal physiological response patterns can predict risk for poorer health outcomes. Low, as well as high, reactivity may be bad for our health.

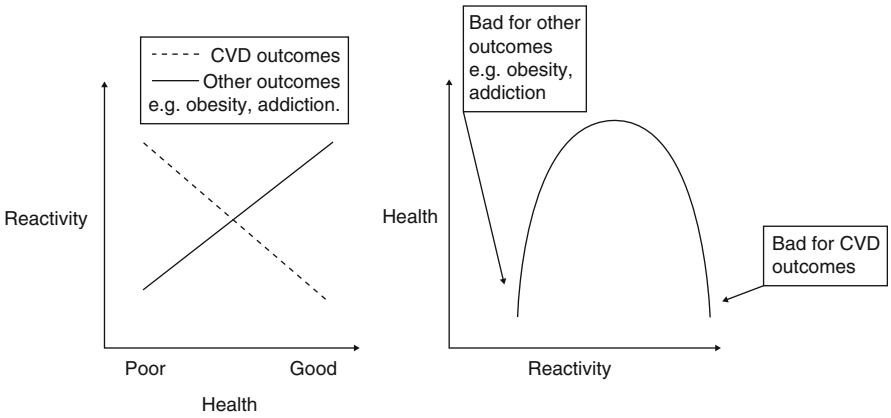


Fig. 1 Conceptualizations of exaggerated and blunted reactivity consequences

References

al'Absi, M. (2006). Hypothalamic-pituitary-adrenocortical responses to psychological stress and risk for smoking relapse. *International Journal of Psychophysiology, 59*(3), 218–227.

al'Absi, M., Hatsukami, D., & Davis, G. L. (2005). Attenuated adrenocorticotropic responses to psychological stress are associated with early smoking relapse. *Psychopharmacology, 181*(1), 107–117.

Bjorntorp, P. (1996). Behavior and metabolic disease. *International Journal of Behavioral Medicine, 3*(4), 285–302.

Boyce, W. T., & Chesterman, E. (1990). Life events, social support, and cardiovascular reactivity in adolescence. *Developmental and Behavioral Pediatrics, 11*, 105–111.

Brinkmann, K., Schupbach, L., Joye, I. A., & Gendolla, G. H. (2009). Anhedonia and effort mobilization in dysphoria: Reduced cardiovascular response to reward and punishment. *International Journal of Psychophysiology, 74*(3), 250–258. doi:10.1016/j.ijpsycho.2009.09.009. [pii]: S0167-8760(09)00229-3.

Brydon, L. (2011). Adiposity, leptin and stress reactivity in humans. *Biological Psychology, 86*(2), 114–120. doi:10.1016/j.biopsycho.2010.02.010. [pii]: S0301-0511(10)00066-9.

Brydon, L., O'Donnell, K., Wright, C. E., Wawrzyniak, A. J., Wardle, J., & Steptoe, A. (2008). Circulating leptin and stress-induced cardiovascular activity in humans. *Obesity (Silver Spring), 16*(12), 2642–2647. doi:10.1038/oby.2008.415. [pii] oby2008415.

Bylsma, L. M., Morris, B. H., & Rottenberg, J. (2008). A meta-analysis of emotional reactivity in major depressive disorder. *Clinical Psychology Review, 28*(4), 676–691.

Cacioppo, J. T., Burleson, M. H., Poehlmann, K. M., Malarkey, W., Kiecolt-Glaser, J. K., Berntson, G. G., et al. (2000). Autonomic and neuroendocrine responses to mild psychological stressors: Effects of chronic stress on older women. *Annals of Behavioral Medicine, 22*, 140–148.

Carney, R. M., Rich, M. W., teVelde, A., Saini, J., Clark, K., & Freedland, K. E. (1988). The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. *Journal of Psychosomatic Research, 32*(2), 159–164.

Carroll, D., & Sheffield, D. (1998). Social psychophysiology, social circumstances, and health. *Annals of Behavioral Medicine, 20*, 333–337.

Carroll, D., Ebrahim, S., Tilling, K., Macleod, J., & Smith, G. D. (2002). Admissions for myocardial infarction and World Cup football: Database survey. *BMJ, 325*(7378), 1439–1442.

Carroll, D., Ring, C., Hunt, K., Ford, G., & Macintyre, S. (2003). Blood pressure reactions to stress and the prediction of future blood pressure: Effects of sex, age, and socioeconomic position. *Psychosomatic Medicine, 65*, 1058–1064. doi:10.1097/01.PSY.0000097330.58739.26.

Carroll, D., Phillips, A. C., Ring, C., Der, G., & Hunt, K. (2005). Life events and hemodynamic stress reactivity in the middle-aged and elderly. *Psychophysiology, 42*, 269–276.

Carroll, D., Phillips, A. C., Hunt, K., & Der, G. (2007). Symptoms of depression and cardiovascular reactions to acute psychological stress: Evidence from a population study. *Biological Psychology, 75*, 68–74.

Carroll, D., Phillips, A. C., & Der, G. (2008). Body mass index, abdominal adiposity, obesity, and cardiovascular reactions to psychological stress in a large community sample. *Psychosomatic Medicine, 70*(6), 653–660. doi:10.1097/PSY.0b013e31817b9382. [pii]: PSY.0b013e31817b9382.

Carroll, D., Phillips, A. C., Der, G., Hunt, K., & Benzeval, M. (2011). Blood pressure reactions to acute mental stress and future blood pressure status: Data from the 12-year follow-up of the West of Scotland study. *Psychosomatic Medicine, 73*(9), 737–742. doi:10.1097/PSY.0b013e3182359808. [pii]: PSY.0b013e3182359808.

Carroll, D., Ginty, A. T., Der, G., Hunt, K., Benzeval, M., & Phillips, A. C. (2012). Increased blood pressure reactions to acute mental stress are associated with 16-year cardiovascular disease mortality. *Psychophysiology, 49*(10), 1444–1448. doi:10.1111/j.1469-8986.2012.01463.x.

Chida, Y., & Hamer, M. (2008). Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: A quantitative review of 30 years of investigations. *Psychological Bulletin, 134*(6), 829–885.

Chida, Y., & Steptoe, A. (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: A meta-analysis of prospective evidence. *Hypertension, 55*(4), 1026–1032. doi:10.1161/HYPERTENSIONAHA.109.146621. [pii] HYPERTENSIONAHA.109.146621.

Davis, M. C., Twamley, E. W., Hamilton, N. A., & Swan, P. D. (1999). Body fat distribution and hemodynamic stress responses in premenopausal obese women: A preliminary study. *Health Psychology, 18*(6), 625–633.

de Boer, D., Ring, C., & Carroll, D. (2006). Time course and mechanisms of hemoconcentration in response to mental stress. *Biological Psychology, 72*(3), 318–324.

De Rooij, S. R., & Roseboom, T. J. (2010). Further evidence for an association between self-reported health and cardiovascular as well as cortisol reactions to acute psychological stress. *Psychophysiology, 47*(6), 1172–1175. doi:10.1111/j.1469-8986.2010.01023.x. [pii]: PSYP1023.

de Rooij, S. R., Schene, A. H., Phillips, D. I., & Roseboom, T. J. (2010). Depression and anxiety: Associations with biological and perceived stress reactivity to a psychological stress protocol in a middle-aged population. *Psychoneuroendocrinology, 35*(6), 866–877. doi:10.1016/j.psyneuen.2009.11.011. [pii]: S0306-4530(09)00354-0.

Dhabhar, F. S. (2002). Stress-induced augmentation of immune function – The role of stress hormones, leukocyte trafficking, and cytokines. *Brain, Behavior, and Immunity, 16*(6), 785–798.

Ginty, A. T., & Conklin, S. M. (2011). High perceived stress in relation to life events is associated with blunted cardiac reactivity. *Biological Psychology, 86*(3), 383–385. doi:10.1016/j.biopsycho.2011.01.002. [pii]: S0301-0511(11)00005-6.

Ginty, A. T., Phillips, A. C., Higgs, S., Heaney, J. L., & Carroll, D. (2011). Disordered eating behaviour is associated with blunted cortisol and cardiovascular reactions to acute psychological stress. *Psychoneuroendocrinology*. doi:10.1016/j.psyneuen.2011.09.004. [pii]: S0306-4530(11)00274-5.

Girdler, S. S., Jamner, L. D., Jarvik, M., Soles, J. R., & Shapiro, D. (1997). Smoking status and nicotine administration differentially modify hemodynamic stress reactivity in men and women. *Psychosomatic Medicine, 59*(3), 294–306.

Glahn, D. C., Lovallo, W. R., & Fox, P. T. (2007). Reduced amygdala activation in young adults at high risk of alcoholism: Studies from the Oklahoma family health patterns project. *Biological Psychiatry, 61*(11), 1306–1309.

Hamer, M., Boutcher, Y. N., & Boutcher, S. H. (2007). Fatness is related to blunted vascular stress responsivity, independent of cardiorespiratory fitness in normal and overweight men. *International Journal of Psychophysiology, 63*(3), 251–257.

Heaney, J. L., Ginty, A. T., Carroll, D., & Phillips, A. C. (2011). Preliminary evidence that exercise dependence is associated with blunted cardiac and cortisol reactions to acute psychological stress. *International Journal of Psychophysiology, 79*(2), 323–329. doi:10.1016/j.ijpsycho.2010.11.010. [pii]: S0167-8760(10)00756-7.

Hughes, B. M. (2007). Social support in ordinary life and laboratory measures of cardiovascular reactivity: Gender differences in habituation-sensitization. *Annals of Behavioral Medicine, 34*(2), 166–176. doi:10.1080/08836610701566860.

Idler, E. L., & Benyamini, Y. (1997). Self-rated health and mortality: A review of twenty-seven community studies. *Journal of Health and Social Behavior, 38*(1), 21–37.

Johnston, D. W., Tuomisto, M. T., & Patching, G. R. (2008). The relationship between cardiac reactivity in the laboratory and in real life. *Health Psychology, 27*(1), 34–42. doi:10.1037/0278-6133.27.1.34. [pii]: 2008-00647-006.

Kibler, J. L., & Ma, M. (2004). Depressive symptoms and cardiovascular reactivity to laboratory behavioral stress. *International Journal of Behavioural Medicine, 11*, 81–87.

Lovallo, W. R. (2005). Cardiovascular reactivity: Mechanisms and pathways to cardiovascular disease. *International Journal of Psychophysiology, 58*, 119–132.

Lovallo, W. R. (2006). Cortisol secretion patterns in addiction and addiction risk. *International Journal of Psychophysiology, 59*(3), 195–202.

Lovallo, W. R., & Wilson, M. F. (1992). The role of cardiovascular reactivity in hypertension risk. In J. R. Turner, A. Sherwood, & K. C. Light (Eds.), *Individual differences in cardiovascular response to stress*. New York: Plenum.

Lovallo, W. R., Dickensheets, S. L., Myers, D. A., Thomas, T. L., & Nixon, S. J. (2000). Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. *Alcoholism: Clinical and Experimental Research, 24*(5), 651–658.

Lovallo, W. R., Farag, N. H., Sorocco, K. H., Cohoon, A. J., & Vincent, A. S. (2012). Lifetime adversity leads to blunted stress axis reactivity: Studies from the Oklahoma family health patterns project. *Biological Psychiatry, 71*(4), 344–349. doi:10.1016/j.biopsych.2011.10.018. [pii]: S0006-3223(11)00999-1.

Lynch, J. W., Everson, S. A., Kaplan, G. A., Salonen, R., & Salonen, J. T. (1998). Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? *American Journal of Public Health, 88*(3), 389–394. doi:10.2105/AGPH.88.3.389.

Maier, S. F., & Watkins, L. R. (1998). Cytokines for psychologists: Implications of bidirectional immune-to-brain communication for understanding behaviour, mood and cognition. *Psychological Review, 105*, 83–107.

Matthews, K. A., Gump, B. B., Block, D. R., & Allen, M. T. (1997). Does background stress heighten or dampen children's cardiovascular responses to acute stress. *Psychosomatic Medicine, 59*, 488–496.

McFarland, B. R., & Klein, D. N. (2009). Emotional reactivity in depression: Diminished responsiveness to anticipated reward but not to anticipated punishment or to nonreward or avoidance. *Depression and Anxiety, 26*(2), 117–122.

Moss, H. B., Vanyukov, M., Yao, J. K., & Kirillova, G. P. (1999). Salivary cortisol responses in prepubertal boys: The effects of parental substance abuse and association with drug use behavior during adolescence. *Biological Psychiatry, 45*(10), 1293–1299.

Musante, L., Treiber, F. A., Kapuku, G., Moore, D., Davis, H., & Strong, W. B. (2000). The effects of life events on cardiovascular reactivity to behavioural stressors as a function of socioeconomic status, ethnicity, and sex. *Psychosomatic Medicine, 62*, 760–767.

Obrist, P. (1981). *Cardiovascular psychophysiology: A perspective*. New York: Plenum.

Panknin, T. L., Dickensheets, S. L., Nixon, S. J., & Lovallo, W. R. (2002). Attenuated heart rate responses to public speaking in individuals with alcohol dependence. *Alcoholism: Clinical and Experimental Research, 26*(6), 841–847.

Phillips, A. C., Carroll, D., Ring, C., Sweeting, H., & West, P. (2005). Life events and acute cardiovascular reactions to mental stress: A cohort study. *Psychosomatic Medicine, 67*, 384–392.

Phillips, A. C., Carroll, D., Burns, V. E., & Drayson, M. (2009a). Cardiovascular activity and the antibody response to vaccination. *Journal of Psychosomatic Research, 67*(1), 37–43. doi:10.1016/j.jpsychores.2008.12.002. [pii]: S0022-3999(08)00580-1.

Phillips, A. C., Der, G., & Carroll, D. (2009b). Self-reported health and cardiovascular reactions to psychological stress in a large community sample: Cross-sectional and prospective associations. *Psychophysiology, 46*(5), 1020–1027. doi:10.1111/j.1469-8986.2009.00843.x. [pii]: PSYP843.

Phillips, A. C., Der, G., Hunt, K., & Carroll, D. (2009c). Haemodynamic reactions to acute psychological stress and smoking status in a large community sample. *International Journal of Psychophysiology, 73*, 273–278.

Phillips, A. C., Hunt, K., Der, G., & Carroll, D. (2011). Blunted cardiac reactions to acute psychological stress predict symptoms of depression five years later: Evidence from a large community study. *Psychophysiology, 48*(1), 142–148. doi:10.1111/j.1469-8986.2010.01045.x. [pii]: PSYP1045.

Phillips, A. C., Roseboom, T. J., Carroll, D., & de Rooij, S. R. (2012). Cardiovascular and cortisol reactions to acute psychological stress and adiposity: Cross-sectional and prospective associations in the Dutch Famine Birth Cohort Study. *Psychosomatic Medicine, 74*(7), 699–710. doi:10.1097/PSY.0b013e31825e3b91. [pii]: PSY.0b013e31825e3b91.

Pomerleau, O. F., Fertig, J. B., Seyler, L. E., & Jaffe, J. (1983). Neuroendocrine reactivity to nicotine in smokers. *Psychopharmacology, 81*(1), 61–67.

Quilliot, D., Bohme, P., Zannad, F., & Ziegler, O. (2008). Sympathetic-leptin relationship in obesity: Effect of weight loss. *Metabolism, 57*(4), 555–562. doi:10.1016/j.metabol.2007.11.020. [pii]: S0026-0495(07)00414-3.

Roy, M. P., Steptoe, A., & Kirschbaum, C. (1994). Association between smoking status and cardiovascular and cortisol stress responsivity in healthy young men. *International Journal of Behavioral Medicine, 1*(3), 264–283.

Roy, M. P., Steptoe, A., & Kirschbaum, C. (1998). Life events and social support as moderators of individual differences in cardiovascular and cortisol reactivity. *Journal of Personality and Social Psychology, 75*, 1273–1281.

Sheffield, D., Smith, G. D., Carroll, D., Shipley, M. J., & Marmot, M. G. (1997). The effects of recent food, alcohol, and tobacco intake and the temporal scheduling of testing on cardiovascular activity at rest and during psychological stress. *Psychophysiology, 34*(2), 204–212.

Sherwood, A., Allen, M. T., Obrist, P. A., & Langer, A. W. (1986). Evaluation of beta-adrenergic influences on cardiovascular and metabolic adjustments to physical and psychological stress. *Psychophysiology, 23*(1), 89–104.

Sorocco, K. H., Lovallo, W. R., Vincent, A. S., & Collins, F. L. (2006). Blunted hypothalamic-pituitary-adrenocortical axis responsivity to stress in persons with a family history of alcoholism. *International Journal of Psychophysiology, 59*(3), 210–217.

Steptoe, A., & Wardle, J. (2005). Cardiovascular stress responsivity, body mass and abdominal adiposity. *International Journal of Obesity, 29*(11), 1329–1337.

Straneva, P., Hinderliter, A., Wells, E., Lenahan, H., & Girdler, S. (2000). Smoking, oral contraceptives, and cardiovascular reactivity to stress. *Obstetrics and Gynecology, 95*(1), 78–83.

Tentolouris, N., Tsigos, C., Perea, D., Koukou, E., Kyriaki, D., Kitsou, E., et al. (2003). Differential effects of high-fat and high-carbohydrate isoenergetic meals on cardiac autonomic nervous system activity in lean and obese women. *Metabolism, 52*(11), 1426–1432.

Treiber, F. A., Kamarck, T., Schneiderman, N., Sheffield, D., Kapuku, G., & Taylor, T. (2003). Cardiovascular reactivity and development of preclinical and clinical disease states. *Psychosomatic Medicine, 65*, 46–62.

Trickett, P. K., Gordis, E., Peckins, M. K., & Susman, E. J. (2014). Stress reactivity in maltreated and comparison male and female young adolescents. *Child Maltreatment, 19*(1), 27–37. doi:10.1177/1077559513520466. [pii]: 1077559513520466.

Waldstein, S. R., Burns, H. O., Toth, M. J., & Poehlman, E. T. (1999). Cardiovascular reactivity and central adiposity in older African Americans. *Health Psychology, 18*(3), 221–228.

Welle, S., Lilavivat, U., & Campbell, R. G. (1981). Thermic effect of feeding in man: Increased plasma norepinephrine levels following glucose but not protein or fat consumption. *Metabolism, 30*(10), 953–958.

WHO. (1997). *Obesity: Preventing and managing the global epidemic*. Geneva: World Health Organisation.

Winzer, A., Ring, C., Carroll, D., Willemsen, G., Drayson, M., & Kendall, M. (1999). Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: Effects of beta-adrenergic blockade. *Psychophysiology, 36*(5), 591–601. doi:10.1111/1469-8986.3650591.

Wulsin, L. R., Vaillant, G. E., & Wells, V. E. (1999). A systematic review of the mortality of depression. *Psychosomatic Medicine, 61*(1), 6–17.

York, K. M., Hassan, M., Li, Q., Li, H., Fillingim, R. B., & Sheps, D. S. (2007). Coronary artery disease and depression: Patients with more depressive symptoms have lower cardiovascular reactivity during laboratory-induced mental stress. *Psychosomatic Medicine, 69*(6), 521–528.

Depression and Cardiovascular Disease: Psychobiological Mechanisms

Arup Kumar Dhar, Gavin William Lambert, and David Anthony Barton

Contents

Abstract

Both major depression and cardiovascular disease are leading causes of burden of disease worldwide. Major depression is common in those suffering cardiovascular disease, and likewise cardiovascular disease is common in those suffering major depression. This chapter aims to look at the association between the two and the underlying biological mechanisms that link them. There now is vast evidence indicating that major depression is a risk factor for the development of coronary heart disease. The mechanisms involved are numerous and certainly multifactorial. These include behavioral and lifestyle factors, the sympathetic

A.K. Dhar (✉) • G.W. Lambert • D.A. Barton
Human Neurotransmitters Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Faculty of Medicine, Nursing Health Sciences, Monash University, Melbourne, VIC, Australia
e-mail: arup.dhar@bakeridi.edu.au; gavin.lambert@bakeridi.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_9

nervous system, platelet function, and the autoimmune and inflammatory systems. Of importance is that major depression increases the mortality in those suffering coronary heart disease. Until recently it was thought that this increased mortality could be explained by the increased co-occurrence of classical cardiac risk factors such as hypertension, diabetes, smoking, and dyslipidemia. It has now been shown that major depression is itself an independent risk factor. There is obvious need to understand the neurobiological mechanisms underpinning both of these disease processes. This would hopefully aid the development of better treatments of these diseases.

Keywords
Cardiovascular disease • Depression • Myocardial infarction • Platelet function • Sympathetic nervous system

Major depression is the third leading cause of disease burden worldwide and is predicted to be the leading cause by 2030 (Chavez et al. 2012). Cardiovascular disease is a prominent concern for people, and therefore it is important to identify causal mechanisms so that prevention and treatment strategies can be developed (Newson et al. 2010). The lifetime prevalence of depression is in the order of 17 %. Major depression is highly prevalent in cardiac patients, with 20–40 % of patients meeting criteria for major depressive disorder (Celano and Huffman 2011). When physical illness and depression occur together, the overall outcome for both diseases is worse.

Depression and coronary artery disease are conditions that both significantly decrease quality of life for the patient and impose a significant economic burden on society (Zellweger et al. 2004). Health- care costs are higher and health-related quality of life is lower in depressed patients in coronary artery disease (Summers et al. 2010), and thus the adequate treatment of both condition is important not only from a clinical but also from a service provision perspective. The possible mechanisms for increased risk of developing heart disease, in those with depression, are varied and complicated.

Evidence Linking Depression with an Increased Risk of Developing Heart Disease

There is now convincing evidence linking depression and cardiovascular disease. Major depression is an independent risk factor for developing heart disease and in an otherwise healthy person doubles the risk of developing coronary heart disease (Srinivasan 2011). It has been shown that when other risk factors (e.g., smoking) for ischemic heart disease were controlled for, depression independently predicted fatal and nonfatal ischemic heart disease. A meta-analysis of 11 studies found that

subjects suffering major depression had an overall relative risk of 1.64 for developing ischemic heart disease compared to nondepressed subjects (Katon et al. 2004). Also the prevalence rates of major depressive disorders in various cardiac conditions are significantly higher than the frequencies that can be expected in a healthy population (Kapfhammer 2011). The relative risk of developing coronary heart disease is proportional to the severity of the depression. Atherosclerosis, the underlying process leading to vascular events, has been associated with depression. Participants in a study who screened positive on the American Health Association depression protocol had a 55 % greater risk of cardiac events than those who screened negative (Elderon et al. 2011). A meta-analysis of studies published between 1945 and 1985 on psychosocial predictors of coronary artery disease concluded that depression is the main psychosocial risk factor for cardiovascular disease (Serrano et al. 2011).

Evidence for Increased Risk of Death After a Myocardial Infarction

Depression increases the risk of cardiac mortality and morbidity in patients with coronary heart disease. Major depression in patients with existing ischemic heart disease confers a relative risk between 1.5 and 2.5 for cardiac morbidity and mortality (Lett et al. 2004). Patients with major depression are at greater cardiac risk of cardiac death in the first few months after a myocardial infarction (Ziegelstein et al. 2000), and in fact much of the mortality risk appears to be in the first 6 months post-myocardial infarction (Jiang et al. 2002). The impact of major depression on mortality in ischemic heart disease seems to be at least equivalent to that of left ventricular dysfunction (Frasure-Smith et al. 1993). It has been shown in men assessed 2 months after acute coronary syndrome that major depression is a prognostic factor for a major adverse cardiac event over 2 years. The mortality risk in patients with ischemic heart disease appears to be proportionate to the severity of the depression. Depression sustained after acute coronary syndrome is also associated with worse cardiac outcomes (Zuidersma et al. 2011). Among survivors of acute myocardial infarction, up to 20 % meet diagnostic criteria for major depression, the presence of which carries a fivefold increase risk of cardiac death within 6 months (Lange-Asschenfeldt and Lederbogen 2011). It has been shown that affective disorders are differentially associated with poorer post-cardiac surgery outcomes independent of cardiac surgery morbidity risk factors. Similar findings of high mortality in subjects with unstable angina and comorbid major depression have been shown (Srinivasan 2011). Major depression is common following an episode of unstable angina, with rates of 35–45 %, is associated with an increased risk of major cardiac events during the following year, and has been found to increase the risk of cardiac death more than fourfold (Lespérance et al. 2000).

Possible Mechanisms for Increased Risk of Developing Heart Disease and Death Post- myocardial Infarction, in Those with Depression

Various candidate mechanisms might explain how depression increases the risk for coronary artery disease and subsequent cardiac mortality and morbidity. Some of these include behavioral and lifestyle factors, the sympathetic nervous system, platelet function, and autoimmune and inflammatory mechanisms.

Behavioral and Lifestyle Factors

One of the pathways mediating the effects of depression on cardiac prognosis is behavioral and acts by making depressed coronary artery disease patients more susceptible to the coronary artery disease risks (Ormel and de Jonge 2011). Depression puts patients twice at risk for nonadherence with prescribed therapies (DiMatteo et al. 2000). A person suffering from major depression is more likely to have maladaptive coping skills. It has been shown that those patients who suffer from depression reported lower adherence to a low-fat diet, regular exercise, reducing stress, and medications. These factors contribute to the lethal properties of depression in cardiovascular disease. This lower adherence may explain why some depressed patients have poorer prognosis post-myocardial infarction. Depression is associated with less frequent modification of lifestyle, and patients present with an unhealthier lifestyle specifically relating to nutrition, smoking, and physical activity. Not only do depressed patients have higher rates of smoking, they are also less likely to give up (John et al. 2004). A meta-analysis has shown that depression is a risk factor for obesity, which of course in turn is a risk factor for metabolic syndrome and cardiovascular disease (Stapelberg et al. 2011). Heavier alcohol use is also seen in patients suffering from major depression. Regarding cardiac rehabilitation, it has been shown that rates of noncompletion were 44.2 % and 28.9 % and rates of nonadherence were 53.0 % and 34.9 % for those with and without major depressive disorder (Swardfager et al. 2011).

Sympathetic Nervous System

Sympathetic hyperactivity has been implicated in increased cardiovascular morbidity and mortality in people suffering major depression (Carney et al. 1995). Studies have shown elevated resting heart rates in patients who suffered major depression and have ischemic heart disease, compared to nondepressed patients (Brown et al. 2009).

It has been demonstrated that cardiac sympathetic activity in patients with major depressive disorder follows a bimodal distribution, with values being very high in some patients and very low in others. Those with secondary panic disorder have

been shown to have higher mean noradrenaline spillover compared to those without secondary panic disorder.

It has also been shown that sympathetic nervous activity is regionalized in that in depressed patients cardiac and total sympathetic activity is raised while muscle sympathetic activity is not. It is suggested that reduced removal of noradrenaline from the sympathetic synapse after its release in the heart, subsequently augmenting the sympathetic neural signal, could be an important causal factor in generating cardiac risk (Barton et al. 2007).

Platelet Function

Depression is associated with mechanisms that promote atherosclerosis (Frasure-Smith and Lespérance 2008). Antiplatelet medication has long been used for secondary prevention in coronary heart disease (Nemeroff and Musselman 2000). Elevated platelet reactivity has been proposed as a mechanism of the association between major depression and increased risk of ischemic heart disease (Musselman et al. 1996). Increased platelet activation can cause increased thrombosis, arterial occlusion, and vasoconstriction (Musselman et al. 1998). Elevated platelet serotonin levels, promoting clotting, may be associated with depression and the occurrence of adverse coronary events (Sanner and Frazier 2011). Plasma levels of platelet factor IV and beta thromboglobulin, which are markers of platelet activation, have also been shown to be higher in patients with depression and ischemic heart disease compared to nondepressed patients with ischemic heart disease (Laghrissi-Thode et al. 1997). It is the high blood cell counts, fibrinogen, and raised platelet activation which contribute to a prothrombotic state, thrombus formation, and myocardial ischemia (Barth et al. 2004). Burg et al. showed that depression symptom severity predicts endothelin-1 elevation, which has been linked to plaque rupture and post-ACS survival (Burg et al. 2011). Acute psychological stress has also been shown to cause endothelial dysfunction (Ghiadoni et al. 2000).

Autoimmune and Inflammatory Mechanisms

It has been proposed that inflammation is a common causal pathway responsible in part for both the development of depressive symptoms and for adverse cardiac outcomes (Poole et al. 2011). Patients with major depression have been shown to have elevated levels of inflammatory cytokines and C-reactive protein (CRP). Studies in depressed patients with ischemic heart disease suggest that elevated markers of inflammation predict poor response to treatment. This may help to explain the increased risk of cardiac events associated with depression (Bot et al. 2011). Elevated levels of pro-inflammatory markers have been reported in depression and ischemic heart disease, specifically pro-inflammatory cytokines such as tissue necrosis factor, interleukin-1, interleukin-2, and interleukin-6

(Kop and Gottdiener 2005). It has been postulated that inflammation causes an increase in atherosclerosis thus increasing cardiac risk (Frasure-Smith and Lespérance 2005).

Effect of Treatment

Depression is present in one of five outpatients with coronary heart disease and in one in three outpatients with congestive heart failure, yet the majority of cases are not recognized or appropriately treated (Whooley 2006). Optimizing treatment for depression cannot only cause significant reduction in depressive symptoms but also improve cardiac prognosis (Davidson et al. 2010). Pharmacological and non-pharmacological treatments are known to improve depressive symptoms in patients with coronary artery disease. Selective serotonin reuptake inhibitors (SSRIs) are the class of drug of choice for treatment of those with major depression and comorbid coronary artery disease. This is primarily due to the better tolerability and absence of significant cardiovascular side effects (Zellweger et al. 2004).

The sertraline antidepressant heart attack randomized trial (SADHART) indicated that sertraline improved depressive symptoms and did not adversely affect cardiac function. Treatment with sertraline in depressed post-acute coronary syndrome patients is associated with reductions in platelet/endothelial activation, and a trend toward a reduction in morbidity and mortality among the sertraline treated patients was observed. SADHART demonstrated safety of sertraline post-acute myocardial infarction along with a decrease in overall mortality, infarction, stroke, unstable angina, and congestive cardiac failure.

Following SSRI treatment, sympathetic nervous activity in patients with major depressive disorder is significantly reduced (Carney et al. 1999). A recent meta-analysis of SSRI medications in patients with depression and coronary heart disease showed a greater decrease in depressive symptoms and also a possible improvement in coronary heart disease prognosis (Pizzi et al. 2011). The ENRICHD trial showed that antidepressant treatment of depression improved prognosis for MI patients (Berkman et al. 2003).

In the platelet sub-study of the SADHART trial, patients who had suffered a myocardial infarction and had comorbid depression treated with sertraline showed less activation of platelets and endothelial cells (Serebruany et al. 2003), even when anticoagulants were accounted for. Also of importance was the fact that this sub-study showed that there were no adverse events regarding bleeding, with the use of sertraline. This again indicates that sertraline is a safe and effective drug.

Although sertraline has been shown to be a safe and effective drug, this cannot be said for all patients and for all SSRIs, as it has been shown that there may be an SSRI-induced vagally mediated inflammation. It has also been indicated that treatment with the SSRI paroxetine can possibly cause mildly abnormal LDL (low-density lipoprotein) levels (Lara et al. 2003).

Non-pharmacological therapy such as aerobic exercise has been shown not only to improve depression but also cardiovascular health. Psychological treatment of

depression, and specifically cognitive behavior therapy in post-myocardial infarction patients, has been shown to decrease depressive symptoms but with no clear effect on survival rates (Berkman et al. 2003).

Research has demonstrated the benefits of cardiac rehabilitation on psychological distress in showing its potential to improve mortality (Alban De Schutter et al. 2011). Huffman et al. showed that a depression collaborative care program for patients with acute cardiac conditions showed improvement in their depressive symptoms as well as improvements in the number and intensity of their cardiac symptoms (Huffman et al. 2011). Telephone-delivered therapy has also been proven to be effective for patients with comorbid depression following a cardiac event (O'Neil et al. 2011). This may be significant in that it may provide some social contact as it has been shown that social isolation can contribute to increased cardiac mortality (House et al. 1982) and also be a trigger for depressive symptoms. In patients with coronary heart disease, exercise training can effectively decrease depressive symptoms resulting in improved survival (Milani et al. 2011).

Tricyclic antidepressants are one class of antidepressants not generally recommended in treating depression in those who have comorbid coronary heart disease. The use of tricyclic antidepressants has been shown to result in a high relative risk of myocardial infarction even after adjustment for other cardiovascular risk factors and may have direct cardiac effects such as QT prolongation (Follath 2003). Tricyclic antidepressants also decrease heart rate variability due to their anticholinergic effects (Bigger et al. 1993). Tricyclic antidepressants may also induce weight gain, and obesity is a well-known risk factor for cardiovascular disease (Aronne and Segal 2002). It is also known that tricyclic antidepressants are diabetogenic which again confers higher cardiac risk. Hamer et al. showed that the use of tricyclic antidepressants was associated with an elevated risk of cardiovascular disease with a multivariate-adjusted hazard ratio of 1.24, but this was not shown for SSRI medications (Hamer et al. 2011).

Conclusions

A definitive mortality study is unlikely to be ever done due to its cost and complexity. We therefore need to be guided by the current evidence to guide us in a choice of therapy that will minimize risk for individuals. The SADHART trials have shown that sertraline is a safe and effective drug in treating major depression in those with comorbid ischemic heart disease. Sertraline has also been shown to be possibly protective in post- acute myocardial infarction patients.

The present findings underscore the need to consider depression as a common and modifiable risk factor for coronary heart disease events (Brown et al. 2011). Interdisciplinary management of these patients would optimize treatment for both major depression and the ischemic heart disease. Screening for depression in patients with cardiac disease should be instituted on a routine basis. The 2010 Global Burden of Disease study which estimated the premature mortality and disability of all major diseases and injuries indicated that it is now appropriate to

consider major depression as a risk factor for coronary heart disease (Charlson et al. 2011). The links between depression and cardiovascular disease have now been well established. Further work is warranted in sympathetics and how SSRI treatment modifies cardiac risk.

References

Alban De Schutter, M., Lavie, C. J., & Milani, R. V. (2011). Relative importance of comorbid psychological symptoms in patients with depressive symptoms following phase II cardiac rehabilitation. *Postgraduate Medicine, 123*(6), 72–78.

Aronne, L. J., & Segal, K. R. (2002). Weight gain in the treatment of mood disorders. *The Journal of Clinical Psychiatry, 64*, 22–29.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine, 66*(6), 802–813.

Barton, D. A., Dawood, T., Lambert, E. A., Esler, M. D., Haikerwal, D., Brenchley, C., ... Hickie, I. (2007). Sympathetic activity in major depressive disorder: identifying those at increased cardiac risk? *Journal of Hypertension, 25*(10), 2117–2124.

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catellier, D., Cowan, M. J.,... Schneiderman, N. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. [Clinical Trial Multicenter Study Randomized Controlled TrialResearch Support, U.S. Gov't, P.H.S.]. *JAMA, 289*(23), 3106–3116. doi: 10.1001/jama.289.23.3106.

Bigger, J. T., Fleiss, J. L., Rolnitzky, L. M., & Steinman, R. C. (1993). Frequency domain measures of heart period variability to assess risk late after myocardial infarction. *Journal of the American College of Cardiology, 21*(3), 729–736.

Bot, M., Carney, R. M., Freedland, K. E., Rubin, E. H., Rich, M. W., Steinmeyer, B. C., & Mann, D. L. (2011). Inflammation and treatment response to sertraline in patients with coronary heart disease and comorbid major depression. *Journal of Psychosomatic Research, 71*(1), 13–17.

Brown, A. D., Barton, D. A., & Lambert, G. W. (2009). Cardiovascular abnormalities in patients with major depressive disorder. *CNS Drugs, 23*(7), 583–602.

Brown, J. M., Stewart, J. C., Stump, T. E., & Callahan, C. M. (2011). Risk of coronary heart disease events over 15 years among older adults with depressive symptoms. *The American Journal of Geriatric Psychiatry, 19*(8), 721–729.

Burg, M. M., Martens, E. J., Collins, D., & Soufer, R. (2011). Depression predicts elevated endothelin-1 in patients with coronary artery disease. *Psychosomatic Medicine, 73*(1), 2.

Carney, R. M., Saunders, R. D., Freedland, K. E., Stein, P., Rich, M. W., & Jaffe, A. S. (1995). Association of depression with reduced heart rate variability in coronary artery disease. *The American Journal of Cardiology, 76*(8), 562–564.

Carney, R. M., Freedland, K. E., Veith, R. C., Cryer, P. E., Skala, J. A., Lynch, T., & Jaffe, A. S. (1999). Major depression, heart rate, and plasma norepinephrine in patients with coronary heart disease. *Biological Psychiatry, 45*(4), 458–463.

Celano, C. M., & Huffman, J. C. (2011). Depression and cardiac disease: A review. *Cardiology in Review, 19*(3), 130–142.

Charlson, F. J., Stapelberg, N. J., Baxter, A. J., & Whiteford, H. A. (2011). Should global burden of disease estimates include depression as a risk factor for coronary heart disease? *BMC Medicine, 9*(1), 47.

Chavez, C. A., Ski, C. F., & Thompson, D. R. (2012). Depression and coronary heart disease: Apprehending the elusive black dog. *International Journal of Cardiology, 158*(3), 335–336.

Davidson, K. W., Rieckmann, N., Clemow, L., Schwartz, J. E., Shimbo, D., Medina, V., ... Burg, M. M. (2010). Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: Coronary psychosocial evaluation studies randomized controlled trial. *Archives of Internal Medicine, 170*(7), 600–608.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine, 160*(14), 2101–2107.

Elderon, L., Smolderen, K. G., Na, B., & Whooley, M. A. (2011). Accuracy and prognostic value of American Heart Association – Recommended depression screening in patients with coronary heart disease data from the heart and soul study. *Circulation. Cardiovascular Quality and Outcomes, 4*(5), 533–540.

Follath, F. (2003). Depression, stress and coronary heart disease – Epidemiology, prognosis and therapeutic sequelae. *Therapeutische Umschau Revue Therapeutique, 60*(11), 697.

Frasure-Smith, N., & Lespérance, F. (2005). Reflections on depression as a cardiac risk factor. *Psychosomatic Medicine, 67*(Supplement 1), S19–S25.

Frasure-Smith, N., & Lespérance, F. (2008). Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Archives of General Psychiatry, 65*(1), 62–71.

Frasure-Smith, N., Lespérance, F., & Talajic, M. (1993). Depression following myocardial infarction: Impact on 6-month survival. *JAMA, 270*(15), 1819–1825.

Ghiadoni, L., Donald, A. E., Cropley, M., Mullen, M. J., Oakley, G., Taylor, M., ... Steptoe, A. (2000). Mental stress induces transient endothelial dysfunction in humans. *Circulation, 102*(20), 2473–2478.

Hamer, M., Batty, G. D., Seldenrijk, A., & Kivimaki, M. (2011). Antidepressant medication use and future risk of cardiovascular disease: The Scottish health survey. *European Heart Journal, 32*(4), 437–442.

House, J. S., Robbins, C., & Metzner, H. L. (1982). The association of social relationships and activities with mortality: Prospective evidence from the Tecumseh Community Health Study. *American Journal of Epidemiology, 116*(1), 123–140.

Huffman, J. C., Mastromauro, C. A., Sowden, G., Fricchione, G. L., Healy, B. C., & Januzzi, J. L. (2011). Impact of a depression care management program for hospitalized cardiac patients [Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *Circulation Cardiovascular Quality and Outcomes, 4*(2), 198–205. doi:10.1161/CIRCOUTCOMES.110.959379.

Jiang, W., Krishnan, R. R., & O'Connor, C. M. (2002). Depression and heart disease: Evidence of a link, and its therapeutic implications [Review]. *CNS Drugs, 16*(2), 111–127.

John, U., Meyer, C., Rumpf, H.-J., & Hapke, U. (2004). Self-efficacy to refrain from smoking predicted by major depression and nicotine dependence. *Addictive Behaviors, 29*(5), 857–866.

Kapfhammer, H. P. (2011). The relationship between depression, anxiety and heart disease – A psychosomatic challenge [Review]. *Psychiatria Danubina, 23*(4), 412–424.

Katon, W. J., Lin, E. H., Russo, J., Von Korff, M., Ciechanowski, P., Simon, G., ... Young, B. (2004). Cardiac risk factors in patients with diabetes mellitus and major depression. *Journal of General Internal Medicine, 19*(12), 1192–1199.

Kop, W. J., & Gottdiener, J. S. (2005). The role of immune system parameters in the relationship between depression and coronary artery disease. *Psychosomatic Medicine, 67*, S37–S41.

Laghrissi-Thode, F., Wagner, W. R., Pollock, B. G., Johnson, P. C., & Finkel, M. S. (1997). Elevated platelet factor 4 and β-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biological Psychiatry, 42*(4), 290–295.

Lange-Asschenfeldt, C., & Lederbogen, F. (2011). Antidepressant therapy in coronary artery disease. *Der Nervenarzt, 82*(5), 657–664. quiz 665–656.

Lara, N., Baker, G. B., Archer, S. L., & Le Mellédo, J.-M. (2003). Increased cholesterol levels during paroxetine administration in healthy men. *The Journal of Clinical Psychiatry, 64*(12), 1455–1459.

Lespérance, F., Frasure-Smith, N., Juneau, M., & Théroux, P. (2000). Depression and 1-year prognosis in unstable angina. *Archives of Internal Medicine, 160*(9), 1354–1360.

Lett, H. S., Blumenthal, J. A., Babyak, M. A., Sherwood, A., Strauman, T., Robins, C., & Newman, M. F. (2004). Depression as a risk factor for coronary artery disease: Evidence, mechanisms, and treatment. *Psychosomatic Medicine, 66*(3), 305–315.

Milani, R. V., Lavie, C. J., Mehra, M. R., & Ventura, H. O. (2011). Impact of exercise training and depression on survival in heart failure due to coronary heart disease. *The American Journal of Cardiology, 107*(1), 64–68.

Musselman, D. L., Tomer, A., Manatunga, A. K., Knight, B. T., Porter, M. R., Kasey, S., ... Nemeroff, C. B. (1996). Exaggerated platelet reactivity in major depression. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *American Journal of Psychiatry, 153*(10), 1313–1317.

Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. *Archives of General Psychiatry, 55*(7), 580–592.

Nemeroff, C. B., & Musselman, D. L. (2000). Are platelets the link between depression and ischemic heart disease? *American Heart Journal, 140*(4), S57–S62.

Newson, R. S., Hek, K., Luijendijk, H. J., Hofman, A., Witteman, J. C., & Tiemeier, H. (2010). Atherosclerosis and incident depression in late life. *Archives of General Psychiatry, 67*(11), 1144–1150.

O'Neil, A., Hawkes, A. L., Chan, B., Sanderson, K., Forbes, A., Hollingsworth, B., ... Eadie, K. (2011). A randomised, feasibility trial of a tele-health intervention for Acute Coronary Syndrome patients with depression ('MoodCare'): Study protocol. *BMC Cardiovascular Disorders, 11*(1), 8.

Ormel, J., & de Jonge, P. (2011). Unipolar depression and the progression of coronary artery disease: Toward an integrative model. *Psychotherapy and Psychosomatics, 80*(5), 264–274.

Pizzi, C., Rutjes, A. W. S., Costa, G. M., Fontana, F., Mezzetti, A., & Manzoli, L. (2011). Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. *The American Journal of Cardiology, 107*(7), 972–979.

Poole, L., Dickens, C., & Steptoe, A. (2011). The puzzle of depression and acute coronary syndrome: Reviewing the role of acute inflammation. *Journal of Psychosomatic Research, 71*(2), 61–68.

Sanner, J. E., & Frazier, L. (2011). The role of serotonin in depression and clotting in the coronary artery disease population. *Journal of Cardiovascular Nursing, 26*(5), 423–429.

Serebruany, V. L., Glassman, A. H., Malinin, A. I., Nemeroff, C. B., Musselman, D. L., van Zyl, L. T., ... Harrison, W. (2003). Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. *Circulation, 108*(8), 939–944.

Serrano, C. V., Jr., Setani, K. T., Sakamoto, E., Andrei, A. M., & Fraguas, R. (2011). Association between depression and development of coronary artery disease: Pathophysiologic and diagnostic implications. *Vascular Health and Risk Management, 7*, 159.

Srinivasan, K. (2011). "Blues" ain't good for the heart. *Indian Journal of Psychiatry, 53*(3), 192.

Stapelberg, N. J., Neumann, D. L., Shum, D. H., McConnell, H., & Hamilton-Craig, I. (2011). A topographical map of the causal network of mechanisms underlying the relationship between major depressive disorder and coronary heart disease. *Australian and New Zealand Journal of Psychiatry, 45*(5), 351–369.

Summers, K. M., Martin, K. E., & Watson, K. (2010). Impact and clinical management of depression in patients with coronary artery disease. *Pharmacotherapy The Journal of Human Pharmacology and Drug Therapy, 30*(3), 304–322.

Swardfager, W., Herrmann, N., Marzolini, S., Saleem, M., Farber, S. B., Kiss, A., ... Lanctôt, K. L. (2011). Major depressive disorder predicts completion, adherence, and outcomes in cardiac

rehabilitation: a prospective cohort study of 195 patients with coronary artery disease. *Journal of Clinical Psychiatry, 72*(9), 1181.

Whooley, M. A. (2006). Depression and cardiovascular disease: Healing the broken-hearted. *JAMA, 295*(24), 2874–2881.

Zellweger, M. J., Osterwalder, R. H., Langewitz, W., & Pfisterer, M. E. (2004). Coronary artery disease and depression. *European Heart Journal, 25*(1), 3–9.

Ziegelstein, R. C., Fauerbach, J. A., Stevens, S. S., Romanelli, J., Richter, D. P., & Bush, D. E. (2000). Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Archives of Internal Medicine, 160*(12), 1818–1823.

Zuidersma, M., Thombs, B. D., & de Jonge, P. (2011). Onset and recurrence of depression as predictors of cardiovascular prognosis in depressed acute coronary syndrome patients: A systematic review [Research Support, Non-U.S. Gov't Review]. *Psychotherapy and Psychosomatics, 80*(4), 227–237. doi:10.1159/000322633.

Stress, Depression, and Cardiovascular Risk in Children

Don Byrne, Lisa Olive, and Rohan Telford

Contents

Abstract

The effective prevention of cardiovascular disease (CVD) lies with the identification and modification of risk markers known to be causally associated with clinical events of CVD – and the evidence would support the view that the earlier this can take place, the more effective CVD prevention will be. Thus, intervention programs targeting such things as diet and obesity, cigarette smoking, and

D. Byrne (✉)
ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia

ANU Medical School, Research School of Psychology, Australian National University, Acton, Canberra, ACT, Australia
e-mail: Don.Byrne@anu.edu.au

L. Olive
Research School of Psychology, The Australian National University, Canberra, ACT, Australia
e-mail: lisa.olive@anu.edu.au

R. Telford
Centre for Research and Action in Public Health, University of Canberra, Bruce, ACT, Australia
e-mail: rohan@look.org.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_12

sedentary physical behavior in children and adolescents have been reported in abundance in the public health literature. A host of risk markers for CVD is now well documented, and their predictive associations with clinical CVD are well established by epidemiological evidence. Among these, psychological risk markers, and in particular psychosocial stress and depression, have recently been prominent in the literature examining CVD risk in adults. It is now clear, however, that children experience both psychosocial stress and depression to a significant degree not really recognized prior to the past two decades. This chapter addresses both stress and depression in children, evident in a large epidemiological study (the LOOK study), which has allowed these psychological states to be related to behavioral, fitness, and metabolic risk markers for future CVD over a 4-year period. The evidence from the LOOK study links both stress and depression in young children (7–8 years old at intake) with fitness deficits 4 years later. It also links stress with unhealthy levels of insulin resistance over the same time course. Both these findings point to the need to address psychosocial stress and depression early in life – along with perhaps more traditionally recognized risk markers for CVD – in the overall public health effort to reduce the incidence of this chronic and potentially life-threatening clinical condition.

Keywords
CVD risk • Children • Stress • Depression • Cardiorespiratory fitness • Physical activity • Early intervention • CVD prevention

Introduction: The Evidence for CVD Risk Markers in Children

The primary manifestations of cardiovascular disease (CVD) are quite clearly to be seen in adulthood (Nichols et al. 2013). Epidemiological evidence indicates that the risk of clinical episodes of CVD increases with age (Daniels et al. 2011) and that the incidence of clinical CVD is most apparent from middle-age onwards.

Determinants of CVD risk are now well understood and involve both the simple actions of, and complex interactions between, a raft of identified risk factors and biomarkers (Balagopal et al. 2011). Traditional – and therefore widely researched – risk factors tend to cluster within the categories of metabolic (e.g., blood lipids, glucose metabolism), hemodynamic (e.g., blood pressure), behavioral (e.g., cigarette smoking, sedentary lifestyle), and psychological (e.g., stress, psychopathology). Though as Balagopal et al. (2011) and Canas et al. (2013) point out, more directed research is required to elucidate the role of biomarkers (e.g., immune characteristics) in more fully describing the process of CVD risk.

All this notwithstanding however, Berenson and Srnivasan (2005), on the basis of a rapidly accumulating body of credible evidence, stated without equivocation that "Evidence that cardiovascular [CVD] risk factors are identifiable in childhood and are predictive of future [CVD] risk is now irrefutable" (p 303). It is now clear that such well-identified CVD risks as obesity (Cote et al. 2013; Friedemann et al. 2012; Haas et al. 2011; Park et al. 2013; Spiotta and Luma 2008; Twisk et al. 1997),

elevated blood lipids (Ayer and Sholler 2012; Daniels 2001; May et al. 2012; Reed et al. 2007; Twisk et al. 1997), higher than normal blood pressure (Ayer and Sholler 2012; May et al. 2012; Reed et al. 2007), both type 1 and type 2 diabetes (Morrison et al. 2012; Schnell et al. 2013; Velasquez-Mieyer et al. 2005), and low physical activity and fitness (Froberg and Andersen 2005) are evident to an apparently increasing degree in children. And there is good evidence that multiple risk factors for CVD predict premature atherosclerosis in children and young adults (Berensen et al. 1998).

Moreover, there is growing evidence that the early appearance of CVD risk factors is linked to an equally early appearance of coronary atherosclerosis in children and young adolescents (Daniels 2001), with the consequent expectation that this will translate directly into a risk for clinical CVD in relatively early adulthood. A novel study by McMahan et al. (2005) used both blood and tissue samples obtained at postmortem examination from more than 2,500 young people 15–34 years old who had died from non-CVD causes, to assess the link between CVD risk factors and atherosclerotic lesions. Postmortem measures of blood lipids, body mass index, hypertension (estimated by examining the intimal thickness of small renal arteries), and smoking (estimated from serum thiocyanate levels) were strongly related to the presence of atherosclerotic lesions likely to endow future risk of clinical CVD. There can be no doubt, therefore, that the development of CVD risk in adulthood is firmly founded in childhood, leading Daniels et al. (2011) to foreshadow the issue of CVD prevention and to conclude that ". . . the development of CVD has its origins in families and . . .. approaches to prevention must be directed at the developing child and adolescent and the family environment . . ." (p 1683).

Depression, Distress, and CVD Risk in Children

Cardiovascular disease risk is, not surprisingly, a widely researched area in medicine. One of the most novel and thought provoking and arguably one of the most useful accumulations of evidence coming out of the past decade or so has been that documenting the causal role of depression as a CVD risk factor. It is well established that depression, often of clinical intensity, is a common consequence of a clinical episode of CVD (Williams 2011). Consistent medical opinion now recommends routine screening for depression among those with identified clinical CVD (Colquhoun et al. 2013; Lichtman et al. 2008) to ensure effective intervention against the possible exacerbation of coronary pathology. Moreover, there is now both extensive and quite persuasive evidence that the existence of clinical depression is causally related to an elevated risk of a clinical CVD event and to a less favorable prognosis when such an event has occurred (Barth et al. 2004; Celano and Huffman 2011; Hare et al. 2013; Zellweger et al. 2004). This link appears to hold for ". . . several decades after the onset of clinical depression . . ." (Ford et al. 1998, p. 1422). Among the elderly, the presence of depression increases the risk of CVD mortality by between 40 % and 60 % relative to those free from depression (Ariyo et al. 2000). Conversely – and interestingly – the experience of positive effect seems to protect against the future

incidence of clinical CVD (Davidson et al. 2010). In seeking to identify possible mechanisms through which depression endows CVD risk, Carney et al. (2002) have suggested the effects of antidepressant cardiotoxicity, the co-occurrence of depression with other CVD risk factors, poor compliance with cardiac prevention and treatment regimes, lower heart-rate variability, an increased tendency for platelet aggregation, and the facilitation of inflammatory processes, as the primary contenders.

But while the prevalence of depression has been investigated mainly in adults, it is now clear that both children and young adolescents quite commonly manifest symptoms of depression and experience depression of clinical severity. A major epidemiological study reported by Ford et al. (2003) suggested the overall prevalence of diagnosable mental disorders in young people to be around 9.5 %. With a specific focus on depression, Zalsman et al. (2006) reported a prevalence of 1–2 % in prepubertal children, 3–8 % in adolescents, and 20 % as an end-of-adolescence "lifetime" estimate. This was essentially consistent with the figures of 2.8 % for children under 13 years old and 5.6 % among those 13–18 years old reported by Costello et al. (2006). And much in line with research on depression in both young people and adults more generally, girls routinely reported higher levels of depression than did boys (Saluja et al. 2004; Costello et al. 2006).

In this light it is not surprising that there is an embryonic – but growing – body of evidence linking the experience of depression and other emotional distress in children with CVD risk in adolescence and adulthood. Young adolescents with a profile of depressive symptoms reported poorer levels of (general) physical health than did nondepressed young people (Wickrama et al. 2009). The same was evident in a very large cohort of later adolescents and young adults at intake, who were followed up over 37 years, with early depression being associated with measurable CVD outcomes at the end of follow-up (Janszky et al. 2010). Bosch et al. (2009) reported significant relationships between measures of depression and autonomic markers indicative of future CVD risk in preadolescents. And severe depression in young adolescents was associated with changes in pulse wave velocity (PWV), which has been found to be indicative of arterial stiffness and therefore of future CVD risk (Dietz and Matthews 2011). The same relationship with depression was, interestingly, not consistently evident for the CVD risk marker of carotid artery intima-media thickening (Elovainio et al. 2005) though standard CVD risk factors were clear predictors of this phenomenon (Raitakiri et al. 2003).

In another large cohort study, 14-year-old girls experiencing both anxiety and depression also exhibited a higher body mass index (BMI) and riskier insulin resistance levels than did those free of affective distress, but this was not evident in boys (Louise et al. 2012). And children manifesting major (diagnosed) depression were more likely than their nondepressed siblings or those in a nondepressed control group to be regular smokers and to be obese – they were also less likely to be physically active (Rottenberg et al. 2014).

Taking the specific nature of childhood distress to a more detailed level, Kendall-Tackett (2002) suggested that early childhood abuse placed older children at risk of developing clinical depression and suggested behavioral pathways – for example, smoking and substance abuse, obesity and eating disorders, and sleep difficulties – through which the experience of an abused childhood might presage future health

risks. Persuasive prospective evidence now links traumatic experiences in childhood with the risk of both depression and CVD later in adulthood (Batten et al. 2004). In a further prospective study (Danese et al. 2009), children from a background of socioeconomic disadvantage who also reported adverse childhood (psychological) experiences showed an increased risk of later depression and elevated inflammatory markers, as well as metabolic markers of CVD risk.

While not all of this evidence comes from investigations uniquely of preadolescent children, it is sufficiently compelling to recommend that further attention be paid to the possible links between childhood depression and future CVD risk among preadult populations. But knowing the evidence, compelling as that may be, constitutes just the first part of the picture – the second part begs the critical question of how that evidence may be translated into practice. And here, Daniels et al. (2011) point clearly to the view that the evidence on childhood risk of CVD is now well established, and the next step – that step of translating evidence into practice – lies with the prevention of future CVD in children identified as being at risk.

Illness Prevention and Health Promotion in Children

Efforts to achieve the primary prevention of CVD through focused interventions with children are, of course, not new. Comprehensive reviews of CVD risk factor reduction in children (Daniels et al. 2011), and the need for targeted CVD health promotion programs in schools (Hayman et al. 2004), point to the centrality of this approach in reducing the future burden of CVD in adulthood at the population level. A good deal of this attention has been paid to the prevention – or the treatment – of obesity in children (Dietz and Gortmaker 2001; Freedman et al. 1999; Sothern 2004; Steinberger and Daniels 2003; Story 1999), with the clear expectation that such preventive attention would reduce the development of atherosclerotic pathology in the coronary arteries (Kavey et al. 2003) and, as a consequence, the eventual incidence of clinical CVD. This is not surprising since the evidence on the high and possibly increasing prevalence of childhood obesity in many countries is now well established (Ebbeling et al. 2002). But other equally well-established risk factors for CVD – for example, diet, physical activity, and smoking – have also been identified as important foci for preventive attention (Daniels et al. 2011). Children at high risk of future CVD for a range of medical reasons, including type 1 diabetes (and also type 2 diabetes in children close to adolescence), have also been targeted for particular preventive attention (Kavey et al. 2006). Intriguingly, though somewhat tangentially to the present discussion, it has been shown that a school-based intervention program directed at CVD risk in children had measureable carry-over effects on levels of some CVD risk factors in their parents (Fornari et al. 2012). Evidence for the utility of school-based programs of CVD risk prevention therefore points to a promising – though not yet conclusively documented – domain of future public health practice (Addison et al. 2006; Bush et al. 1989).

There is an emerging case for a more concerted effort to establish programs of CVD risk prevention in children as a routine – and indeed necessary – part of

childhood health and health promotion. There seem, however, to be two principal difficulties in solidifying this case into accepted practice. First, the evidence required to persuasively argue the case necessarily involves very long-term prospective studies, with large cohorts of children adequately screened for CVD risk at intake, and then followed through to early adulthood and beyond. Studies such as these are methodologically difficult and expensive to undertake, and with the possible exceptions of the Framingham study in the USA, the Young Finns study in Finland, and the HUNT study in Norway, the evidence is presently sparse. And second, both the risk targets themselves, and the approaches taken to achieving CVD risk interventions, are frequently fragmented and oftentimes more intuitively than empirically or theoretically driven. They are therefore difficult to enshrine into the accepted wisdom of clinical public health practice.

The evidence becomes even more difficult to marshal into a persuasive argument for early intervention when it rests with the psychological attributes of a young population. Studies overviewed earlier in this chapter establish beyond reasonable doubt that many known risk factors for CVD in adulthood are established in childhood. And it follows from this that the foundation for clinical events of CVD in adulthood can be traced back, at least in part, to the development of CVD risk among children. There is, moreover, some evidence that this line of potential causality holds for the (psychological) risk factor of depression (Ford et al. 1998). The evidence also notes the growing problem of depression (and other psychological distress more generally) in children and begs the question of whether depression experienced in childhood might go on to form the basis for an elevated risk of CVD somewhat later in adulthood. The elements of a coherent research question, posed within the context that risk factors for future CVD have some foundation in childhood, therefore present themselves for consideration. Both depression and stress in adulthood constitute known risks for CVD, and there are likely plausible biological mechanisms that may link these psychological risk factors with CVD risk markers. Given that depression and stress are clearly evident among children, the question logically arises as to whether childhood depression and stress also constitute identifiable – and early – risks for future CVD (Low et al 2009). And by extension, could the effective prevention of depression and stress in childhood have a noticeable effect on rates of CVD later in adulthood?

Interventions based on the worthy objective of promoting future health or of reducing the incidence of future illness are now relatively commonplace. But the practice of health promotion over the past decade and a half has become increasingly dependent on the availability of sound evidence, both epidemiological and clinical, to guide the targets of health-promoting interventions and the forms they take (Nutbeam 1999; Green 2000; Juneau et al. 2011). The difficulty with the risk sequence just proposed – that psychological distress in children may influence the later development of CVD in adults – is that it does not yet have sufficient targeted evidence to justify the development and implementation of intervention strategies based solely on the view that psychological distress experienced by children will place them at greater risk of CVD sometime later in life. This chapter now goes on to look at a recent and significant study which may provide that evidence.

The LOOK Study

The lifestyle of our kids (LOOK) study is an ongoing, collaborative, multidisciplinary, and longitudinal study of the development of health and health behaviors, beginning in childhood and progressing through to adolescence. The uniqueness of the LOOK study lies in the breadth of health areas examined simultaneously and prospectively across a number of domains, both biomedical and psychosocial (see Telford et al. 2009 for a more detailed outline).

The study cohort was drawn from a population of children attending public primary schools in suburban areas of a major Australian city; 30 schools were approached to participate in the study and 29 agreed. Every grade 2 student from each of the schools was invited to participate in the study, and a very large acceptance rate (from children and parents) provided an initial sample of 853 prepubescent children aged 7–8 years, with most (86 %) children being of Caucasian descent. Schools were approximately matched for their socioeconomic status (SES) as indicated by the Australian Bureau of Statistics (ABS) Socio-Economic Indexes for Areas (SEIFA; ABS 2006). This index is a continuum of advantage (high values) and disadvantage (low values) derived from government census variables such as income, educational attainment, and employment. The catchment area SES was, however, relatively higher than the national average.

Children were followed for the course of childhood, with major measurement periods occurring in grade 2 (baseline), grade 4, and then grade 6. Additional psychological measurements were collected in grade 3 to ensure validity and reliability of instruments developed for the study. Attrition over the course of follow-up was largely due to child absences on the day of testing, temporary school closures, or relocation of students to non-LOOK schools. An analysis of data from children who left the study revealed no evidence of any attrition bias in regard to any of the measured variables, and there is no reason to suspect that withdrawal of children had any impact on conclusions reached in this study.

From the outset of the LOOK study, both biomedical and psychosocial data at a detailed level were collected to provide (*inter alia*) comprehensive individual profiles of current CVD risk markers in children, based on contemporary evidence linking these risk markers to elevated risk or incidence of CVD later in adulthood. The data to be examined now can be summarized as follows:

Measures

Stress: The Children's Stress Questionnaire

Psychosocial stress is now a well-established risk marker for CVD in adults, and evidence has been reviewed earlier in this chapter which suggests that the origins of this condition may be found, in part, in children. Stress in childhood therefore constituted a primary variable in the LOOK study. The Children's Stress Questionnaire (CSQ; Byrne et al. 2011) is a 50-item self-report questionnaire developed specifically for the study to assess the occurrence and impact of a range of stressor

experiences relevant to children. Children reported their stressor experience for the last 12 months on a 5-point Likert scale, ranging from 1 (*This didn't happen to me*) to 5 (*It made me very upset*). While the literature on life events has expressed general concern regarding the 12-month time frame for recall, Turner and Wheaton (1995) consider this to be the standard in studies of the kind reported here. Individual item scores thus spanned the range of 1–5, while the full-scale score spanned 50–250. Based on data from the LOOK cohort, the CSQ has strong internal reliability and both construct and predictive validity, as a measure of stressor experience in children.

Depression: The Children's Depression Inventory

Depression too, as the evidence reviewed earlier in this chapter reveals, is now well accepted as a risk marker for CVD in adults. Once more, the origins of adult depression may be found, again in part, in children, and therefore the measurement of depression in children was considered an important component in the LOOK study. All children were given a modified (19-item) form of the Children's Depression Inventory (CDI; Kovacs 1982, 1992), with a forced choice (symptom present or absent response format). The CDI has demonstrated validity and reliability (Kovacs 1992) in assessing clinical and subclinical depression in preadolescent groups. For the present study, items indicating conspicuous clinical depression (persistent crying, suicidal ideation, and worthlessness) were removed from the CDI because (a) the sample was deliberately unselected for either mental or physical dysfunction and (b) the inclusion of such items may have inadvertently induced a negative mood state in a sample of otherwise normal 7–8-year-olds.

Physical Activity

A sedentary lifestyle has long been considered to endow elevated risk for CVD in adults (Manson et al. 2004) – the childhood origins of this lifestyle pattern were therefore fully explored in the LOOK study. *New Lifestyles* pedometers (Lee's Summit, MO, USA) were used to measure the number of steps per day taken by children, since the validity of this measure has been established in children of this age group (Beets et al. 2005). Children wore pedometers on their hip for seven consecutive days, though measurements taken on the first day were excluded to account for the potential influence of the novelty of wearing a pedometer and because the sampling period did not form a complete day. While the simple metric of steps/day provided an indication of physical activity, a physical activity index was also calculated using best linear unbiased predictor (BLUPS) to maximize the use of data. A more detailed description of this measure has been previously described (Telford et al. 2009).

Cardiorespiratory Fitness (CRF)

Poor CRF evident in childhood has been related to elevated metabolic risk of CVD in adults (Dwyer et al. 2009), and so CRF was assessed for all children in the LOOK study. The 20-m multi-stage shuttle test (MSST) was used as a measure of CRF and has been well established as a reliable field test of fitness among children (Tomkinson et al. 2003). The MSST requires maximal effort, and therefore

performance may be influenced by participant motivation, but it is a practical and commonly used method to measure CRF in a large sample.

Percent Body Fat (%BF) and Body Mass Index (BMI)

Obesity in childhood has been a recent focus of work predicting adult obesity and has been shown to relate to the later development of CVD (Hubert et al. 1983; Rexrode et al. 1996; Steinberger and Daniels 2003). Body composition in the LOOK study was measured using dual-energy X-ray absorptiometry (DXA, Hologic Discovery QDR Series, Hologic Inc., Bedford, MA, USA), and QDR Hologic Software Version 12.4:7 was used to generate fat mass from which %BF was calculated. Height and weight were used to calculate BMI, where height was measured by a portable stadiometer to the nearest 0.001 m and body mass by portable electronic scales to the nearest 0.05 kg.

Biochemical and Metabolic Data

Elevated levels of low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), and elevated triglycerides are also established risk factors for CVD (Di Angelantonio et al. 2009; Lewington et al. 2007). Also, insulin resistance assessed by homeostasis model assessment (HOMA) has been shown to be independently predictive of CVD in several studies (Bonora et al. 2002; Reddy et al. 2010). Blood samples for the LOOK study were collected after an overnight fast to measure glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and insulin levels. The insulin resistance index by homeostasis model assessment (HOMA-IR) was calculated from fasting plasma glucose and insulin levels using the formula published by Katz et al. (2000).

Smoking was not assessed in the LOOK cohort since the evidence on smoking onset in children and adolescents would indicate that the age range in this cohort, either at intake or at follow-up, was too low to reveal statistically useful numbers of children regularly using tobacco.

Stress, Depression, and the Presence of CVD Risk Markers in Children: Evidence from the LOOK Study

CVD Risk Marker Profiles in the LOOK Sample

Since complete LOOK study data on both the psychological attributes of children (stress and depression), and on CVD risk markers, were available both at intake and 4 years later, retrospective and prospective analyses were undertaken to reveal associations between these two sets of measures. Some 397 boys and 394 girls in the age range of 7–8 years were fully assessed at intake (mean age 8.18 for boys and 8.13 for girls) – 4 years later, 266 boys (67.0 % of the intake sample) and 255 girls (64.7 % of the intake sample), this time in the age range of 11–12 years old, were assessed at follow-up. The principal reason for attrition between intake and follow-up was movement of families out of location.

Table 1 Changes in children's profiles for stress and depression over time (from intake to follow-up)

Scale	% of children with a decrease in stress/ depression scores over 4 years	% of children with an increase in stress/ depression scores over 4 years	% of children remaining stable in stress/ depression scores over 4 years
Stress full-scale change	71.5 %	26.0 %	2.5 %
Depression full-scale change	61.5 %	28.5 %	9.0 %

Stress levels at both intake and follow-up closely approximated a normal distribution – levels of depression at both time points were somewhat skewed toward low depression, but this was expected in a measure which was oriented toward a clinical state (Byrne et al. 2011), though it was clear that even at that young age, some children (7–8 years old) showed signs of experiencing troubling levels of both stress and depression. Equally importantly, however, there was change in psychological state over time – between intake and follow-up 4 years later – and this change can be seen in Table 1.

Encouragingly, the majority of children decreased in both stress and depression scores over the 4-year follow-up period – but more than a quarter in each case showed an increase in these scores. There is no obvious explanation for this pattern of change in either stress or depression. What was evident, however, was that depression appeared to follow stress – as stress levels fluctuated over time, so did levels of depression. Stress levels at intake were significantly related to depression levels at follow-up in both boys ($r = 0.25, p < 0.01$) and girls ($r = 0.27, p < 0.01$) providing evidence that stress in young children predicts depression some 4 years later. At follow-up, levels of stress and depression were strongly related ($r = 0.72$, $p < 0.001$ in boys and $r = 0.61, p < 0.001$ in girls).

A comprehensive risk assessment both at intake and at follow-up 4 years later established CVD risk marker profiles for the samples at both points in time. Table 2 shows percents of each sample already, at this young age, who manifested elevated levels of metabolic risk markers, assessed according to standard published criteria for blood lipids (Daniels and Greer 2008; Kavey et al. 2003) and HOMA-IR (Tresaco et al. 2005).

Levels of LDL-C indicating CVD risk appeared to be higher at intake than at follow-up, but the reverse was quite apparent for levels of HOMA-IR, where children 4 years into the study had very noticeably higher levels of insulin resistance – or more accurately in this age group, insulin sensitivity – than was evident at intake.

Risk profiles based on assessments of physical activity (PA), cardiorespiratory fitness (CRF), and body mass index (BMI – as a proxy for %BF) can be seen in Table 3.

Table 2 Percentage of children with elevated metabolic risk profiles at intake and at follow-up

Risk marker	% of children with elevated risk marker level at intake	% of children with elevated risk marker level at follow-up
LDL-C	>3.36 mmol/L	
Boys	14.7 %	11.1 %
Girls	17.0 %	9.4 %
HDL-C	<0.9 mmol/L	
Boys	1.0 %	1.7 %
Girls	1.1 %	2.3 %
TG	>4.52 mmol/L	
Boys	0.0 %	0.0 %
Girls	0.0 %	0.4 %
HOMA-IR	≥3.00[a]	
Boys	1 %	17 %
Girls	3 %	36 %

[a]Using the formula {Fasting INS (mUL) × fasting Glucose (mmol/L)}/22.5

Physical activity decreased quite markedly over the course of the follow-up, with 70 % of both boys and girls at follow-up showing less than optimal levels of daily activity. Although children of the LOOK cohort were measured with lower CRF at follow-up relative to the Australian normative group from Catley and Tomkins (2013), children's CRF increased over the course of follow-up as would be developmentally expected – this was more evident for boys than for girls. Levels of obesity assessed by BMI showed a slightly increasing trend over 4 years, but something approaching 25 % of children in the sample overall showed evidence of obesity when judged according to BMI – but bearing in mind the concerns posed by Telford et al. (2014) regarding the capacity of the BMI to reflect adiposity in children.

Not surprisingly, gender differences in risk marker profiles were evident, even in samples of quite young children. Boys had significantly higher HDL-C levels than did girls at both time points, but this was not evident for LDL-C. Neither gender nor time differences, however, were evident in triglyceride levels. Insulin resistance increased significantly over time for both boys and girls, but the increase was more marked for girls, and girls generally had a higher insulin resistance (HOMA-IR) level than did boys. Boys were significantly more physically active than girls at both intake and follow-up – levels of PA declined with age through to follow-up, but the PA of boys declined at a greater rate than that of girls. Boys did, however, show significantly better levels of CRF than did girls at both time points. At both intake and follow-up, girls had a significantly greater %BF than boys. Over time, however, %BF for girls remained stable, while for boys it increased.

But as with the experience of childhood stress and depression, levels of CVD risk markers also fluctuated over the time course of the data collection, and these may be seen in Table 4.

Fluctuations were not, however, consistent either across time or gender. Levels of HDL-D, TG, and HOMA-IR all rose over the 4-year follow-up period and for both

Table 3 Percentage of children with elevated risk profiles based on fitness measures at intake and at follow-up

Risk marker	% of children with elevated risk marker level at intake	% of children with elevated risk marker level at follow-up
PA measured here as steps/day	<13,000 steps/day for boys; <11,000 steps/day for girls	
Boys	58 %	70 %
Girls	63 %	70 %
CRF[a]	Low/very low	Low/very low
Boys	1 %	14 %
Girls	2 %	5 %
BMI[b]	Overweight/obese	Overweight/obese
Boys	20 %	23 %
Girls	24 %	26 %

[a]Currently there are no universally accepted recommendations for health-related levels of fitness. Our 20-m shuttle run data was compared to normative data for Australian children (see Catley and Tomkinson 2013), where children with fitness in the lowest 40th percentile were classified as having low to very low fitness. Note that these data are not criterion referenced and do not indicate whether children in the lowest 40th percentile have unhealthy cardiovascular fitness or increased metabolic risk. However, previous Australian evidence has linked low CRF in childhood with increased metabolic risk in adulthood (Dwyer et al. 2009)

[b]Due to inconsistencies in different measurement methods of classifying developing children and no agreed upon cutoff for %BF, children were classified for the purposes of this comparison according to their BMI, to assist a comparison of the body composition of this cohort with those of other studies, notwithstanding the limitations associated with BMI in children (see Cole et al. 2000; Telford and Cunningham 2008; Telford et al. 2014)

boys and girls. The same was noted for both CRF and %BF, with both boys and girls showing higher levels of CRF as would be expected with development and higher levels of %BF over the 4-year time span – by contrast, both boys and girls appeared to have noticeably lower levels of PA at follow-up than at intake.

Psychological State (Stress and Depression) at Intake in Relation to Risk Marker Profiles Both at Intake and at Follow-Up 4 Years Later

The question remains, however, as to whether psychological state (stress and depression) evident at intake bears any relationship to identified risk markers either at intake or 4 years later. Table 5 shows the patterns of relationships between measures of psychological state and CVD risk markers both retrospectively (at intake) and prospectively, examining psychological state at intake in relation to CVD risk markers at the 4-year follow-up.

In unadjusted analyses, psychological state at intake did not relate at all to levels of blood fats (LDL-C, HDL-C, or TG) either retrospectively or prospectively, and this was the case as well for %BF. There was a significant relationship between stress at intake and insulin resistance (HOMA-IR) 4 years later and a trend in this regard for depression as well. But the strongest and most consistent associations between psychological state and CVD risk markers appeared when both CRF and PA were

Table 4 Changes in children's risk profiles for LDL-C, HDL-C, TG, HOMA-IR, CRF, %BF, and PA over time (from intake to follow-up), reported separately for gender

Risk marker	% of children decreasing in risk level over 4 years	% of children increasing in risk level over 4 years	% of children with no change in risk level over 4 years
LDL-C			
Boys	59.2 %	39.0 %	1.8 %
Girls	66.0 %	1.3 %	32.7 %
HDL-C			
Boys	59.6 %	38.6 %	1.8 %
Girls	54.6 %	43.7 %	1.7 %
TG			
Boys	30.7 %	67.9 %	1.4 %
Girls	54.6 %	43.7 %	1.7 %
HOMA-IR			
Boys	9.2 %	85.3 %	5.5 %
Girls	4.2 %	95.4 %	0.4 %
CRF[a]			
Boys	90.1 %	9.1 %	0.8 %
Girls	92.8 %	6.8 %	0.4 %
%BF			
Boys	35.3 %	64.7 %	0.0 %
Girls	49.4 %	50.6 %	0.0 %
PA[a]			
Boys	8.5 %	91.5 %	0.0 %
Girls	20.3 %	79.7 %	0.0 %

[a]Note that an increase in physical activity and CRF confers a decrease in risk level

examined. Unadjusted analyses indicated that psychological state at intake could in fact predict both CRF and PA 4 years later.

However, the risk markers measured in the children participating in the LOOK study cannot be seen as isolated and encapsulated entities – they relate in close and intricate fashions to one another and to other factors as well. A more informative analysis must therefore take account of these interrelationships, and so adjustments were made in a manner guided by the relevant literature (Krekoukia et al. 2007; Rowlands et al. 1999). Specifically, the following statistical adjustments were made for all analyses involving CVD risk markers:

- Percent Body Fat (%BF) – adjusted for height, physical activity, and gender
- Cardiorespiratory Fitness (CRF) – adjusted for height and gender
- Physical Activity (PA) – adjusted for %BF and gender
- HOMA-Insulin Resistance (IR) – adjusted for %BF, PA, and gender
- Low-Density Lipoprotein (LDL)-C – adjusted for %BF, PA, and gender
- High-Density Lipoprotein (HDL)-C – adjusted for %BF, PA, and gender
- Triglycerides (TGs) – adjusted for %BF, PA, and gender (Table 6)

Table 5 Retrospective and prospective relationships between psychological state (stress and depression) and CVD risk markers *unadjusted* for possible intervening factors

Psychological state / CVD risk marker	Stress and CVD markers (intake only)	Stress (intake) and CVD markers (follow-up)	Depression and CVD markers (intake only)	Depression (intake) and CVD markers (follow-up)
Percent body fat (%BF)	**X**	**X**	**X**	**X**
Cardiorespiratory fitness (CRF)	✓	✓	✓	✓
Physical activity (PA)	**?**	✓	✓	✓
Insulin resistance HOMA-IR	**X**	✓	**X**	**?**
Low-density lipoprotein cholesterol (LDL-C)	**X**	**X**	**X**	**X**
High-density lipoprotein cholesterol (HDL-C)	**X**	**X**	**X**	**X**
Triglycerides (TGs)	**X**	**X**	**X**	**X**

✓ Statistically significant relationship ($p < 0.05$)
X Statistically nonsignificant relationship ($p > 0.05$)
? Statistical trend ($0.05 < p < 0.1$)

Not surprisingly, associations between variables were somewhat attenuated by these statistical adjustments. Neither blood lipids nor %BF related in any way to measures of psychological state. Levels of CRF did, however, continue to show associations with psychological state except prospectively with depression – and levels of PA were prospectively associated with both stress and depression. Insulin resistance (HOMA-IR) was also prospectively associated with stress but not with depression.

So does psychological state in early childhood relate persuasively to CVD risk profiles in children 4 years later, and is the evidence sufficiently compelling to mark psychological state in young children as an appropriate focus for intervention? There are two answers to this, the first being that if children are experiencing distress or depression, intervention of a professional kind is warranted. The evidence on rates of both stress and depression in children, as reviewed earlier in this chapter, clearly indicates a growing problem for the well-being of young people, not unlike observed increases in the levels of obesity or rates of smoking among older children. More fundamentally, well-being should be carefully nurtured – professionally and otherwise – for no other reason than that children deserve to be free of emotional pain.

But the second answer to the question of whether intervention to address emotional pain in children will have demonstrable benefits for later physical health and,

Table 6 Retrospective and prospective relationships between psychological state (stress and depression) and CVD risk markers *adjusted* for possible intervening factors

Psychological state / CVD risk marker	Stress and CVD markers (intake only)	Stress (intake) and CVD markers (follow-up)	Depression and CVD markers (intake only)	Depression (intake) and CVD markers (follow-up)
Percent body fat (%BF)	**X**	**X**	**X**	**X**
Cardiorespiratory fitness (CRF)	✓	✓	✓	**X**
Physical activity (PA)	**X**	✓	**X**	✓
Insulin resistance HOMA-IR	**X**	✓	**X**	**X**
Low-density lipoprotein cholesterol (LDL-C)	**X**	**X**	**X**	**X**
High-density lipoprotein cholesterol (HDL-C)	**X**	**X**	**X**	**X**
Triglycerides (TGs)	**X**	**X**	**X**	**X**

✓ Statistically significant relationship ($p < 0.05$)
X Statistically nonsignificant relationship ($p > 0.05$)
? Statistical trend ($0.05 < p < 0.1$)

from the particular perspective of this book, for the health of the cardiovascular system remains somewhat open. Much of the evidence reviewed earlier suggests this to be the case and to recite Daniels et al. (2011): ". . . the development of CVD has its origins in families and . . .. approaches to prevention must be directed at the developing child and adolescent and the family environment . . ." (p 1683). The evidence arising thus far from the LOOK study indicates a somewhat more cautious conclusion. Longitudinal associations between stress and depression in 7–8-year-old children and CVD risk profiles 4 years later, unadjusted for possible interrelationships between the very variables contributing to those risk profiles, would suggest that both stress and depression statistically predict measures of cardiovascular fitness. Psychological state in 7–8-year-olds does not, however, predict levels of metabolic risk markers 4 years later (with the exception of insulin resistance). The links between stress and insulin resistance offer one potentially very useful insight into how a psychological state may influence the future development of CVD. The capacity for increased stress to elevate blood sugar levels in children – possibly maintained over adolescence and into adulthood – marks a possible pathway which bears closer examination in further studies (and will be taken up in chapter "► Nonlinear Analyses of Data in Cardiovascular Physiology and Epidemiology" of the current *Handbook*).

When analyses were adjusted for potentially confounding covariates, the strengths of predictive associations were overall truncated, but remained for CRF, and PA, and (again to some extent) for insulin resistance – further underscoring the possible importance of this latter metabolic variable in foreshadowing CVD risk in children.

Conclusion

Would results such as this justify a concerted program of preventive intervention for stress and depression in young children, with a view to preventing CVD in adulthood? On this basis alone, the evidence is too weak to recommend a step such as this. But given that the mood in the public and preventive health arena is now right for the introduction of comprehensive programs of CVD prevention in children, targeting a broad range of potential CVD risk markers for future adult disease (e.g., fitness and exercise, weight and diet, smoking, and alcohol use), there is every reason to incorporate psychological interventions into such comprehensive programs of CVD prevention. The proof will ultimately be in the results of an appropriately well-designed and resourced trial to achieve this.

References

Addison, C. C., Jenkins, B. W., White, M. S., & Young, L. (2006). Implementation of a cardiovascular disease prevention program among school-aged children: A pilot study. *International Journal of Environmental Research and Public Health, 3*, 274–277.

Ariyo, A. A., Haan, M., Tange, C. M., Rutledge, J. C., Cushman, M., Dobs, A., & Furbert, C. D. (2000). Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. *Circulation, 102*, 1773–1779.

Australian Bureau of Statistics. (2006). *Information paper: An introduction to Socio-economic Indexes for Areas (SEIFA)*. Retrieved from. http://www.abs.gov.au/ausstats/abs@.nsf/mf/2039.0/.

Ayer, J. G., & Sholler, G. F. (2012). Cardiovascular risk factors in Australian children: Hypertension and lipid abnormalities. *Australian Prescriber, 35*, 51–55.

Balogopal, P., de Ferranti, S., Cook, S., Daniels, S. R., Gidding, S. S., Hayman, L. L., McCrindle, B. W., . . ., Steinberger, J. (2011). *Circulation, 123*, 2749–2769.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine, 66*, 802–813.

Batten, S. V., Aslan, M., Maciejewski, P. K., & Mazure, C. M. (2004). Childhood maltreatment as a risk factor for adult cardiovascular disease and depression. *Journal of Clinical Psychiatry, 65*, 249–254.

Beets, M. W., Patton, M. M., & Edwards, S. (2005). The accuracy of pedometer steps and time during walking in children. *Medicine and Science in Sports and Exercise, 37*, 513–520.

Berensen, G. S., & Srnivasan, S. R. (2005). Cardiovascular risk factors in youth with implications for aging: The Bogalusa Heart Study. *Neurobiology of Aging, 26*, 303–307.

Berensen, G. S., Srnvasan, S. R., Bao, W., Newman, W. P., III, Tracy, R. E., & Wattigney, W. A. (1998). Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *New England Journal of Medicine, 338*, 1650–1656.

Bonora, E., Formentini, G., Calcaterra, F., Lombardi, S., Marini, F., Zenari, L., Saggiani, F., . . ., Muggeo, M. (2002). HOMA-estimated insulin resistance is an independent predictor of

cardiovascular disease in type 2 diabetic subjects prospective data from the Verona Diabetes Complications Study. *Diabetes Care, 25*, 1135–1141.

Bosch, N. M., Riese, H., Dietrich, A., Ormel, J., Verhulst, F. C., & Oldehinkel, A. J. (2009). Preadolescents' somatic and cognitive-affective depressive symptoms are differentially related to cardiac autonomic function and cortisol: The TRAILS study. *Psychosomatic Medicine, 71*, 944–950.

Bush, P. J., Zuckerman, A. E., Theiss, P. K., Taggart, V. S., Horowitz, C., Sheridan, M. J., & Walter, H. J. (1989). Cardiovascular risk factor prevention in black schoolchildren: Two-year results of the "Know Your Body" program. *American Journal of Epidemiology, 129*, 466–482.

Byrne, D. G., Thomas, K. A., Burchell, J. L., Olive, L. S., & Mirabito, N. S. (2011). Stressor experience in primary school-aged children: Development of a scale to assess profiles of exposure and effects on psychological well-being. *International Journal of Stress Management, 18*, 88–111.

Canas, J. A., Sweeten, S., & Balagopal, P. (2013). Biomarkers for cardiovascular risk in children. *Current Opinion Cardiology, 28*, 103–114. doi:10.1097/HCO.0b013e32835dd0ce.

Carney, R. M., Freedland, K. E., Miller, G. E., & Jaffe, A. S. (2002). Depression as a risk factor for cardiac mortality and morbidity: A review of potential mechanisms. *Journal of Psychosomatic Research, 53*, 897–902.

Cateley, M. J., & Tomkinson, G. R. (2013). Normative health-related fitness values for children: Analysis of 85347 test results on 9–17-year-old Australians since 1985. *British Journal of Sports Medicine, 47*, 98–108. doi:10.1136/bjsports-2011-090218.

Celano, C. M., & Huffman, J. C. (2011). Depression and cardiac disease: A review. *Cardiology in Review, 19*, 130–142.

Cole, T. J., Bellizzi, M. C., Flegal, K. M., & Dietz, W. H. (2000). Establishing a standard definition for child overweight and obesity worldwide: An international study. *BMJ, 320*, 1240–1243.

Colquhoun, D. M., Bunker, S. J., Clarke, D. M., Glozier, N., Hare, D. L., Hickie, I. B., . . ., Branagan, M. G. (2013). Screening, referral and treatment for depression in patients with coronary heart disease. *Medical Journal of Australia, 198*, 483–484.

Costello, E. J., Erkanli, A., & Angold, A. (2006). Is there an epidemic of child or adolescent depression? *Journal of Child Psychology & Psychiatry, 47*, 1263–1271.

Cote, A. T., Harris, K. C., Panagiotopoulos, C., Sandor, G. G. S., & Develin, A. M. (2013). Childhood obesity and cardiovascular dysfunction. *Journal of the American College of Cardiology, 62*, 1309–1319.

Danese, A., Moffit, T. E., Harrington, H., Milne, BV., Polanczyk, G., Pariante, C. M., . . ., Caspi, A. (2009). Adverse childhood experiences and adult risk factors for age-related disease: Depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatrics & Adolescent Medicine, 163*, 1135–1143. doi: 10.1001/archpediatrics.2009.214.

Daniels, S. R. (2001). Cardiovascular disease risk factors and atherosclerosis in children and adolescents. *Current Atherosclerosis Reports, 3*, 479–485.

Daniels, S. R., & Greer, F. R. (2008). Lipid screening and cardiovascular health. *Childhood Pediatrics, 122*, 198–208.

Daniels, S. R., Pratt, C. A., & Hayman, L. L. (2011). Reduction of risk for cardiovascular disease in children and adolescents. *Circulation, 124*, 1673–1686.

Davidson, K., Mostofsky, E., & Whang, W. (2010). Don't worry, be happy: Positive affect and reduced 10-year incident coronary heart disease: The Canadian Nova Scotia Health Survey. *European Heart Journal, 31*, 1065–1070. doi:10.1093/eurheartj/ehp603.

Di Angelantonio, E., Sarwar, N., Perry, P., Kaptoge, S., Ray, K. K., Thompson, A., . . ., Danesh, J. (2009). Major lipids, apolipoproteins, and risk of vascular disease. *JAMA, 302*, 1993–2000.

Dietz, L. J., & Gortmaker, S. L. (2001). Preventing obesity in children and adolescents. *Annual Review of Public Health, 22*, 337–353.

Dietz, L. J., & Matthews, K. A. (2011). Depressive symptoms and subclinical markers of cardiovascular disease in adolescents. *Journal of Adolescent Health, 48*, 579–584.

Dwyer, T., Magnussen, C. G., & Schmidt, M. D. (2009). Decline in physical fitness from childhood to adulthood associated with increased obesity and insulin resistance in adults. *Diabetes Care, 32*, 683–687.

Ebbeling, C. B., Pawlac, D. B., & Ludwig, D. S. (2002). Childhood obesity: Public health crisis, common sense cure. *Lancet, 360*, 473–482.

Elovainio, M., Keltikangas-Järvinen, L., Kivimäki, M., Pulkki, L., Puttonen, S., Heponiemi, T., . . ., Raitakari, O. T. (2005). Depressive symptoms and carotid artery intima-media thickness in young adults: The Cardiovascular Risk in Young Finns Study. *Psychosomatic Medicine 67,* 561–567.

Ford, D. E., Mead, L. A., Chang, P. P., Cooper-Patrick, L., Wang, N., & Klag, M. J. (1998). Depression is a risk factor for coronary artery disease in men. *Archives of Internal Medicine, 158*, 1422–1426.

Ford, T., Goodman, R., & Meltzer, H. (2003). The British child and adolescent mental health survey 1999: The prevalence of DSM-IV disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*, 1203–1211. doi:10.1136/bmj.e4759.

Fornari, L. S., Giuliano, I., Azevedo, F., Pastana, A., Vieira, C., & Caramelli, B. (2012). Children First Study: How an educational program in cardiovascular prevention at school can improve parents' cardiovascular risk. *European Journal of Preventive Cardiology, 20*, 301–309.

Freedman, D. S., Dietz, W. H., Srnivasan, S. R., & Berenson, G. S. (1999). The relation of overweight to cardiovascular risk factors among children and adolescents: The Bogalusa Heart Study. *Pediatrics, 103*, 1175–1182.

Friedemann, C., Heneghan, C., Mahtani, K., Thompson, M., Perera, R., & Ward, A. M. (2012). Cardiovascular disease risk in healthy children and its association with body mass index: Systematic review and meta-analysis. *BMJ, 25*, 345–e4759. doi:10.1136/bmj.e4759.

Froberg, K., & Andersen, L. B. (2005). Mini review: Physical activity and fitness and its relations to cardiovascular disease risk factors in children. *International Journal of Obesity, 29*, S34–S39.

Green, J. (2000). The role of theory in evidence-based health promotion practice. *Health Education Research, 15*, 125–129.

Haas, G., Liepold, E., & Schwandt, P. P. (2011). Predicting cardiovascular risk factors by different body fat patterns in 3850 German children: The PEP Family Heart Study. *International Journal of Preventive Medicine, 2*, 15–19.

Hare, D. L., Toukhsati, S. R., Johansson, P., & Jaarsma, T. (2013). Depression and cardiovascular disease: A clinical review. *European Heart Journal, 35*, 1365–1372. doi:10.1093/eurheartj/eht462.

Hayman, L. L., Williams, C. L., Daniels, S. R., Steinberger, J., Paridon, S., Dennison, B. A., & McCrindle, B. W. (2004). Cardiovascular health promotion in schools. A statement for health and education professions and child health advocates from the Committee on Atherosclerosis, Hypertension, and Obesity in Youth (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation, 110*, 2266–2275.

Hubert, H. B., Feinleib, M., McNamara, P. M., & Castelli, W. P. (1983). Obesity as an independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the Framingham Heart Study. *Circulation, 67*, 968–977.

Janszky, I., Ahnve, S., Lundberg, I., & Hemmingsson, T. (2010). Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-Year follow-up of 49,321 young Swedish men. *Journal of American College of Cardiology, 56*, 31–37.

Juneau, C.-E., Jones, C. M., McQueen, D. V., & Potvin, L. (2011). Evidence-based health promotion: An emerging field. *Global Health Promotion, 18*(1), 79–89.

Katz, A., Nambi, S. S., Mather, K., Baron, A. D., Follmann, D. A., Sullivan, G., & Quon, M. J. (2000). Quantitative insulin sensitivity check index: A simple, accurate method for assessing insulin sensitivity in humans. *Journal of Clinical Endocrinology and Metabolism, 85*, 2402–2410.

Kavey, R. W., Daniels, S. R., Lauer, R. M., Atkins, D. L., Hayman, L. L., & Taubert, K. (2003). American Heart Association Guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *Circulation, 107*, 1562–1566.

Kavey, R. W., Allada, V., Daniels, S. R., Hayman, L. L., McCrindle, B. W., Newburger, J. W., ..., Steinberger, J. (2006). Cardiovascular risk reduction in high-risk pediatric patients. A scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. *Circulation, 114*, 000–000. doi:10.1161/CIRCULATIONAHA.106.179568.

Kendall-Tackett, K. (2002). The health effects of childhood abuse: Four pathways by which abuse can influence health. *Child Abuse and Neglect, 6*(7), 715–730.

Kovacs, M. (1982). *The children's depression inventory.* Toronto: Multi-Health Systems.

Kovacs, M. (1992). *Children's depression inventory manual*. North Tonawanda: Multi-Health Systems.

Krekoukia, M., Nassis, G. P., Psarra, G., Skenderi, K., Chrousos, G. P., & Sidossis, L. S. (2007). Elevated total and central adiposity and low physical activity are associated with insulin resistance in children. *Metabolism, 56*, 206–213.

Lewington, S., Whitlock, G., Clarke, R., Sherliker, P., Emberson, J., Halsey, J.,. . ., Collins, R. (2007). Blood cholesterol and vascular mortality by age, sex, and blood pressure: A meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet, 370*, 1829–1839.

Lichtman, J. H., Bigger, J. T., Blumenthal, J. A., Frasure-Smith, N., Kaufmann, P. T., Lespérance, F., & Froelicher, S. (2008). Depression and coronary heart disease: Recommendations for screening, referral and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. *Circulation, 118*, 1768–1775. doi: 10.1161/CIRCULATIONAHA.108.190769.

Louise, S., Warrington, N. M., McCaskie, P. A., Oddy, W. H., Zubrick, S. R., Hands, B., . . ., Beilin, L. J. (2012). Associations between anxious-depressed symptoms and cardiovascular risk factors in a longitudinal childhood study. *Preventive Medicine, 54*. doi:10.1016/j.ypmed.2012.03.004.

Low, C. A., Salomon, K., & Matthews, K. A. (2009). Chronic life stress, cardiovascular reactivity, and subclinical cardiovascular disease in adolescents. *Psychosomatic Medicine, 71*, 927–931.

Manson, J. E., Skerrett, P. J., Greenland, P., & VanItallie, T. B. (2004). The escalating pandemics of obesity and sedentary lifestyle: A call to action for clinicians. *Archives of Internal Medicine, 164*, 249–258.

May, A. L., Kuklina, E. V., & Yoon, P. W. (2012). Prevalence of cardiovascular disease risk factors among US adolescents, 1999–2008. *Pediatrics*, *120*. doi:10.1542/peds.2011-1082.

McMahan, C. A., Gidding, S. S., Fayad, Z. A., Zieske, A. W., Malcolm, G. T., Tracy, R E., . . ., McGill Jr, H. C. (2005). Risk scores predict atherosclerotic lesion in young people. *Archives of Internal Medicine*, *165*, 883–890.

Morrison, J. A., Glueck, C. J., Woo, J. G., & Wang, P. (2012). Risk factors for cardiovascular disease and type 2 diabetes retained from childhood to adulthood predict adult outcomes: The Princeton LRC follow-up study. *International Journal of Pediatric Endocrinology, 2012*, 6.

Nichols, M., Townsend, N., Scarborough, P., & Rayner, M. (2013). Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980–2009. *European Heart Journal, 34*, 3014–3016. doi:10.1093/eurheartj/eht159.

Nutbeam. (1999). The challenge to provide evidence in health promotion. *Health Promotion International, 14*(2), 99–101.

Park, M. H., Sovio, U., Viner, R. M., Hardy, R. J., & Kinra, S. (2013). Overweight in childhood, adolescence and adulthood and cardiovascular risk in later life: Pooled analysis of three British birth cohorts. *Plos One*. doi:10.137/journalpone.0070684.

Raitakari, O. T., Juonala, M., Kähönen, M., Taittonnen, L., Mäki-Torkko, N., Järvisalo, M. J., . . ., Viikari, J. S. A. (2003). Cardiovascular risk factors in childhood and carotid artery intima-media

thickness in adulthood. The Cardiovascular Risk in Young Finns Study. *Journal of the American Medical Association, 290*, 2277–2205.

Reddy, K. J., Singh, M., Bangit, J. R., & Batsell, R. R. (2010). The role of insulin resistance in the pathogenesis of atherosclerotic cardiovascular disease: An updated review. *Journal of Cardiovascular Medicine, 11*, 633–647.

Reed, K. E., Warburton, D. E. R., & McKay, H. A. (2007). Determining cardiovascular disease risk in elementary school children: Developing a healthy heart score. *Journal of Sports Science and Medicine, 6*, 142–148.

Rexrode, K. M., Manson, J. E., & Hennekens, C. H. (1996). Obesity and cardiovascular disease. *Current Opinion in Cardiology, 11*, 490–495.

Rottenberg J., Yaroslavsky, I., Carney, R. M., Freedland, K. E., George, Charles, J., . . ., Kovacs, M. (2014). The association between major depressive disorder in childhood and risk factors for cardiovascular disease in adolescence. *Psychosomatic Medicine, 76*, 122–127.

Rowlands, A. V., Eston, R. G., & Ingledew, D. K. (1999). Relationship between activity levels, aerobic fitness, and body fat in 8- to 10-yr-old children. *Journal of Applied Physiology, 86*, 1428–1435.

Saluja, G., Iachan, R., Schiedt, P. E., Overpeck, M. D., Sun, W., & Giedd, J. N. (2004). Prevalence of and risk factors for depressive symptoms among young adolescents. *Archives of Pediatric Adolescent Medicine, 158*, 760–765.

Schnell, O., Cappuccio, F., Genovese, S., Standl, E., Valensi, P., & Ceriello, A. (2013). Type 1 diabetes and cardiovascular disease. *Cardiovascular Diabetology, 12*, 156.

Sothern, M. S. (2004). Obesity prevention in children: Physical activity and nutrition. *Nutrition, 20*, 704–708. doi:10.1016/j.nut.2004.04.007.

Spiotta, R. T., & Luma, G. (2008). Evaluating obesity and cardiovascular risk factors in children and adolescents. *American Family Physician, 78*, 1052–1058.

Steinberger, J., & Daniels, S. R. (2003). Obesity, insulin resistance, diabetes and cardiovascular risk in children. An American Heart Association Scientific Statement from the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism. *Circulation, 107*, 1448–1453.

Story, M. (1999). School-based approaches for preventing and treating obesity. *International Journal of Obesity, 23*, S43–S51.

Telford, R. D., & Cunningham, R. B. (2008). Reformulation of BMI and percent body fat to remove the height bias in 8-year-olds. *Obesity, 16*, 2175–2181.

Telford, R. D., Bass, S. L., Budge, M. M., Byrne, D. G., Carlson, J. S., Coles, D., . . ., Waring, P. J. (2009). The lifestyle of our kids (LOOK) project: Outline of methods**.** *Science and Medicine in Sport*, *12*, 156–163.

Telford, R. D., Cunningham, R. B., & Telford, R. M. (2009b). Day-dependent step-count patterns and their persistence over 3 years in 8-10-year-old children: The LOOK project. *Annals of Human Biology, 36*, 669–679.

Telford, R. D., Cunningham, R. B., & Abhayaratna, W. P. (2014). Temporal divergence of percent body fat and body mass index in pre-teenage children: The LOOK longitudinal study. *Pediatric Obesity, 9*(6), 448–454. doi:10.1111/j.2047-6310.2013.00194.x. Epub 2013.

Tomkinson, G. R., Leger, L. A., Olds, T. S., & Cazorla, G. (2003). Secular trends in the performance of children and adolescents (1980–2000): An analysis of 55 studies of the 20m shuttle run test in 11 countries. *Sports Medicine, 33*, 285–300.

Tresaco, B., Bueno, G., Pineda, Moreno, L. A., Garagorri, J. M., & Bueno, M. (2005). Homeostatic model assessment (HOMA) index cut-off values to identify the metabolic syndrome in children. *Journal of Physiology and Biochemistry, 61*, 381–388.

Turner, R. J., & Wheaton, B. (1995). Checklist measurement of stressful life events. In S. Cohen, R. C. Kessler, & L. U. Gordon (Eds.), *Measuring stress: A guide for health and social scientists* (pp. 29–53). New York: Oxford University Press.

Twisk, J. W. R., Kemper, H. C. G., van Mechelen, W., & Post, G. B. (1997). Tracking of risk factors for coronary heart disease over a 14 year period: A comparison between lifestyle and biologic

risk factors with data from the Amsterdam growth and health study. *American Journal of Epidemiology, 145*, 888–898.

Velasque-Mieyer, P., Perez-Fuastinelli, S., & Cowan, P. A. (2005). Identifying children at risk for obesity, Type 2 diabetes, and cardiovascular disease. *Diabetes Spectrum, 18*, 213–220.

Wickrama, K. A. S., Wickrama, T., & Lott, R. (2009). Heterogeneity in youth depressive symptom trajectories: Social stratification and implications for young adult physical health. *Journal of Adolescent Health, 45*, 335–343.

Williams, R. B. (2011). Depression after heart attack: Why should I be concerned about depression after a heart attack? *Circulation, 123*, e639–e640. doi:10.1161/CIRCULATIONAHA.110.017285.

Zalsman, G., Brent, D. A., & Weersing, V. R. (2006). Depressive disorders in childhood and adolescence: An overview epidemiology, clinical manifestation and risk factors. *Child and Adolescent Psychiatric Clinics of North America, 15*, 827–841.

Zellweger, M. J., Osterwalder, R. H., Langewitz, W., & Pfisterer, M. E. (2004). Coronary artery disease and depression. *European Heart Journal, 25*, 3–9.

Childhood Stress, Emotional Distress, and Cardiovascular Function in Adolescents

Lisa Olive, Don Byrne, Richard Telford, Walter Abhayaratna, and Rohan Telford

Contents

L. Olive (✉)
Research School of Psychology, The Australian National University, Canberra, ACT, Australia
e-mail: lisa.olive@anu.edu.au

D. Byrne
ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia
e-mail: don.byrne@anu.edu.au

R. Telford
Research Institute of Sport and Exercise, University of Canberra, Bruce, Canberra, ACT, Australia
e-mail: richard.telford@canberra.edu.au

W. Abhayaratna
ANU Medical School, College of Medicine, Biology and Environment, Australian National University, Garran, Canberra, ACT, Australia

Academic Unit of Internal Medicine, Canberra Hospital, Garran, Canberra, ACT, Australia
e-mail: Walter.P.Abhayaratna@act.gov.au

R. Telford
Centre for Research and Action in Public Health, University of Canberra, Bruce, Canberra, ACT, Australia
e-mail: rohan@look.org.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_13

Abstract

Associations between depression, chronic stress, and cardiovascular disease (CVD) are often reported in the literature, suggesting that individuals with poor psychological health are at a higher risk for developing CVD and CVD-related mortality. Much of the research in this area has been carried out among adult populations, but there is growing evidence that the origins of these relationships occur at a much younger age. In the current chapter, the childhood and adolescent literature is reviewed with a focus on the effects of depression and psychosocial stress on a set of intermediary markers for CVD, namely, endothelial function and arterial stiffness. Findings arising from the adolescent phase of the Lifestyle of Our Kids (LOOK) study, a collaborative longitudinal study, are presented. From these findings, it is clear that children as young as 12 years old are already experiencing stress and depressive symptoms and more so in less fit and fatter children. Although we did not uncover any direct impact of psychological health on cardiovascular function, given the risks associated with low fitness and obesity, depression and psychosocial stress in childhood and adolescence may be exerting an early impact on the risk of developing CVD in later life.

Keywords

Emotional distress • Cardiovascular function, adolescence • Lifestyle of our Kids (LOOK) study • Psychosocial stress • Depression • Pulse wave velocity (PWV) • Cardiorespiratory fitness (CRF)

Introduction

The experience of adversity, chronic ongoing stress, and emotional distress during childhood and adolescence is associated with a number of risk markers for cardiovascular disease (CVD; Low et al. 2009; Tomfohr et al. 2011) and with an increased risk of developing CVD later in life (Dong et al. 2004; Korkeila et al. 2010). Ongoing chronic psychological stress and clinical depression have been linked to dysregulation of the stress response (Lopez-Duran et al. 2009), and it is this dysregulation which is thought to play a causal role in the relationship between dysfunctional psychological states and CVD (Grippo and Johnson 2009). The precise mechanisms underlying these relationships are not well understood but likely include both direct biological mechanisms across multiple interacting systems (e.g., neuroendocrine changes, autonomic and cardiovascular dysregulation, and immune alterations) and indirect pathways mediated through behavioral,

social, and lifestyle factors. During adolescence, a vast number of important developmental changes are occurring, both physiologically and psychologically, that may plausibly impact on these biological systems if disrupted.

When considering adolescent development, be that physical growth and maturation; cognitive and emotional development; psychological development, including developing autonomy from parents and a sense of purpose; and social changes centered around relationships, it is not surprising that this period is seen as being particularly sensitive to "stressors" (Eiland and Romeo 2013; Grant et al. 2003, 2004). An amplified stress response in a typically healthy adolescent may be seen as adaptive in facing this set of unique challenges, but for those exposed to excessive or ongoing psychosocial stressors or adversity, chronic activation of stress response systems may tip the balance toward stress response dysregulation.

Given the evidence that exists among adults linking clinical depression, and to some degree psychosocial stress, with an elevated risk of CVD, research among children and adolescence has adopted a similar focus. Psychosocial stress and depression have been linked to a number of physiological processes underlying the progression of CVD (Allen and Patterson 1995; Grippo and Johnson 2002; Pereira et al. 2013). In addition, stress and depression have been associated with potentially health-compromising behaviors and their outcomes. These include physical inactivity (Allison et al. 2005; Goldfield et al. 2011), low levels of cardiorespiratory fitness (CRF: Olive et al. 2014), poor calorie control and obesity (Cartwright et al. 2003; Michaud et al. 1990), and cigarette smoking (Byrne and Mazanov 2003), behaviors known to increase the risk of CVD (Baum and Posluszny 1999).

Two key markers of cardiovascular function include arterial stiffness and endothelial function. Although these are not the only markers that may be affected by psychological health, previous evidence has indicated that both endothelial dysfunction and the beginnings of arterial stiffness occur in younger populations, making them an appropriate indicator of vascular health at this early age. In addition, the significant effects of depression and stress on these two prognostic measures have been reported. Therefore, the current chapter focuses on endothelial function and arterial stiffness as measures of cardiovascular function to investigate what impacts stress and depression have on cardiovascular health among youth.

Emotional Distress and Cardiovascular Function in Adolescence: A Review of the Evidence

Depression, Psychosocial Stress, and Arterial Stiffness

Arterial stiffness, and specifically aortic stiffness, has been identified as a prognostically significant marker for the development of CVD (Mattace-Raso et al. 2006; Vlachopoulos et al. 2010). The experience of both chronic and brief episodes of psychological stress and depression has been associated with increases in arterial stiffening among adults (Logan et al. 2012; Seldenrijk et al. 2011). These

associations have also been shown to extend to younger apparently healthy adults with no established cardiovascular risk (Vlachopoulos et al. 2006). A review of the most current research literature undertaken with younger populations is presented here.

Among adolescents, significant associations between depressive symptoms and arterial stiffness, as measured by pulse wave velocity (PWV), were documented among 157 healthy boys and girls in the United States after adjustments for a number of established confounders (Dietz and Matthews 2011). Sub-analyses in this study, which separated adolescents based on depression severity (moderate vs. severe), indicated that more severe depressive symptoms were associated with higher PWV (where higher PWV is indicative of greater arterial stiffness) compared to moderate symptoms. This is suggestive of a dose-response relationship between impaired arterial function and depression. Similarly, Su et al. (2014) found that in healthy adolescents and young adults, those exposed to a moderate/severe level of adverse events during the first 18 years of life had higher PWV compared to those not exposed. Studies like these are important for progressing our understanding of the earliest stages of CVD and therefore facilitating preventive medical strategies in children and adolescents.

What is evident from searching the literature on the effects of psychological health on arterial stiffness, however, is the need for more research and, specifically, well-developed longitudinal studies that can increase the current evidence base in this area. It is a similar case for studies investigating the effects of psychological distress on endothelial function.

Depression, Psychosocial Stress, and Endothelial Function

The adverse impact of clinical depression and depressive symptoms on endothelial function has been consistently reported among the few studies undertaken with younger populations (Osika et al. 2011; Tomfohr et al. 2008, 2011). In one of the earliest investigations, Tomfohr et al. (2008) found that among adolescent girls, aged 15–19 years, depressive symptoms were associated with impaired endothelial function after adjustments for age, race, and contraception use. This association was found despite reports of only mild levels of depressive symptoms by participants, providing initial evidence that even low levels of depressive symptoms are sufficient to produce negative changes in endothelial function. This work was extended to include follow-up data from the original cohort, collected over a 2.5-year period. Consistent with their earlier findings, members of this young cohort with more depressive symptoms showed increased endothelial dysfunction (Tomfohr et al. 2011). A Swedish study involving children and adolescence aged 12–16 years found that higher levels of depressive symptoms among girl were associated with greater endothelial dysfunction after adjustment for age and parental education (Osika et al. 2011). However, these finding did not extend to boys.

Similar to depression, brief episodes of psychosocial stress have been shown to effect endothelial dysfunction in a number of experimental and observational studies in adults (Ghiadoni et al. 2000; Gottdiener et al. 2003; Spieker et al. 2002; Takase et al. 2004); and the weight of evidence concluded that acute experiences of mental stress impaired endothelial function, although this finding was not consistent across all of the reviewed studies (Poitras and Pyke 2013). In a study of adolescents, Chen et al. (2012) experimentally tested the effect of acute mental stress on endothelial function and found that in response to mental stress, boys had a greater vasoconstrictive response, followed by a lesser vasodilatory response, and needed longer time to return to baseline level than girls.

The paucity of studies of the relationships between psychosocial stress, emotional distress, and cardiovascular health among children and adolescents opens up a new and productive area of research. Despite the complexities of research in rapidly developing young bodies, one advantage of working with children and adolescents is the absence of symptomatic CVD and its treatments, especially those pharmacological, which are potentially confounding and require careful control. And perhaps more importantly, longitudinal studies beginning in childhood will allow evidence-based decisions on the efficacy of psychological interventions in youth to prevent cardiovascular disease in later life. This was the thinking behind investigations undertaken as a component of the Lifestyle of Our Kids (LOOK) study.

The LOOK Study

The Lifestyle of Our Kids (LOOK) study is a collaborative, multidisciplinary longitudinal study beginning in childhood and finishing in old age (Telford et al. 2009). A more detailed introduction to this study was presented in chapter "► Stress, Depression, and Cardiovascular Risk in Children," and an outline of the multiple areas of health being investigated in the LOOK study is presented in Fig. 1. To recap briefly, the main objective of the LOOK study is to determine how physical activity and early physical education impact upon quality of life, not just in childhood and adolescence, but right through a lifetime. Further to these main objectives, the LOOK study investigates the interaction between physical and psychological health.

The LOOK study has four main phases: (1) the completed primary school phase (age 8–12 years), (2) the completed adolescent phase (age 15–16 years), (3) the young adult phase (age 16–21 years), and (4) the adult, middle, and old age phases (each decade through to age 80). Our study group is 850 boys and girls who we studied longitudinally from ages 8 through to 16 years and who we will study into later life. A timeline of LOOK is presented in Fig. 2. It is our hope that the results of the LOOK study will provide health, education, and policy makers with solid data on which to build cooperative plans into the twenty-first century.

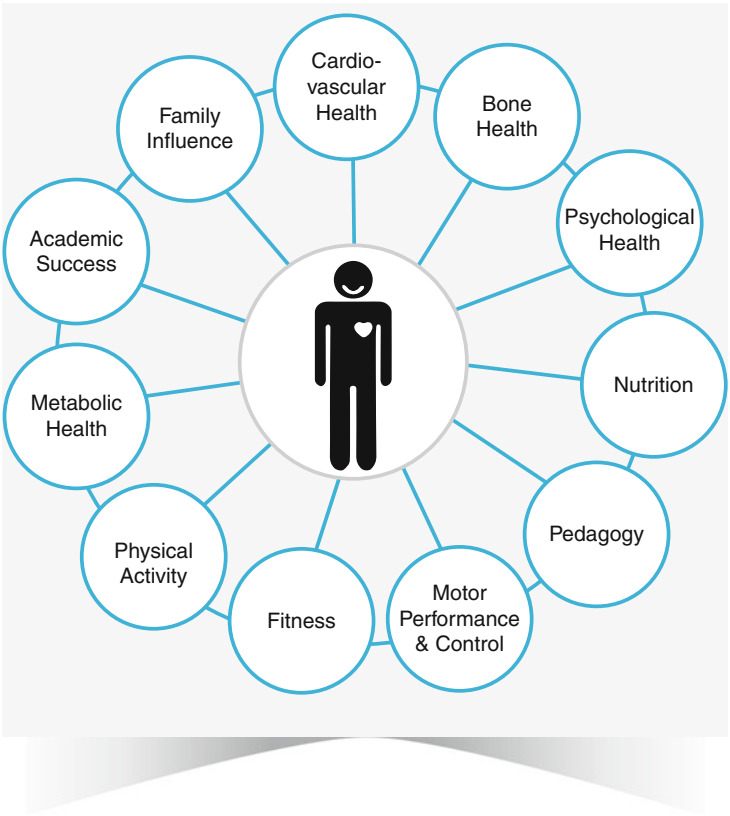


Fig. 1 The multiple areas of health investigated in the LOOK study

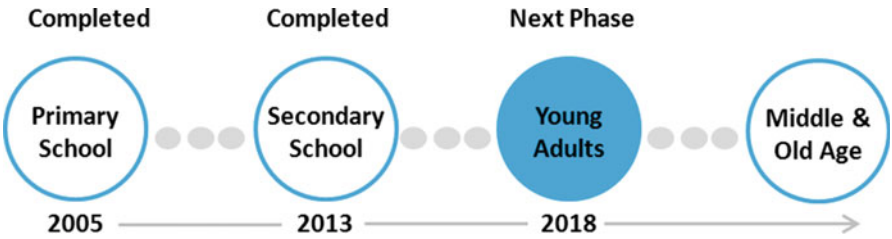


Fig. 2 Timeline and progress of the LOOK study

The current and previous chapters focus purposely on the effect of psychological health on cardiovascular health outcomes measured in the LOOK study. For findings relating to the childhood phase of the study, the reader is referred to chapter "▶ Stress, Depression, and Cardiovascular Risk in Children."

In this chapter, we focus on the transition from childhood to adolescence. Firstly, we address the changes in stress and depression during this period and, secondly,

the relationships of these psychological variables with our two prognostic measures of cardiovascular health, namely, endothelial function and arterial stiffness.

Measures

Emotional Distress

Stress: The Children's Stress Questionnaire

Psychosocial stress was assessed in the LOOK study using the Children's Stress Questionnaire (CSQ: Byrne et al. 2011), which is a 50-item self-report questionnaire developed specifically for the LOOK study. The CSQ assesses the occurrence and impact of a range of stressor experiences relevant to children and is an extension of the well-validated and reliable Adolescent Stress Questionnaire (ASQ: Byrne et al. 2007; McKay et al. 2014). Higher scores on the CSQ indicate greater levels of stressor experience. A more detailed explanation of the development of the CSQ can be found in Byrne et al. (2011).

Depression: The Children's Depression Inventory

Depression was assessed in the LOOK study using a modified version of the Children's Depression Inventory (CDI: Kovacs 1982, 1992). Response options were limited to a forced choice (symptom present or absent response format), and items indicating conspicuous clinical depression (persistent crying, suicidal ideation, and worthlessness) were removed from the CDI in order to gain ethics approval among this young population. Higher scores on the CDI indicate greater depressive symptoms. The CDI has demonstrated validity and reliability in assessing clinical and subclinical depression in 12–16-year-olds (Kovacs 1992).

Cardiovascular Function

Endothelial Function

Endothelial dysfunction is commonly described as the "inability of the artery to sufficiently dilate in response to an appropriate endothelial stimulus" and is an early predictor of CVD (Heitzer et al. 2001; Lerman and Zeiher 2005). In the LOOK study, endothelial function was assessed noninvasively using the EndoPAT 2000 (Itamar). The EndoPAT device captures a beat-to-beat plethysmographic recording of the finger arterial pulse wave amplitude (PWA) with pneumatic probes and has demonstrated reliability and validity as a measure of endothelial function among adolescents (Selamet Tierney et al. 2009). EndoPAT measures have also been used in accurately identifying the early stages of atherosclerosis (e.g., Bonetti et al. 2004). The EndoPAT examination involves three phases: (1) the baseline phase, which is recorded for 5 min; (2) the occlusion phase, where a blood pressure cuff is inflated to suprasystolic pressure for 5 min; and (3) the reactive hyperemia (RHI) phase, which occurs after the cuff is released and the signal is recorded for 5 min. "Reactive hyperemia is considered an important hemodynamic response to a

period of ischemia. Reactive hyperemia increases blood flow and thereby the delivery of oxygen and removal of metabolic products. After cuff deflation (phase 3), the pulse amplitude of a healthy individual will rise rapidly, whereas a low response is observed in individuals with endothelial dysfunction."

Arterial Stiffness

Pulse wave velocity (PWV), a measure of arterial stiffness, was assessed noninvasively using the SphygmoCor system (AtCor Medical, Sydney, Australia). Electrocardiogram-gated carotid and femoral waveforms were recorded using applanation tonometry. Carotid-femoral path length was measured as the difference between the surface distances joining (i) the suprasternal notch, the umbilicus, and the femoral pulse and (ii) the suprasternal notch and the carotid pulse. Carotid-femoral transit time was estimated in 8–10 sequential femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. Pulse wave velocity was calculated as the carotid-femoral path length divided by the carotid-femoral transit time.

Blood Pressures

Supine brachial blood pressure (BP) was determined using an automated oscillometric Omron 7051T. The average of two measurements made at 1-min intervals was recorded.

Metabolic Health

Physical Activity, Cardiorespiratory Fitness, and Percent Body Fat

Measures of physical activity, CRF, and percent body fat were also collected as part of the LOOK study. The methods used to assess these metabolic factors are described in more detail in chapter "► Stress, Depression, and Cardiovascular Risk in Children," Briefly, physical activity was assessed using pedometers worn for seven consecutive days, CRF was assessed using the 20-m multistage shuttle test (MSST), and percent body fat was assessed using dual energy x-ray absorptiometry (DEXA, Hologic Discovery QDR Series, Hologic Inc., Bedford, MA, USA). These models included adjustment for any effect of variation in the initial (grade 6) measurements on these differences. Other concomitant variables such as gender, physical activity, cardiorespiratory fitness (CRF), pubertal stage, systolic blood pressure, and percentage of body fat were considered and assessed as possible confounders for cardiovascular measures.

Stress, Depression, and CVD Risk Profiles in Adolescence: Evidence from the LOOK Study

With a focus on the transition from childhood into adolescence, firstly, we investigated the effect of psychosocial stress and depression on the two prognostically significant markers of CVD we have discussed, namely, endothelial function and

Table 1 Mean and standard deviations (in brackets) of psychological and physical characteristics with raw data classified by grade for boys and girls

Variable	Grade 6	Grade 10
Depression		
Boys	22.84 (3.24)	26.10 (4.18)
Girls	23.04 (3.14)	27.28 (4.38)
Psychosocial stress		
Boys	80.54 (21.41)	81.26 (17.46)
Girls	83.80 (19.78)	86.08 (18.19)
Endothelial function		
Boys	N/A	2.20 (0.60)
Girls	N/A	2.21 (0.63)
Pulse wave velocity m/s		
Boys	5.04 (1.97)	5.17 (0.69)
Girls	4.99 (1.84)	4.95 (0.58)
Systolic blood pressure mmHg		
Boys	115.79 (11.81)	127.07 (9.08)
Girls	116.02 (11.45)	116.90 (8.36)
Physical activity[a]		
Boys	12255 (3744)	9071 (3264)
Girls	10064 (3438)	8183 (2664)
Cardiorespiratory fitness[b]		
Boys	6.39 (2.14)	9.01 (2.71)
Girls	5.48 (1.77)	5.86 (1.93)
% body fat		
Boys	24.44 (7.20)	17.46 (7.13)
Girls	27.65 (6.36)	31.29 (6.08)

[a]Physical activity represents raw data – steps per day
[b]Cardiorespiratory fitness represents raw data – stages completed of multistage shuttle test

the measure of arterial stiffness, pulse wave velocity (PWV). However, given we have already reported the effects of physical activity, cardiorespiratory fitness (CRF), and percent body fat on blood-borne CVD factors (Telford et al. 2014), we have taken the opportunity to investigate the effects of psychosocial stress and depression on physical activity, CRF, and percent body fat. For this part of our study, measures were taken in grade 6 (11–13 years) and grade 10 (15–17 years). Some 520 children (265 boys and 255 girls) completed all measures in grade 6, with 263 children (125 boys and 138 girls) completing all measures at follow-up 4 years later. The natural attrition from a longitudinal study such as this is not likely to affect relationships between our variables of interest, but it is pertinent to report that the primary reason for attrition between intake and follow-up was movement of families out of location, or absence on the day of testing.

Table 1 shows the characteristics of the participants at baseline (grade 6) of the current investigation and 4 years later at follow-up (grade 10). The first thing we observed was the change in psychological state during the important developmental period spanning grade 6 (11–13 years) to grade 10 (15–17 years). Increases in both

Table 2 Changes in children's profiles for stress and depression from childhood to adolescence

Scale	% with a decrease in stress/depression	% with an increase in stress/depression	% remaining stable in stress/depression
Stress full scale	38.4 %	57.9 %	3.7 %
Depression full scale	17.9 %	76 %	6.1 %

depression (76 % of participants) and psychosocial stress (57.9 % of participants) were evident among the majority of participants, with some children experiencing symptoms that would be considered troubling, if not clinically significant. However, this was not the case for all children as summarized in Table 2, which shows the proportion of children showing changes in stress and depression over time. This pattern of change in psychological health contrasts with that observed during childhood, where levels of both psychosocial stress and depression decreased between age 7 and 12 years. Nonetheless it is consistent with previous research among adolescents, highlighting that this developmental period can be a particularly vulnerable time for developing mental health problems (ABS, 2007; World Health Organization [WHO] 2012). Similar to that observed during childhood, depression appeared to follow the same pattern as stress – as stress levels fluctuated over time, so did levels of depression.

On average participants endothelial function as measured by EndoPAT fell into what might be considered a "healthy range." Reference values for reactive hyperemia (RHI) from the manufacturer of the EndoPAT test suggest an index of 1.67 and below as indicating endothelial dysfunction (Itamar-Medical 2015). This index is based on adult data and its clinical significance for younger populations has not yet been determined explicitly. Therefore, caution is needed when using this reference value for interpreting scores among younger populations. With this in mind, our data may provide some cause for concern. Among adolescents of the LOOK sample, 20.7 % of participants recorded RHI scores of 1.67 or below, potentially indicating endothelial dysfunction. A further 19.2 % of participants recorded RHI scores between 1.68 and 2.00, which has generally been considered as dysfunction among adults (Bruyndonckx et al. 2013), with the remaining 60.1 % of participants recording scores indicative of healthy endothelial function.

In characterizing arterial stiffness, 23.8 % of participants had a decrease in PWV scores, 0.4 % showed no change, and 73.2 % were measured with an increase in PWV (indicative of arterial stiffness), with a mean increase of 0.14 m/s (SD = 1.91) for the group. Reference scores for PWV, indicating a level that may be considered clinically significant, have not been set among adolescence. Mean PWV values reported in previous studies were slightly higher than LOOK study participants, with reported means from previous studies reviewed in the current chapter ranging from 5.16 to 7.8 m/s (Chen et al. 2012; Dietz and Matthews 2011; Midei and Matthews 2009).

In terms of lifestyle and metabolic factors, CRF increased as children progressed through high school, boys more so than girls. In terms of physical activity, there was

a small but nonsignificant decrease over this period, which was again observed for both boys and girls. As indicated in Table 1, boys were found to be significantly more active than girls, a gender difference that has been maintained from early childhood (Telford et al. 2013). Finally, a significant increase in percent body fat was observed for girls, but in contrast, a significant decrease was observed among boys. Given the differences found between boys and girls on these factors, it was important to take gender into account when analyzing the effect of stress and depression on these candidate variables for the combined cohort.

Effects of Changes in Psychological State (Stress and Depression) on Cardiovascular Function and Risk Marker Profiles

During the period of transition between late childhood and adolescence, our data did not reveal any effects of stress and depression on our two measures of cardiovascular function for our cohort. When investigating longitudinal effects of stress and depression on arterial stiffness, changes in depression and stress between grade 6 and grade 10 had no effect on change in arterial stiffness. Furthermore, cross-sectional relationships at age 10 indicated that psychosocial stress and depression had no significant effect on endothelial function or arterial stiffness at this late adolescent phase in the LOOK cohort.

On the other hand, we found that changes in depression over this time period were significantly associated with changes in CRF and percent body fat but not physical activity. Increases in depressive symptoms were associated with a decrease in CRF and an increase in percent body fat. These associations were found both before and after adjusting for potentially confounding variables (CRF adjusted for gender and height; and physical activity adjusted for percent body fat and gender). However, we found no evidence of any effect of psychosocial stress on CRF, physical activity, or percent body fat.

Taken together, findings arising from the adolescent phase of the LOOK study indicate children as young as 12 years old are already experiencing stress and depressive symptoms and more so in less fit and fatter children. We did not uncover any direct impact of stress and depression on cardiovascular function, but we are careful to point out that our tools of measurement may not have been sufficiently sensitive. Considering the relationships between depression and percent body fat; together with our previously published findings in this cohort of the impact of changes in (1) percent body fat on other risk factors such as cholesterol (Telford et al. 2014) and (2) cross-sectional relationships between physical activity and percent body fat with blood and other risk factors for CVD (Sakuragi et al. 2009), it does remain that depression and psychosocial stress in childhood and adolescence may well be implicated in the risk of developing CVD in later life.

Indeed this premise is supported by previous publications outlined above. There are a number of plausible reasons our data were not in agreement with any direct effect of psychological factors on cardiovascular function, including differences in measurement tools utilized to capture psychological disturbance. Most notably, the

LOOK study relied on self-reports from children. Future studies would benefit from using more detailed clinical interviews in capturing the level of distress and symptom patterns to better discriminate between children who are experiencing low mood versus those who are suffering clinical levels of depression. This level of data collection presents its own set of logistical difficulties in large-scale research projects such as LOOK, and detailed interviews were not viable in this particular study. Furthermore, our participants were younger than those of previous studies. This may have impacted on their understanding and ability to report on changes in their psychological state and also on the progression of subclinical CVD markers, such as arterial stiffness and endothelial function. Their young age may have contributed to a greater uniformity and low incidence of any cardiovascular dysfunction, which again would tend to offset findings of any relationships between their psychology and cardiovascular health.

Further to this observation, although our LOOK study data provided evidence of increasing stress and depression as the children moved into adolescence, the level of symptoms experienced for the majority of participants fell in what could be characterized as a "psychologically healthy" range. We suggest that the level of symptoms of stress and depression experienced by our cohort was, in general, not severe enough to have a direct impact on cardiovascular function. The underlying strength of the LOOK study lies in its longitudinal design and projection through to stages during adulthood where cardiovascular disease will, unfortunately, become evident. At this stage, we will be in a position to better interpret the symptoms shown in childhood and adolescence in terms of their real risk of CVD.

Conclusion

Our review indicates a paucity of published research investigating the effect of psychological health on direct measures of cardiovascular function in children and adolescents. Findings from the LOOK study contribute to the literature but thus far did not uncover a direct effect of psychosocial stress or depression on cardiovascular function in apparently healthy children and adolescents. However, our findings of relationships between depression and other well-established risk factors for CVD, namely, obesity and low fitness, do suggest that psychological health may play a role in the early stages of CVD. It is only through continuing longitudinal studies such as the LOOK study that the clinical significance of early signs of stress and depression in children will be understood.

References

Allen, M. T., & Patterson, S. M. (1995). Hemoconcentration and stress: A review of physiological mechanisms and relevance for cardiovascular disease risk. *Biological Psychology, 41*, 1–27.

Allison, K. R., Adlaf, E. M., Irving, H. M., Hatch, J. L., Smith, T. F., Dwyer, J. J., & Goodman, J. (2005). Relationship of vigorous physical activity to psychologic distress among adolescents. *Journal of Adolescent Health, 37*, 164–166. doi:10.1016/j.jadohealth.2004.08.017.

Australian Bureau of Statistics. (2007). *Mental health of young people* (Report No. 4840.0.55.001). Retrieved from. http://www.abs.gov.au/ausstats/abs@.nsf/mf/4840.0.55.001/.

Baum, A., & Posluszny, D. M. (1999). Health psychology: Mapping biobehavioral contributions to health and illness. *Annual Review of Psychology, 50*, 137–164.

Bonetti, P. O., Pumper, G. M., Higano, S. T., Holmes, D. R., Kuvin, J. T., & Lerman, A. (2004). Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. *Journal of the American College of Cardiology, 44*, 2137–2141.

Bruyndonckx, L., Radtke, T., Eser, P., Vrints, C. J., Ramet, J., Wilhelm, M., & Conraads, V. M. (2013). Methodological considerations and practical recommendations for the application of peripheral arterial tonometry in children and adolescents. *International Journal of Cardiology, 168*, 3183–3190. doi:10.1016/j.ijcard.2013.07.236.

Byrne, D., & Mazanov, J. (2003). Adolescent stress and future smoking behaviour: A prospective investigation. *Journal of Psychosomatic Research, 54*, 313–321.

Byrne, D. G., Davenport, S. C., & Mazanov, J. (2007). Profiles of adolescent stress: The development of the adolescent stress questionnaire (ASQ). *Journal of Adolescence, 30*, 393–416. doi:10.1016/j.adolescence.2006.04.004.

Byrne, D. G., Thomas, K. A., Burchell, J. L., Olive, L. S., & Mirabito, N. S. (2011). Stressor experience in primary school-aged children: Development of a scale to assess profiles of exposure and effects on psychological well-being. *International Journal of Stress Management, 18*, 88–111. doi:10.1037/a0021577.

Cartwright, M., Wardle, J., Steggles, N., Simon, A. E., Croker, H., & Jarvis, M. J. (2003). Stress and dietary practices in adolescents. *Health Psychology, 22*, 362–369.

Chen, Y., Dangardt, F., Osika, W., Berggren, K., Gronowitz, E., & Friberg, P. (2012). Age- and sex-related differences in vascular function and vascular response to mental stress. Longitudinal and cross-sectional studies in a cohort of healthy children and adolescents. *Atherosclerosis, 220*, 269–274. doi:10.1016/j.atherosclerosis.2011.10.030.

Dietz, L. J., & Matthews, K. A. (2011). Depressive symptoms and subclinical markers of cardiovascular disease in adolescents. *Journal of Adolescent Health, 48*, 579–584.

Dong, M., Giles, W. H., Felitti, V. J., Dube, S. R., Williams, J. E., Chapman, D. P., & Anda, R. F. (2004). Insights into causal pathways for ischemic heart disease: Adverse childhood experiences study. *Circulation, 110*, 1761–1766. doi:10.1161/01.cir.0000143074.54995.7f.

Eiland, L., & Romeo, R. D. (2013). Stress and the developing adolescent brain. *Neuroscience, 249*, 162–171. doi:10.1016/j.neuroscience.2012.10.048.

Ghiadoni, L., Donald, A. E., Cropley, M., Mullen, M. J., Oakley, G., Taylor, M., . . . Deanfield, J. E. (2000). Mental stress induces transient endothelial dysfunction in humans. *Circulation, 102*, 2473–2478.

Goldfield, G. S., Henderson, K., Buchholz, A., Obeid, N., Nguyen, H., & Flament, M. F. (2011). Physical activity and psychological adjustment in adolescents. *Journal of Physical Activity and Health, 8*, 157–163.

Gottdiener, J. S., Kop, W. J., Hausner, E., McCeney, M. K., Herrington, D., & Krantz, D. S. (2003). Effects of mental stress on flow-mediated brachial arterial dilation and influence of behavioral factors and hypercholesterolemia in subjects without cardiovascular disease. *American Journal of Cardiology, 92*, 687–691.

Grant, K. E., Compas, B. E., Stuchlmacher, A. F., Thurn, A. E., McMahon, S. D., & Halpert, J. A. (2003). Stressors and child and adolescent psychopathology: Moving from markers to mechanisms of risk. *Psychological Bulletin, 129*, 447–466.

Grant, K. E., Compas, B. E., Thurm, A. E., McMahon, S. D., & Gipson, P. Y. (2004). Stressors and child and adolescent psychopathology: Measurement issues and prospective effects. *Journal of Clinical Child & Adolescent Psychology, 33*, 412–425.

Grippo, A. J., & Johnson, A. K. (2002). Biological mechanisms in the relationship between depression and heart disease. *Neuroscience & Biobehavioral Reviews, 26*, 941–962. doi:10.1016/s0149-7634(03)00003-4.

Grippo, A. J., & Johnson, A. K. (2009). Stress, depression and cardiovascular dysregulation: A review of neurobiological mechanisms and the integration of research from preclinical disease models. *Stress, 12*, 1–21. doi:10.1080/10253890802046281.

Heitzer, T., Schlinzig, T., Krohn, K., Meinertz, T., & Münzel, T. (2001). Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation, 104*, 2673–2678. doi:10.1161/hc4601.099485.

Itamar-Medical. (2015). Retrieved 20 Jan 2015, from http://www.itamar-medical.com/Support/FAQ_EndoPAT%E2%84%A2.

Korkeila, J., Vahtera, J., Korkeila, K., Kivimaki, M., Sumanen, M., Koskenvuo, K., & Koskenvuo, M. (2010). Childhood adversities as predictors of incident coronary heart disease and cerebrovascular disease. *Heart, 96*, 298–303. doi:10.1136/hrt.2009.188250.

Kovacs, M. (1982). *The children's depression inventory*. Toronto: Multi-Health Systems.

Kovacs, M. (1992). *Children's depression inventory manual*. North Tonawanda: Multi-Health Systems.

Lerman, A., & Zeiher, A. M. (2005). Endothelial function: Cardiac events. *Circulation, 111*, 363–368.

Logan, J. G., Barksdale, D. J., Carlson, J., Carlson, B. W., & Rowsey, P. J. (2012). Psychological stress and arterial stiffness in Korean Americans. *Journal of Psychosomatic Research, 73*, 53–58. doi:10.1016/j.jpsychores.2012.04.008.

Lopez-Duran, N. L., Kovacs, M., & George, C. J. (2009). Hypothalamic–pituitary–adrenal axis dysregulation in depressed children and adolescents: A meta-analysis. *Psychoneuroendocrinology, 3*, 1272–1283. doi:10.1016/j.psyneuen.2009.03.016.

Low, C. A., Salomon, K., & Matthews, K. A. (2009). Chronic life stress, cardiovascular reactivity, and subclinical cardiovascular disease in adolescents. *Psychosomatic Medicine, 71*, 927–931.

Mattace-Raso, F. U. S., van der Cammen, T. J. M., Hofman, A., van Popele, N. M., Bos, M. L., Schalekamp, M. A. D. H., . . . Witteman, J. C. M. (2006). Arterial stiffness and risk of coronary heart disease and stroke: The Rotterdam Study. *Circulation, 113*, 657–663. doi:10.1161/circulationaha.105.555235.

McKay, M. T., Percy, A., & Byrne, D. G. (2014). Support for the multidimensional adolescent stress questionnaire in a sample of adolescents in the United Kingdom. *Stress and Health*. doi:10.1002/smi.2570. early online.

Michaud, C., Kahn, J. P., Musse, N., Burlet, C., Nicolas, J. P., & Mejean, L. (1990). Relationships between a critical life event and eating behaviour in high-school students. *Stress Medicine, 6*, 57–64.

Midei, A. J., & Matthews, K. A. (2009). Social relationships and negative emotional traits are associated with central adiposity and arterial stiffness in healthy adolescents. *Health Psychology, 28*, 347–353.

Olive, L. S., Byrne, D. G., Cunningham, R. B., Telford, R. D., & Telford, R. M. (2014). *Depression and body image in children: Is physical activity beneficial and how is this translated into clinical practice? Lifestyle of our Kids study*. Paper presented at the Australian Conference Of Science And Medicine In Sport: Be Active, Canberra.

Osika, W., Montgomery, S. M., Dangardt, F., Wahrborg, P., Gan, L. M., Tideman, E., & Friberg, P. (2011). Anger, depression and anxiety associated with endothelial function in childhood and adolescence. *Archives of Disease in Childhood, 96*, 38–43. doi:10.1136/adc.2008.152777.

Pereira, V. H., Cerqueira, J. J., Palha, J. A., & Sousa, N. (2013). Stressed brain, diseased heart: A review on the pathophysiologic mechanisms of neurocardiology. *International Journal of Cardiology, 166*, 30–37. doi:10.1016/j.ijcard.2012.03.165.

Poitras, V. J., & Pyke, K. E. (2013). The impact of acute mental stress on vascular endothelial function: Evidence, mechanisms and importance. *International Journal of Psychophysiology, 88*, 124–135.

Sakuragi, S., Abhayaratna, K., Gravenmaker, K. J., O'Reilly, C., Srikusalankui, W., Budge, M. M., Telford, R. D., & Abhayaratna, W. P. (2009). Influence of adiposity and physical activity on arterial stiffness in healthy children: the lifestyle of our kids study. *Hypertension, 53*, 611–616.

Selamet Tierney, E. S., Newburger, J. W., Gauvreau, K., Geva, J., Coogan, E., Colan, S. D., & de Ferranti, S. D. (2009). Endothelial pulse amplitude testing: Feasibility and reproducibility in adolescents. *Journal of Pediatrics, 154*, 901–905. doi:10.1016/j.jpeds.2008.12.028.

Seldenrijk, A., van Hout, H. P., van Marwijk, H. W., de Groot, E., Gort, J., Rustemeijer, C., . . . Penninx, B. W. (2011). Depression, anxiety, and arterial stiffness. *Biological Psychiatry, 69*, 795–803.

Spieker, L. E., Hurlimann, D., Ruschitzka, F., Corti, R., Enseleit, F., Shaw, S., . . . Noll, G. (2002). Mental stress induces prolonged endothelial dysfunction via endothelin-A receptors. *Circulation*, *105*, 2817–2820.

Su, S., Wang, X., Kapuku, G. K., Treiber, F. A., Pollock, D. M., Harshfield, G. A., . . . Pollock, J. S. (2014). Adverse childhood experiences are associated with detrimental hemodynamics and elevated circulating endothelin-1 in adolescents and young adults. *Hypertension, 64*, 201–207. doi:10.1161/hypertensionaha.113.02755.

Takase, B., Akima, T., Uehata, A., Ohsuzu, F., & Kurita, A. (2004). Effect of chronic stress and sleep deprivation on both flow-mediated dilation in the brachial artery and the intracellular magnesium level in humans. *Clinical Cardiology, 27*, 223–227.

Telford, R. D., Bass, S. L., Budge, M. M., Byrne, D. G., Carlson, J. S., Coles, D., . . . Waring, P. (2009). The lifestyle of our kids (LOOK) project: Outline of methods. *Journal of Science and Medicine in Sport, 12*, 156–163. doi:10.1016/j.jsams.2007.03.009.

Telford, R. M., Telford, R. D., Cunningham, R. B., Cochrane, T., Davey, R., & Waddington, G. (2013). Longitudinal patterns of physical activity in children aged 8 to 12 years: The LOOK study. *The International Journal of Behavioral Nutrition and Physical Activity*, 10. doi:10.1186/1479-5868-10-81.

Telford, R. D., Cunningham, R. B., Waring, P., Potter, J. E., Hickman, P. E., Telford, R. M., & Abhayaratna, W. P. (2014). Sensitivity of blood lipids to changes in adiposity, fitness and diet: The LOOK longitudinal study. *Medicine and Science in Sports and Exercise*. doi:10.1186/1479-5868-10-81. Epub ahead of print.

Tomfohr, L. M., Martin, T. M., & Miller, G. E. (2008). Symptoms of depression and impaired endothelial function in healthy adolescent women. *Journal of Behavioral Medicine, 31*, 137–143. doi:10.1007/s10865-007-9141-4.

Tomfohr, L. M., Murphy, M. L., Miller, G. E., & Puterman, E. (2011). Multiwave associations between depressive symptoms and endothelial function in adolescent and young adult females. *Psychosomatic Medicine, 73*, 456–461. doi:10.1097/PSY.0b013e3182228644.

Vlachopoulos, C., Kosmopoulou, F., Alexopoulos, N., Ioakeimidis, N., Siasos, G., & Stefanadis, C. (2006). Acute mental stress has a prolonged unfavorable effect on arterial stiffness and wave reflections. *Psychosomatic Medicine, 68*, 231–237.

Vlachopoulos, C., Aznaouridis, K., & Stefanadis, C. (2010). Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. *Journal of the American College of Cardiology, 55*, 1318–1327. doi:10.1016/j.jacc.2009.10.061.

World Health Organisation. (2012). *Risks to mental health: An overview of vulnerabilities and risk factors*. Retrieved from http://www.who.int/mental_health/mhgap/risks_to_mental_health_EN_27_08_12.pdf.

Bereavement and the Risk of Cardiovascular Disease

Roger Bartrop, Thomas Buckley and Geoffrey H. Tofler

Contents

R. Bartrop (✉)
Discipline of Psychiatry, Sydney Medical School-Northern, St Leonards, University of Sydney, Sydney, NSW, Australia

Department of Mental Health, Blacktown-Mt Druitt Clinical School, School of Medicine, Western Sydney University, Sydney, NSW, Australia
e-mail: roger.bartrop@sydney.edu.au; r.bartrop@uws.edu.au

T. Buckley
Sydney Nursing School, University of Sydney, Sydney, NSW, Australia

Department of Cardiology, Royal North Shore Hospital, Sydney Medical School, University of Sydney, Sydney, NSW, Australia
e-mail: tom.buckley@sydney.edu.au

G.H. Tofler
Department of Cardiology, Royal North Shore Hospital, Sydney Medical School, University of Sydney, Sydney, NSW, Australia
e-mail: geoffrey.tofler@health.nsw.gov.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_18

Abstract

"The doctor died unexpectedly at home. His wife of 45 years passed away 4 days previously. He was known for his professional, surgical expertise, and his compassionate care for patients and their families." From a notice in a local paper.

The death of a loved one has long been known to convey an adverse health risk, including increased cardiac events, although the mechanisms remain uncertain. While the mortality risk appears to be greatest in the initial weeks following bereavement, it remains significantly elevated during the first 6 months. Despite the difficulties conducting studies at this time, early bereavement has been associated with neuroendocrine activation, hemodynamic and prothrombotic changes, altered sleep, and immune imbalance, all of which may contribute to increased cardiovascular risk. Further research, based on an understanding of the underlying mechanisms and identified physiological changes, is required to pursue the goal of reducing health risk during this major life stress.

Keywords

Bereavement • Neuroendocrine • Sleep • Immune • Prothrombotic • Heart rate • Cardiovascular risk

Introduction

The death of a loved one is a ubiquitous and often highly stressful event, requiring the bereaved to frequently make significant mental and social adjustments (Stroebe et al. 2007). The mainstream media and even scientific literature still describes "death from a broken heart" affecting the spouse following the bereavement. Well-conducted epidemiological studies reveal an increased mortality risk for the surviving spouse, although some of this risk has been critically debated as an association rather than caused by the bereavement (Buckley et al. 2010). The response to bereavement, commonly referred to as grief, persists for varying periods ranging potentially from several weeks where the death is seen as a release from unbearable misery, to much longer periods of months and, for some, even years of chronic psychological distress. Bereavement can be further complicated for a surviving spouse, when that person is often required to deal with simultaneous disruption to their home life, financial insecurity, and limitation of past activities (Stroebe et al. 2007). In addition to the material changes, there may be social isolation further impacting on cardiovascular health in the longer term (Bunker et al. 2003). The death of a child has been rated to be more severe than spousal bereavement (Goodenough et al. 2004; Miyabayashi and Yasuda 2007).

In recent years emotional stress has been strongly associated with accelerated atherosclerosis and cardiovascular disease (CVD) events. In the case-control INTERHEART study, which included 11,119 cases of acute myocardial infarction (AMI) from 52 countries, perceived life event stressors and depressive illnesses together accounted for 32.5 % of the population attributable risk (PAR) for coronary heart disease (CHD), with a similar PAR to smoking and greater than hypertension (PAR 17.9 %) and diabetes (PAR 9.9 %) (Yusuf et al. 2004). The role of behavioral variables in CVD has long been suspected. An Australian National Heart Foundation position statement (Bunker et al. 2003) found that acutely stressful life events could trigger CVD events but that the relevant researchers were unable to quantify their magnitude. Since then, further publications have supported the link between acute stressors and CVD (Glozier et al. 2013). Acute psychological stressors might trigger an AMI, via a surge in heart rate and blood pressure resulting in increased myocardial oxygen demand and possible plaque disruption, vasoconstriction, and a prothrombotic effect (Tofler et al. 2012).

Protection during times of peak risk of myocardial infarction requires innovative preventative measures (Tofler and Muller 2006). However, the absence of insight into the appropriate strategies during this known risk period has not led to translatable measures in clinical practice.

This paper will discuss the evidence for increased CVD risk during the early bereavement period, in order to identify risk factors in those who are vulnerable. Additionally, the potential mechanisms of such risk need to be built into a putative representation by which grief stressors may trigger acute CVD events to inform future research directions.

Bereavement and Risk of Mortality for the Surviving Spouse

The majority of studies reporting excess mortality in early bereavement have focused on bereaved spouses, due in part to the ability to monitor spousal survival records (Buckley et al. 2010). In 1963, an early report by Young and colleagues described a follow-up of 4,486 widowers of 55 years or older comparing mortality among widowers to that of married men (Young et al. 1963). There were 66 excessive deaths in the bereaved group in the first 6 months following spousal death, representing an odds ratio of 1.39 with little difference thereafter. Since then, further retrospective cohort and case-matched studies have confirmed these data of an increased mortality risk in this period. Parkes et al. (1969), in a follow-up of almost 4,500 bereaved spouses, reported that 22.5 % of deaths were from the same diagnostic category (often cardiovascular) as the spouses' death and considered unlikely to be by chance. One explanation proposed is for there to be an attraction between individuals who are physiologically similar, while an environmental theory posits that the bereaved and their spouses share the same pathogenic environment, dietary, and social factors (Genevro et al. 2004). However, while exploring such theories, some workers found only minimal changes to the relative risks of the bereaved after adjustment for spouses' covariates (Schaefer et al. 1995),

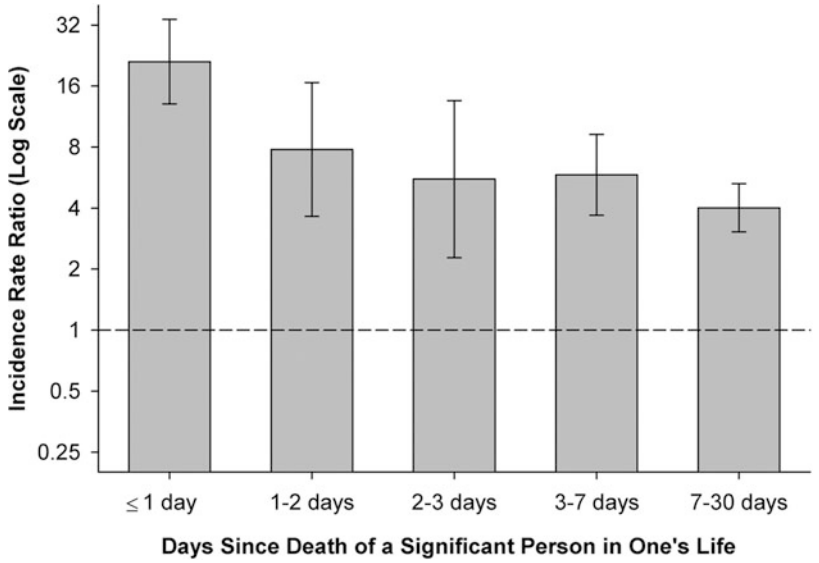


Fig. 1 Relative risk of AMI following bereavement (Adapted from Mostovsky et al. 2014)

bias from environmental influences, and common lifestyles, accidents, age, ethnicity, and education (Manor and Eisenbach 2003; Martikainen and Valkonen 1996).

The greatest mortality risk period for a surviving spouse appears to be the immediate weeks following bereavement, although the risk remains elevated for the first 6 months (Christakis and Iwashyna 2003; Hart et al. 2007). In the Renfrew/Paisley Study, bereaved spouses had a relative risk of 1.27 compared to married individuals, with the risk of death from CVD or CHD highest in the first 6 months (RR 1.21 or 1.31, respectively), even after adjustment for known cardiac risk factors (Hart et al. 2007). On the other hand, in one study of women aged <70 years who had survived 4 years after bereavement, their subsequent hazard ratio was reduced to 0.64 (Lichtenstein et al. 1998).

Among 1,985 subjects with symptoms suggestive of acute myocardial infarction (MI) enrolled in the Myocardial Infarction Onset Study (MIOS), 270 (13.6 %) had experienced a bereavement (close relative or friend) in the prior 6 months, including 19 within 1 day prior to their MI. Comparing the frequency of bereavements in the days preceding the onset of MI symptoms to its expected frequency using self-matched control data by using a crossover design, the incidence rate of MI onset was elevated 21.1-fold (95 % CI 13.1–34.1) within 1 day of the bereavement and declined steadily on each subsequent day (Mostofsky et al. 2012) (Fig. 1). The relative risk was fourfold increased for the first month and remained elevated for the first 3 months after bereavement. Since angiographic data were not routinely available in this population, some of the early cardiac events, especially in the

first day, were possibly due to Takotsubo stress cardiomyopathy rather than coronary thrombosis (Glozier et al. 2013; Lindsay et al. 2010; Mostofsky et al. 2012).

Predictors of Increased Risk

Because of the greater longevity for women than men, spousal bereavement is frequently a female phenomenon. However, men may be more at risk following spousal death, especially in the initial 6 months (Manor and Eisenbach 2003). In that study, increased risk was present across all age groups, although younger men (<54 years) and older men (>75 years) are possibly most at risk. Among bereaved women, increased mortality risk is also seen across all age groups, although those aged <75 years may be most at risk of CHD-related death following death of a spouse (Lichtenstein et al. 1998). Although an unexpected death might be expected to result in a greater risk for the surviving spouse than an expected death, this has not been consistently reported (Christakis and Iwashyna 2003) and remains an important question for further study. Reduced social support has been linked to an increased risk of CVD (Bunker et al. 2003). In one study, women with families of one to three children had a lower risk than those with either no children or more than three, suggesting that having no children resulted in less support, while more than three may have added to the pressures of the grief and subsequent mortality risk (Manor and Eisenbach 2003).

Psychological Risk Factors During Bereavement

Early bereavement is frequently associated with psychological stress evidenced by symptoms of depression, anxiety, and anger (Buckley et al. 2009; Maciejewski et al. 2007).

Depression

Symptoms of depression usually decline after the first few months of bereavement, but in some bereaved, the symptoms remain unresolved at 6 months (Buckley et al. 2009; Maciejewski et al. 2007). Both major depression and depressive symptoms in the absence of the constellation of diverse symptoms of major depression are associated with increased CVD risk (Rozanski et al. 1999; Lichtman et al. 2008). Although their relative contribution requires further elucidation, several potential mechanisms have been proposed for the increased CVD risk during depression. These include both behavioral risk factors, including medication nonadherence, increased smoking and physical inactivity and direct biological mechanisms, such as hypothalamic–pituitary–adrenal axis dysfunction, inflammatory and prothrombotic

changes, dietary factors, low omega-3 fatty acid levels, and reduced heart rate variability enhancing arrhythmogenic risks (Rozanski et al. 1999; Steptoe et al. 2006).

Anxiety

As with depressive features, anxiety symptoms usually peak early and decline after the first few months of bereavement (Gerra et al. 2003; Buckley et al. 2009; Maciejewski et al. 2007). A link between anxiety and increased risk of sudden cardiac death has been suggested (Rozanski et al. 1999). While anxiety as a CVD risk factor has not been studied as extensively as other psychosocial factors, a 2-year follow-up study of 33,999 male health professionals in the United States aged 42–77 years and initially free of diagnosed disease, revealed the age-related relative risk of fatal CVD was threefold greater for those having the highest levels of phobic anxiety, compared with those with the lowest levels (Kawachi et al. 1994).

In the MIOS study of patients interviewed after MI, 5 % reported anxiety symptoms above the 75th percentile on a standardized scale in the 2-h prior to symptom onset (Mittleman et al. 1995). Using the case-crossover methodology, when this time period was compared to a control period 24–26 h earlier, the relative risk was 1.6 (95 % confidence intervals (CI) 1.1–2.2). Additional evidence also indicates that higher symptoms of anxiety are associated with poorer outcome in patients with prior cardiac disease (Benninghoven et al. 2006). Increased sympathetic activation predisposing to life-threatening arrhythmias has been proposed as a likely pathway for the increased cardiac risk during states of increased anxiety, in addition to adverse behavioral risk factors (Rogowski et al. 2007).

Anger

Elevated anger symptoms due to frustration are not uncommon during bereavement with one study suggesting a peak in anger at 5 months after loss (Maciejewski et al. 2007). In the MIOS study, 39 (2.4 %) patients with MI reported anger $\geq$5 on a 7-point scale within 2 h of onset of MI symptoms. The relative risk was 4.0 (95 % confidence intervals 1.9–9.4) compared to the same 2 h period the day before the MI (Mittleman et al. 1995). An association between acute anger and MI was also reported in a Swedish study of 700 patients (Moller et al. 1999), with a relative risk of 9.0 (95 % CI 4.4–18.2) within 1 h after an episode of anger. Proposed mechanisms include sympathetic activation resulting in increased heart rate and blood pressure, prolonged vasoconstriction aggravating endothelial dysfunction, and a prothrombotic state (Tofler et al. 2012; Mostovsky et al. 2014).

Behavioral Changes in Bereavement

Anorexia in conjunction with bereavement has been previously reported (Shahar et al. 2001; Parkes et al. 1969) suggesting that altered nutritional or health practices

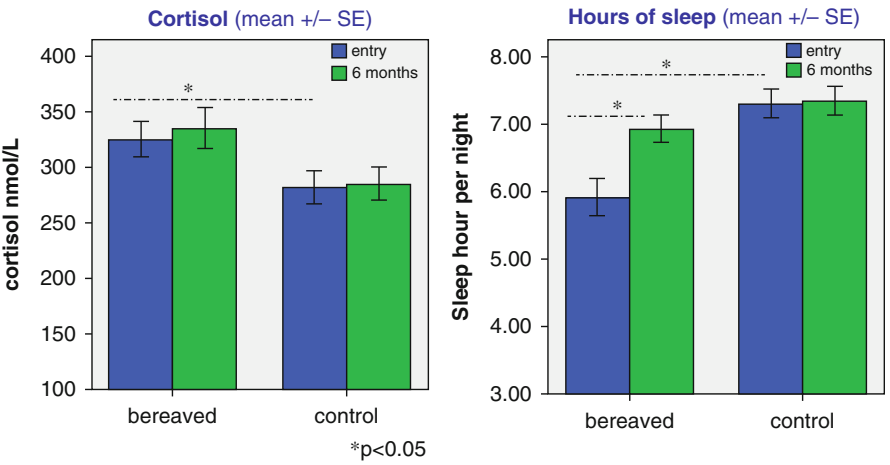


Fig. 2 Cortisol levels and self-reported hours of sleep (Adapted from Buckley et al. 2009). Morning blood cortisol levels and self-reported hours of sleep in bereaved participants at 2 weeks (entry) and 6 months compared to non-bereaved controls in the Cardiovascular Health in Bereavement Study.

particularly among widowed men make them more susceptible to CVD. In the Sydney-based Cardiovascular Health in Bereavement Study (CARBER 1) study, early bereaved subjects reported reduced appetite as well as lower cholesterol levels (Buckley et al. 2009). Increased alcohol consumption has also been reported in bereavement, particularly among men (Stroebe et al. 2007). Mor et al. (1986) reported in a sample of mainly bereaved spouses that 6 % reported increased use of alcohol and 18 % reported use of antianxiety medications. In the CARBER 1 study, 19 % of bereaved participants increased their alcohol intake in the first 2 weeks of bereavement with men more likely to increase their consumption than women (Buckley et al. 2009). However, the complex relationship between alcohol consumption and CVD risk warrants further investigation (Baer et al. 2002). Altered sleep patterns in bereavement have been reported by several research groups including the CARBER 1 study (Buckley et al. 2009) (Fig. 2). While sleep disturbance in bereavement can become chronic and debilitating for some individuals, it returns to pre-bereavement levels for most with uncomplicated grief (Richardson et al. 2003). Disturbed sleep patterns are a prominent feature of depressive symptomatology, affecting more than 80 % of people experiencing such an illness (Armitage and Hoffmann 2001). Preservation of normal sleep has been associated with less depression in bereavement (Armitage and Hoffmann 2001). Reduced sleep time as a sequel to an increased hypothalamic–pituitary–adrenal axis stress reaction may exacerbate depressive symptoms, since a strong bidirectional relationship between sleep and depression has been previously suggested (Riemann et al. 2001). In view of reported links between sleep loss and inflammatory activation (Irwin et al. 2006) and increased CVD risk (Taylor

et al. 2003), future research is needed to determine if a disturbed circadian rhythm, with reduced sleep early in bereavement, contributes to increased CVD risk.

Biological Changes in Bereavement

Cortisol

Elevated cortisol levels have been described following bereavement (Irwin et al. 1988; Nicolson 2004) with higher cortisol levels inversely associated with quality of life (Breier 1989). In the CARBER 1 study, the cortisol levels were higher in bereaved spouses compared with non-bereaved at both 2 weeks and 6 months. Levels were higher in men and associated with elevated alcohol intake (Buckley et al. 2009) (Fig. 2). In view of the potential association between cortisol and increased CVD risk, future research is needed to establish if cortisol mediates health risks in early bereavement.

Immune and Inflammatory Changes

Immune changes have been well described in bereavement. The first study to report immune changes found reduced lymphocyte responses to mitogenic stimulation at 2 and 8 weeks of bereavement (Bartrop et al. 1977). Since then, changes such as altered T-cell subpopulations and natural killer (NK) cell activity have been reported during bereavement (Goodkin et al. 1996; Irwin et al. 1988; Linn et al. 1984), although it remains unclear what role, if any, these changes contribute toward CVD risk. Altered T-cell responses have been reported by Bartrop et al. (1977) at intervals following bereavement and by Schleifer et al. (1983) at 1 month following such a loss and at 12 but not 6 months following loss of a close friend or partner in homosexual men participating in a longitudinal study of HIV-1 infection (Goodkin et al. 1996).

While reduced T-lymphocyte proliferation has been described in bereavement, the absolute number of lymphocytes is not consistently altered (Gerra et al. 2003; Irwin et al. 1988; Spratt and Denney 1991). One study of bereaved parents showed subtle changes in lymphocyte subpopulations, with Spratt suggesting that parental response to the death of a child may differ in physiological response to other bereaved adult groups (Spratt and Denney 1991). An association between reduced natural killer (NK) cell activity and bereavement has also been reported (Gerra et al. 2003; Irwin et al. 1988). Higher depression scores have been associated with an array of changes in inflammatory parameters including an absolute loss of suppressor/cytotoxic cells and an increase in the ratio of T helper to T suppressor/cytotoxic cells in bereaved women and, in some studies, lower immunoglobulin-M levels at 4–6 weeks following loss and reduced lymphocyte response (Irwin et al. 1988; Linn et al. 1984).

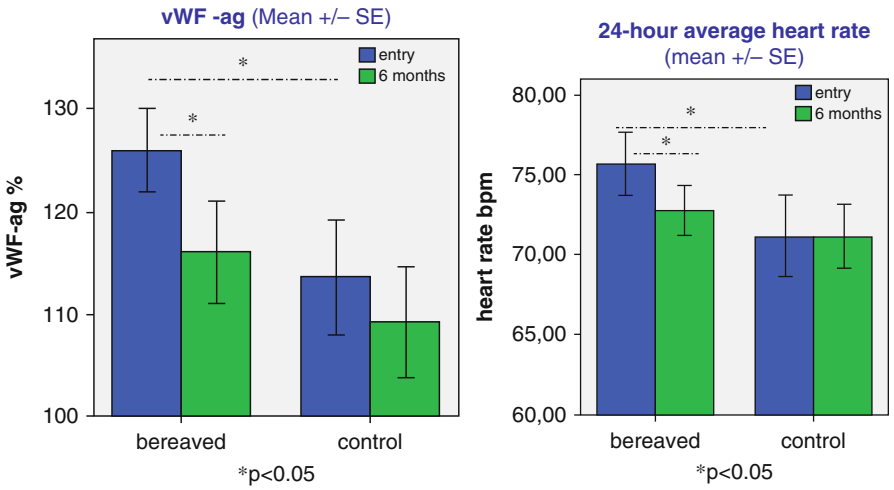


Fig. 3 Von Willebrand factor levels and 24 h average heart rate in bereaved subjects versus non-bereaved controls (Adapted from Buckley et al. 2011, 2012a). vWF-ag levels and 24-h average HR in bereaved participants at 2 weeks (entry) and 6 months compared to non-bereaved controls in the Cardiovascular Health in Bereavement Study

Recent evidence also suggests that neutrophils (nonspecific inflammatory cells) increase in number (Buckley et al. 2012a) but may decrease in function (Khanfer et al. 2011). In 24 elderly bereaved subjects at 2 months following loss, the interesting finding that neutrophil superoxide production was reduced in response to a challenge with Escherichia coli (E. coli) suggested altered ability to respond to an antigen during the early months of bereavement in this elderly population (Fig. 3) (Khanfer et al. 2011).

In the CARBER 1 study, the neutrophil count was higher in early bereaved participants compared to a matched non-bereaved sample at 2 weeks with a fall to non-bereaved levels at 6 months (Buckley et al. 2012a). Smoking was associated with this higher neutrophil count highlighting the complex potential interactions between altered health behaviors and physiological response. While the significance of increased leucocytes in bereavement is unclear to date, there may be dividends for research groups in further exploration of the inflammatory process as it plays a significant role in atherosclerosis, and inflammatory markers, including leucocytes, correlate with cardiovascular mortality (Ridker et al. 1997).

Unresolved grief may also be associated with an altered immune response. In one study, bereaved characterized by harm-avoidant personality temperaments and contemporaneous long-lasting dysphoric mood at 6 months after such bereavement had reduced immune responsiveness compared to participants whose grief levels were significantly lower (Gerra et al. 2003). Coping style in bereavement may also be a determinant of immune function in bereavement as has been shown by a North American group (Goodkin et al. 2001).

Regarding past studies in immune function in the early period of bereavement, timing of assessment appears important, suggesting that immune imbalance is not an immediate response in bereavement. Assessments in the first few weeks of bereavement reported increased circulation of inflammatory cells (neutrophils and macrophages) but not changes to lymphocyte and NK cells. However, assessments conducted 1–2 months after loss have reported altered immune response (decreased lymphocyte and NK cell function) and assessments which are conducted 6 months since the loss report normal immune and inflammatory function, except for bereaved individuals who continue to demonstrate unresolved or sustained high levels of grief response.

Prothrombotic State

Increased levels of von Willebrand factor (vWF) and increased platelet activation have been observed in early bereavement by our research group, with both changes resolving 6 months later (Buckley et al. 2012) (Fig. 3). Von Willebrand factor, a major haemostatic regulatory molecule synthesized by endothelium and involved in platelet aggregation, has previously been associated in other studies with posttraumatic stress (von Kanel et al. 2008) and clinical depression (Morel-Kopp et al. 2009). Increased platelet activation may also contribute toward CVD risk (Wang et al. 2007). One approach to prevention of CVD for those at increased risk in bereavement could be the prescribing for short-term use of antithrombotic medications, such as aspirin, in the early weeks of bereavement, as has previously proposed for other transient periods of increased risk (Tofler and Muller 2006).

Heart Rate

Both acute and chronic psychological stressors have been associated with increased heart rates (HR). For instance, symptoms of anxiety were associated with raised HR during exposure to laboratory-induced stress (Cumming et al. 2007) and during times of mental stress in air force cadets (Falaschi et al. 2003). Likewise, symptoms of anger have been associated with increases in HR (Fredrickson et al. 2000).

Twenty-four-hour monitoring carried out in the CARBER 1 study revealed higher HR in the acutely bereaved compared with a non-bereaved reference group, whereas at 6 months, HR in the bereaved had fallen to non-bereaved levels (Buckley et al. 2012a) (Fig. 3). Higher HR was also associated with higher levels of anxiety and cortisol, suggesting that elevated HR in bereavement is mediated by the hypothalamo-pituitary-adrenal axis activation. In another study of ten bereaved individuals assessed between 2 and 24 months following loss, the bereaved individuals had a higher resting HR, measured over a 5-min interval, compared to both a depressed group and a nondepressed control group (O'Connor et al. 2002).

Elevated HR in bereavement may be a significant contributor to CVD risk in early bereavement since higher HR has been linked to coronary artery plaque

rupture and CVD events (Heidland and Strauer 2001). In that study of patients with existing heart disease, an increase of five beats per minute in a 24-h assessment, as seen in the acutely bereaved participants in the Sydney-based CARBER study, increased the risk of new coronary events by 14 %, after controlling for other risk factors. Lower heart rates recorded during that study in those taking HR-lowering medications, while not surprising, suggested to our research group that these medications could be cardioprotective during early bereavement, especially in those at increased CVD risk (Buckley et al. 2012a). Higher heart rates have been linked to greater cardiovascular risk and mortality (Kizilbash et al. 2008) and coronary artery plaque rupture (Heidland and Strauer 2001).

Heart Rate Variability

There is an association between diverse psychological stressors and reduced heart rate variability (HRV) (Virtanen et al. 2003; Horsten et al. 1999) and between lower HRV and increased cardiovascular risk (Bigger et al. 1996). In the small bereavement study of O'Connor et al. (2002), no difference was reported in heart rate variability between bereaved, depressed and nondepressed groups assessed between 2 and 24 months following bereavement. However, in the larger CARBER study, early-bereaved subjects did have reduced heart rate variability, associated with higher depression scores, in the early weeks of bereavement; this variable returned to control levels at 6 months (Buckley et al. 2012b).

Blood Pressure

Hemodynamic changes including an increased blood pressure (BP) have been reported in bereavement. Among surviving spouses from deceased Alzheimer patients compared to controls, higher clinic systolic BP measures were reported studied at 6-month intervals for 18 months (Grant et al. 2002). Despite improvements in mood symptoms, raised systolic blood pressure persisted at the final assessment, on average 12 months after bereavement (Grant et al. 2002). In a prospective study, traumatic grief symptoms, often due to the nature or longevity of the loved one's illness or trauma, resulted in self-reported high blood pressure at 13- or 25-month follow-up. The sample consisted of 150 future widows and widowers interviewed at the time of their spouse's hospital admission and at follow-up. More recently, an increased prevalence of hypertension was reported among family members of deceased soldiers (Santic et al. 2006) compared to neighboring control families. Only the stress of mourning was associated with hypertension in this cohort after controlling for other cardiac risk factors. Over an average of 4 years, the proportion of hypertensive participants decreased supporting the suggestion that at least a part of the hypertension was psychologically mediated, and that the elevated BP in such instances can take considerable time to resolve (Santic et al. 2006). In the CARBER 1 study, daytime systolic blood pressure and

systolic load (% of BP measurements above 140 mmHg) were elevated in early bereavement (Buckley et al. 2011). The elevated systolic BP persisted at 6 months and was associated with variables such as longer duration of relationship with the deceased, higher anxiety and in those living alone (Buckley et al. 2011).

Discussion

Bereavement, a unique and ubiquitous psychological stressor where acute mood symptoms of depression, anxiety, and anger may last for time periods extending over several weeks or months, has been associated with increased morbidity and mortality, most notably in surviving spouses. CVD events account for a substantial proportion of such increased deaths during early bereavement. The risk is highest in the early weeks of bereavement and continues for the first 6 months among all ages and both genders. Our research and the work of others indicate that risk is elevated irrespective of whether the death is expected or not, although social support at the time of death appears to have a protective effect for the surviving spouse.

Recent advances have led to a greater understanding of the physiological mechanisms of acute coronary events and activities that might promote such acute changes. As a corollary, these data might provide new directions for future physiological evaluations during bereavement. It is now accepted that most, but not all, acute coronary occlusions occur as the result of rupture of an unstable atherosclerotic plaque and superimposed thrombus formation. But it is also known that myocardial necrosis may occur secondary to coronary vasospasm, with or without thrombus formation (Kloner 2006). Takotsubo stress cardiomyopathy may also have similarities in presentation to acute myocardial infarction (AMI), although without significant coronary stenosis or thrombosis (Wittstein et al. 2005).

A representation of the mechanisms by which bereavement may trigger MI and sudden cardiac death has been proposed (Fig. 4). Evidence suggests that increased heart rate and blood pressure, reduced heart rate variability, and prothrombotic and inflammatory change may contribute but there remains a need for further prospective longitudinal evaluations. While immune imbalance has been widely reported during bereavement, future work is also needed to establish if these changes are associated with CVD events. Nonetheless, the data are compelling for a link between bereavement and increased cardiovascular risk, and evidence supports potential mechanisms for the increased risk. Characterization of the biological changes in bereavement is an important step toward identifying those most at risk and provide encouragement to clinicians to monitor such individuals more closely, particularly in the early weeks of bereavement. Since the loss of a loved one is a universal experience, consideration should also be given to potential interventions to reduce cardiac risk, although large international collaborative studies may be required to evaluate their effectiveness. Our research group believes that the early bereavement period may be susceptible to increased cardiac protection, particularly if risk factors such as elevated heart rate and blood pressure, or increased procoagulant factors, are found to be elevated in prospective evaluations.

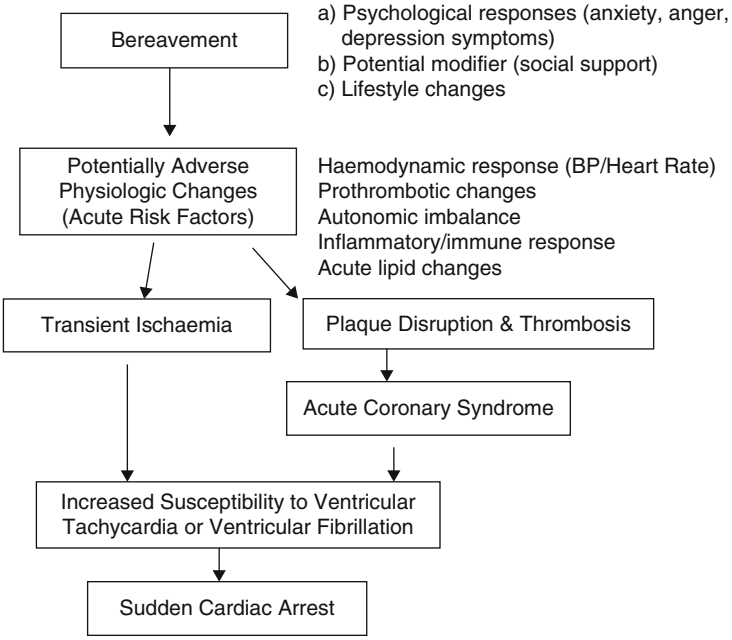


Fig. 4 Representation of how bereavement may trigger Acute Myocardial Infarction and Sudden Cardiac Death (Adapted from Tofler et al. 2012)

Conclusion

Despite the practical difficulties in conducting physiologically based studies during early bereavement, current evidence suggests that bereavement is associated with increased cortisol secretion that potentially contributes to increased cognitive arousal resulting in sleep disturbance, especially in those with intense or prolonged grief. It is likely that cortisol secretion and disruptions to sleep circadian rhythm partially contribute toward or exacerbate such apparently diverse systemic phenomena as immune, hemodynamic, and prothrombotic responses, especially in the early months following loss, and in those where grief intensity is particularly high (Fig. 4).

It is difficult to ascertain the impact of bereavement interventions on physiological correlates due to the limited number of controlled intervention studies, and the limitation of studies focusing on predominantly elderly populations. Complex grief therapy (CGT) (Prigerson et al. 1995) and antidepressant therapies (Taylor et al. 1999) show potential promise in instances where sleep disturbance becomes a prolonged feature of complex grief, especially in the elderly. However, further adequately controlled randomized controlled studies

with longer-term follow-up data are required before such therapies could be recommended broadly.

Since the work of Bartrop et al. (1977), studies have shown downregulation in T-cell function as well as mobilization of inflammatory cells. These temporary fluctuations have not yet been clearly shown to be related to increased cardiac risk. Thus it is premature to consider interventions that promote immune function except where certain inflammatory disorders are known to have a substratum of immune suppression (Miller and Cohen 2001). Even though the significance of the immunopathology is unclear, scope exists to minimize infections by appropriate hygiene for the bereaved individual and initiating efforts to avoid contracting respiratory infections. Hemodynamic and prothrombotic changes in early bereavement raise the possibility that therapies that impact on these changes may reduce CVD risk; an ongoing study (CARBER 2) is currently evaluating this hypothesis using low-dose beta-blocker and aspirin.

Where possible, clinicians should also make themselves aware of and influence potentially adverse behavioral changes in the early- or medium-term periods of bereavement such as increases in tobacco and alcohol intake, as well as poor dietary choices. Although the focus before bereavement is naturally directed toward the ill or dying person, the health and welfare of bereaved survivors should be of great concern to health care professionals, family, and friends.

Much has been achieved since predictions that there would soon be evidence of physiological correlates of health risk in early bereavement. Now that evidence for increased CVD risk is present in bereavement, it is time to consider and test preventative interventions aimed at reducing the health risk during this significant and universal period of exposure to a major life stressor. The key message, however, is one of hope for a satisfactory passage through what is, after all, a natural process and one that mankind will all have to navigate.

References

Armitage, R., & Hoffmann, R. (2001). Sleep EEG, depression and gender. *Sleep Medicine Reviews, 5*, 237–246.

Baer, D. J., Judd, J. T., Clevidence, R. A., Muesing, R. A., Campbell, W. S., Brown, E. D., et al. (2002). Moderate alcohol consumption lowers risk factors for cardiovascular disease in postmenopausal women fed a controlled diet. *American Journal Clinical Nutrition, 75*, 593–599.

Bartrop, R. W., Luckhurst, E., Lazarus, L., Kiloh, L. G., & Penny, R. (1977). Depressed lymphocyte function after bereavement. *Lancet, 1*(8016), 834–836.

Benninghoven, D., Kaduk, A., Wiegand, U., Specht, T., Kunzendorf, S., & Jantschek, G. (2006). Influence of anxiety on the course of heart disease after acute myocardial infarction – risk factor or protective function. *Psychotherapy and Psychosomatics, 75*, 56–61.

Bigger, J. T., Jr., Steinman, R. C., Rolnitzky, L. M., Fleiss, J. L., Albrecht, P., & Cohen, R. J. (1996). Power law behaviour of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplant. *Circulation, 93*, 2142–2151.

Breier, A. (1989). A.E. Bennett award paper. Experimental approaches to human stress research: Assessment of neurobiological mechanisms of stress in volunteers and psychiatric patients. *Biological Psychiatry, 26*, 438–462.

Buckley, T., Bartrop, R., McKinley, S., Ward, C., Bramwell, M., Roche, D., Miahilidou, A. S., Morel-Kopp, M.-C., & Spinaze, M. (2009). A prospective study of early bereavement on psychological and behavioural cardiac risk factors. *International Medical Journal, 39*, 370–378.

Buckley, T., McKinley, S., Tofler, G. H., & Bartrop, R. (2010). Cardiovascular risk in early bereavement: A literature review and proposed mechanisms. *International Journal of Nursing Studies, 45*, 229–238.

Buckley, T., Mihailidou, A., Bartrop, R., et al. (2011). Haemodynamic changes during early bereavement: Potential contribution to increased cardiovascular risk. *Heart, Lung & Circulation, 20*, 91–98.

Buckley, T., Morel-Kopp, M. C., Ward, C., Bartrop, R., McKinley, S., Mihailidou, A. S., Spinaze, M., Chen, W., & Tofler, G. (2012a). Inflammatory and thrombotic changes in early bereavement: A prospective evaluation. *European Journal Prevention Cardiology, 19*, 1145–1152.

Buckley, T., Stannard, A., Bartrop, R., McKinley, S., Ward, C., Mihailidou, A. S., Morel-Kopp, M.-C., Spinaze, M., & Tofler, G. (2012b). Effect of early bereavement on heart rate and heart rate variability. *The American Journal of Cardiology, 110*, 1378–1383.

Bunker, S. J., Colquhoun, D. M., & Esler, M. D. (2003). "Stress" and coronary heart disease: Psychosocial risk factors. *The Medical Journal of Australia, 178*, 272–276.

Christakis, N. A., & Iwashyna, T. J. (2003). The health impact of health care on families: A matched cohort study of hospice use by decedents and mortality outcomes in surviving, widowed spouses. *Social Science and Medicine, 57*, 465–475.

Cumming, J., Olphin, T., & Law, M. (2007). Self-reported psychological states and physiological responses to different types of motivational general imagery. *Journal of Sport & Exercise Psychology, 29*, 629–644.

Falaschi, P., Proietti, A., De Angelis, C., et al. (2003). Effects of mental stress on cardiovascular and endocrine response in Air Force Academy cadets. *Neuro Endocrinology Letters, 24*, 197–202.

Fredrickson, B. L., Maynard, K. E., MHElms, M. J., Haney, T. L., Siegler, J. C., & Barefoot, J. C. (2000). Hostility predicts magnitude and duration of blood pressure response to anger. *Journal of Behavioral Medicine, 23*, 229–243.

Genevro, J. L., Marshall, T., & Miller, T. (2004). Report on bereavement and grief research. *Death Studies, 28*(6), 491–575.

Gerra, G., Monti, D., Panerai, A., Sacerdote, P., Anderlini, R., Avanzini, P., Zaimovic, A., Brambilla, F., & Franceschi, C. (2003). Long-term immune-endocrine effects of bereavement: Relationships with anxiety levels and mood. *Psychology Research, 121*, 145–158.

Glozier, N., Tofler, G. H., Colquhoun, D. M., Bunker, S. J., Clarke, D. M., Hare, D. L., Hickie, I. B., Tatoulis, J., Thompson, D. R., Wilson, A., & Branagan, M. G. (2013). Psychosocial risk factors for coronary heart disease. *The Medical Journal of Australia, 199*, 179–180.

Goodenough, B., Drew, D., Higgins, S., & Trethewie, S. (2004). Bereavement outcomes for parents who lost a child to cancer: Are place of death and sex of parent associated with differences in psychological functioning. *Psychooncology, 13*, 779–791.

Goodkin, K., Feaster, D. J., Tuttle, R., Blaney, N. T., Kumar, M., Baum, M. K., Shapshak, P., & Fletcher, M. A. (1996). Bereavement is associated with time-dependent decrements in cellular immune function in asymptomatic human immunodeficiency virus type 1-seropositive homosexual men. *Clinical and Diagnostic Laboratory Immunology, 3*, 109–118.

Goodkin, K., Baldewicz, T. T., Asthana, D., Khamis, I., Blaney, N. T., Kumar, M., Burkhalter, J. E., Leeds, B., & Shapshak, P. (2001). A bereavement support group intervention affects plasma burden of human immunodeficiency virus type 1. Report of a randomized controlled trial. *Journal of Human Virology, 4*, 44–54.

Grant, I., Adler, K. A., Patterson, T. L., Dimsdale, J. E., Ziegler, M. G., & Irwin, M. R. (2002). Health consequences of Alzheimer's caregiving transitions: Effects of placement and bereavement. *Psychosomatic Medicine, 64*, 477–486.

Hart, C. L., Hole, D. J., Lawlor, D. A., Smith, G. D., & Lever, T. F. (2007). Effect of conjugal bereavement on mortality of the bereaved spouse in participants of the Renfrew/Paisley study. *Journal Epidemiology and Communication Health, 61*, 455–460.

Heidland, U. E., & Strauer, B. E. (2001). Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. *Circulation, 104*, 1477–1482.

Horsten, M., Ericson, M., Perski, A., Wamala, S. P., Schenck-Gustafsson, K., & Orth-Gomer, K. (1999). Psychosocial factors and heart rate variability in healthy women. *Psychosomatic Medicine, 61*(1), 49–57.

Irwin, M., Daniels, M., Risch, S. C., Bloom, E., & Weiner, H. (1988). Plasma cortisol and natural killer cell activity during bereavement. *Biological Psychiatry, 24*, 173–178.

Irwin, M., Wang, M., Ribeiro, D., Cho, H. J., Olmstead, R., Breen, E. C., et al. (2006). Sleep loss activates cellular inflammatory signaling. *Biological Psychiatry, 63*, 538–540.

Kawachi, I., Colditz, G. A., Ascherio, A., et al. (1994). Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation, 89*(5), 1992–1997.

Khanfer, R., Lord, J. M., & Phillips, A. C. (2011). Neutrophil function and cortisol: DHEAS ratio in bereaved older adults. *Brain, Behavior, and Immunity, 25*, 1182–1186.

Kizilbash, M. A., Daviglus, M. L., Dyer, A. R., Garside, D. B., Hankinson, A. L., Yan, L. L., Tian, L., Van, L., Wang, R., & Greenland, P. (2008). Relation of heart rate with cardiovascular disease in normal-weight individuals: The Chicago Heart Association Detection Project in Industry. *Preventive Cardiology, 11*, 141–147.

Kloner, R. A. (2006). Natural and unnatural triggers of myocardial infarction. *Progress Cardiovascular Diseases, 48*, 285–300.

Lichtenstein, P., Gatz, M., & Berg, S. (1998). A twin study of mortality after spousal bereavement. *Psychological Medicine, 28*, 635–643.

Lichtman, J. H., Bigger, J. T., Jr., Blumenthal, J. A., et al. (2008). Depression and coronary heart disease: Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. *Circulation, 118*, 1768–1775.

Lindsay, J., Paixao, A., Chao, T., & Pichard, A. D. (2010). Pathogenesis of the takotsubo syndrome: A unifying hypothesis. *The American Journal of Cardiology, 106*, 1360–1363.

Linn, M. W., Linn, B. S., & Jensen, J. (1984). Stressful events, dysphoric mood, and immune responsiveness. *Psychological Reports, 54*, 219–222.

Maciejewski, P. K., Zhang, B., Block, S. D., & Prigerson, H. G. (2007). An empirical examination of the stage theory of grief. *JAMA, 297*, 716–723.

Manor, O., & Eisenbach, Z. (2003). Mortality after spousal loss: Are there socio-demographic differences? *Social Science & Medicine, 56*, 405–413.

Martikainen, P., & Valkonen, T. (1996). Mortality after the death of a spouse: Rates and causes of death in a large Finnish cohort. *American Journal of Public Health, 86*, 1087–1093.

Miller, G. E., & Cohen, S. (2001). Psychological interventions and immune system: A meta-analytic review and critique. *Health Psychology, 20*, 47–63.

Mittleman, M. A., Maclure, M., Sherwood, J. B., Mulry, R. P., Tofler, G. H., Jacobs, S. C., Friedman, R., Benson, H., & Muller, J. E. (1995). Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators. *Circulation, 92*, 1720–1725.

Miyabayashi, S., & Yasuda, J. (2007). Effects of loss from suicide, accidents, acute illness and chronic illness on bereaved spouses and parents in Japan: Their general health, chronic depressive mood, and grief reaction. *Psychiatry and Clinical Neurosciences, 61*, 502–508.

Moller, J., Hallqvist, J., Diderichsen, F., Theorell, T., Reuterwall, C., & Ahglbom, A. (1999). Do episodes of anger trigger myocardial infarction? A case-crossover analysis in the Stockholm Heart Epidemiology Program (SHEEP). *Psychosomatic Medicine, 61*, 842–849.

Mor, V., McHorney, C., & Sherwood, S. (1986). Secondary morbidity among the recently bereaved. *American Journal Psychology, 143*, 158–163.

Morel-Kopp, M. C., McLean, L., Chen, Q., Tofler, G. H., Tennant, C., Maddison, V., & Ward, C. M. (2009). The association of depression with platelet activation: Evidence for a treatment effect. *Journal of Thrombosis and Haemostasis, 7*, 573–581.

Mostofsky, E., Maclure, M., Sherwood, J. B., Tofler, G. H., Muller, J. E., & Mittleman, M. A. (2012). Death of a significant person increases the risk of acute myocardial infarction onset: The Determinants of MI Onset Study. *Circulation, 125*, 491–496.

Mostovsky, E., Penner, E. A., & Mittleman, M. A. (2014). Outbursts of anger as a trigger of acute cardiovascular events: A systematic review and meta-analysis. *European Heart Journal, 35* (21), 1404–1410.

Nicolson, N. A. (2004). Childhood parental loss and cortisol levels in adult men. *Psychoneuroendocrinology, 29*, 1012–1018.

O'Connor, M. F., Allen, J. J., & Kaszniak, A. W. (2002). Autonomic and emotion regulation in bereavement and depression. *Journal of Psychosomatic Research, 52*, 183–185.

Parkes, C. M., Benjamin, B., & Fitzgerald, R. C. (1969). Broken heart: A statistical study of increased mortality among widowers. *BMJ, 1*(646), 740–743.

Prigerson, H. G., Maciejewski, P. K., Reynolds, C. F., 3rd, Bierhals, A. J., Newsom, J. T., Fasiczka, A., Frank, E., Doman, J., & Miller, M. (1995). Inventory of complicated grief: A scale to measure maladaptive symptoms of loss. *Psychiatry Research, 59*, 65–79.

Richardson, S., Lund, D., Caserta, M., Dudley, W., & Obray, S. (2003). Sleep patterns in older bereaved spouses. *Omega – Journal Death & Dying, 47*, 361–383.

Ridker, P. M., Cushman, M., Stampfer, M. J., Tracy, R. P., & Hennekens, C. H. (1997). Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *The New England Journal of Medicine, 336*, 973–979.

Riemann, D., Berger, M., & Voderholzer, U. (2001). Sleep and depression – results from psychobiological studies: An overview. *Biological Psychology, 57*, 67–103.

Rogowski, O., Shapira, I., SHirom, A., Melamed, S., Toker, S., & Berliner, S. (2007). Heart rate and microinflammation in men: A relevant atherothrombotic link. *Heart, 93*, 940–944.

Rozanski, A., Blumenthal, J. A., & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation, 99*, 2192–2217.

Santic, Z., Lukic, A., Sesar, D., Milicevic, S., & Ilakovac, V. (2006). Long-term follow-up of blood pressure in family members of soldiers killed during the war in Bosnia and Herzegovina. *Croatian Medical Journal, 47*, 416–423.

Schaefer, C., Quesenberry, C. P., & Wi, S. (1995). Mortality following conjugal bereavement and the effects of a shared environment. *American Journal of Epidemiology, 141*, 1142–1152.

Schleifer, S. J., Keller, S. E., Camerino, M., Thornton, J. C., & Stein, M. (1983). Suppression of lymphocyte stimulation following bereavement. *JAMA, 250*, 374–377.

Shahar, D. R., Schultz, R., Shahar, A., & Wing, R. R. (2001). The effect of widowhood on weight change, dietary intake and eating behaviour. *Journal of Aging and Health, 13*, 189–199.

Spratt, M. L., & Denney, D. R. (1991). Immune variables, depression, and plasma cortisol over time in suddenly bereaved parents. *The Journal of Neuropsychiatry and Clinical Neurosciences, 3*, 299–306.

Steptoe, A., Strike, P. C., Perkins-Porras, L., McEwan, J. R., & Whitehead, D. L. (2006). Acute depressed mood as a trigger of acute coronary syndromes. *Biology Psychology, 60*, 837–842.

Stroebe, M., Schut, H., & Stroebe, W. (2007). Health outcomes of bereavement. *Lancet, 370*, 1960–1973.

Taylor, M. P., Reynolds, C. F., 3rd, Frank, E., Dew, M. A., Mazumdar, S., Houck, P. R., & Kupfer, D. J. (1999). EEG sleep measures in later-life bereavement depression. A randomized, double-

blind, placebo-controlled evaluation of nortriptyline. *American Journal Geriatric Psychiatry, 7*, 41–47.

Taylor, D. J., Lichstein, K. L., & Durrence, H. H. (2003). Insomnia as a health risk factor. *Behavioral Sleep Medicine, 1*, 227–247.

Tofler, G. H., & Muller, J. E. (2006). Triggering of acute cardiovascular disease and potential preventive strategies. *Circulation, 114*, 1863–1872.

Tofler, G. H., O'Farrell, A., & Buckley, T. (2012). Psychological triggers for plaque rupture. In P. Hjemdahl, A. Rosengren, & A. Steptoe (Eds.), *Stress and cardiovascular disease*. London: Springer.

Virtanen, R., Jula, A., Salminen, J. K., Voipio-Pulkki, L. M., Helenius, H., Kuusela, T., et al. (2003). Anxiety and hostility are associated with reduced baroreflex sensitivity and increased beat-to-beat blood pressure variability. *Psychosomatic Medicine, 65*, 751–756.

von Kanel, R., Hepp, U., Traber, R., Kraemer, B., Mica, L., Keel, M., Mausbach, B. T., & Schnyder, U. (2008). Measures of endothelial dysfunction in plasma of patients with posttraumatic stress disorder. *Psychiatry Research, 158*, 363–373.

Wang, J., Zhang, S., Jin, Y., Qin, G., Yu, L., & Zhang, J. (2007). Elevated levels of platelet-monocyte aggregates and related circulating biomarkers in patients with acute coronary syndrome. *International Journal of Cardiology, 115*, 361–365.

Wittstein, I. S., Thiemann, D. R., Lima, J. A., et al. (2005). Neurohumoral features of myocardial stunning due to sudden emotional stress. *The New England Journal of Medicine, 352*, 539–548.

Young, M., Benjamin, B., & Wallis, C. (1963). The mortality of widowers. *Lancet, 13*, 454–456.

Yusuf, S., Hawken, S., Ounpuu, S., et al. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*, 937–952.

Anxiety and Cardiovascular Disease: Epidemiology and Proposed Mechanisms

Marlies E. Alvarenga and Don Byrne

Contents

Abstract

Anxiety disorders tend to be highly prevalent in heart disease, particularly amongst patients recovering from acute cardiac events. Yet, the role of anxiety in heart disease has not received as much attention in the literature as has depression. Epidemiologic studies indicate that there is an increased risk of

M.E. Alvarenga (✉)
MonashHEART, Monash Cardiovascular Research Centre, Monash Health and Department of Medicine (SCS at Monash), Monash University, Melbourne, VIC, Australia
e-mail: marlies.alvarenga@monash.edu

D. Byrne
ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia

ANU Medical School, Research School of Psychology, Australian National University, Acton, Canberra, ACT, Australia
e-mail: Don.Byrne@anu.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_10

sudden death and myocardial infarction in patients experiencing panic anxiety. Pathophysiologic correlates of anxiety appear to contribute to an increased cardiac risk, leading to the appreciation that anxiety disorders might in fact constitute a risk to life as exemplified by the cardiovascular disease link. Explanatory mechanisms of cardiac risk point to a link between anxiety and heart disease being mediated by stress giving way to increased cardiac sensitivity and reactivity.

The present chapter reviews the psychobiological link between anxiety and heart disease. It also supports an integrative approach for the analysis of psychogenic heart disease, that cardiac patients can benefit from cardiologists educating them about the influence of psychosocial factors on their cardiac conditions and that further research is required on the development of specific psychologically based therapies which tap into the proposed pathophysiological mechanisms associated with the mind-heart nexus.

Keywords

Anxiety • Heart disease • Psychogenic heart disease • Explanatory models • Psychobiology

The link between the mind and heart is not an entirely new proposition; it has in fact been a long-standing philosophical argument until the reductionist medical model of health ultimately led to research and treatment of mental and physical diseases being carried out separately by psychological and medical disciplines. Indeed, it was Descartes who initially proposed dualism as an explanation for how mental and physical processes were independent of one another (Descartes 1649). Yet this philosophical proposition cannot deny both anecdotal and empirical accounts that the body and mind work collaboratively rather than autonomously and that the relationship between these systems appears to be bidirectional.

Anxiety and Heart Disease

The recognition that emotions might be regulated as much by the heart as they are by the mind supports an integrative approach between these seemingly unrelated entities. The pioneering psychologist William James was of the clear view that our emotions generally, and anxiety in particular, were little more than self-reports of our subjective perceptions of the somatic changes occurring during the flight/fight response (James 1892). And since the cardiovascular system figures too prominently in that most basic of all systemic biological phenomena, it is not surprising that the heart has been tied so closely to the experience of anxiety.

The epistemology of the heart and mind link is indeed more than a philosophical argument that explores how mental processes have the capacity to influence the manifestation of physical phenomena and vice versa; it also raises the challenge of exploring precise mechanisms linking the body and mind. Pathophysiologic

correlates of anxiety appear to contribute to an increased risk of heart disease (Roest et al. 2010; Janszky et al. 2010) leading to the appreciation that anxiety disorders might in fact constitute a risk to life mediated by the cardiovascular disease link.

The research literature on the mental illness–heart disease link has in the most part focused on the effect of depression on the heart, which has led to the recognition of depression as an independent risk factor for the development of heart disease (Bunker et al. 2003; Wulsin and Singal 2003). Less extensible research has been the role of anxiety as a formative influence on cardiovascular pathology and its possible role as a precipitant to acute cardiac events in those with an already compromised cardiovascular system. In the 1870s, during the American Civil War, Jacob Mendes Da Costa (1833–1900) investigated and described what was then colloquially known as "soldier's heart" or "irritable heart," a condition where the individual described the experience of symptoms of heart disease, accompanied by feelings of fear but which upon physical examination failed to detect any physiological abnormalities (Da Costa 1871). Today, ICD-10 still classifies this condition as Da Costa's syndrome, a type of health anxiety disorder focused on the heart; however, in DSM-V the term has been superseded by more specific diagnoses such as panic disorder, somatic symptom disorder, or illness anxiety disorder. The phenomena of anxiety being linked to cardiac symptomatology have therefore had a long recognition which requires further exploration. Indeed, the potential of anxiety as a direct risk factor for heart disease both in terms of morbidity and mortality requires more attention, particularly in light of the associations that have been established between anxiety and coronary artery disease (Fleet et al. 2000) and sudden cardiac death (Kawachi et al. 1994).

Anxiety

Anxiety is a commonly experienced sense of alarm in response to perceived threat that includes pronounced apprehension about the future (Barlow 2002). When anxiety is frequently experienced at high levels of intensity and/or in inappropriate situations, it can then be categorized as a disorder (Thurston et al. 2013). The EUROASPIRE III Study (Kotseva et al. 2009) assessed the prevalence of anxiety and depression in heart disease across 22 countries and found that anxiety varied from 12.0 % to 41.8 % in men and from 21.5 % to 63.7 % in women, with older age, female sex, low education, and no history of invasive treatment being associated with more frequent depression and anxiety (Pajak et al. 2013). Anxiety is a major problem in cardiac patients that can increase heartbeat rate and blood pressure and also the risk of cardiac dysrhythmias (Brunner et al. 2004; Heikkila et al. 1998; Uzun et al. 2008). Anxiety increases psychological and physiological activity of the body such as heartbeat, blood pressure, and heart output, and this probably puts the cardiovascular system of patients at risk (Brunner et al. 2004). Raised heart rate is a marker of cardiovascular risk in the general population as well as those with existing heart disease (Kannel et al. 1987; Kolloch et al. 2008; Fox et al. 2008).

DSM-V

Anxiety is ubiquitous by nature, and its severity and prevalence can significantly fluctuate over time, to a point where an individual might not meet clinical criteria for an anxiety disorder but where anxiety and chronic worry might nonetheless be evident. This can pose as a challenge when researching the role of this condition in heart disease, particularly as subclinical levels of anxiety have also been found to be linked to an increased risk of developing coronary heart disease (Rozanski et al. 1999). Thus, further understanding of how anxiety may impact heart disease risk may be enhanced by studies also including subclinical measures of anxiety. In addition, anxiety is a more persistent disorder than depression and historically a harder disorder to treat effectively; therefore, it could be argued that the role of this condition in the pathogenesis of heart disease might require a novel research approach to effectively elucidate the anxiety–heart disease link.

Prevalence of Anxiety

It has been estimated that anxiety disorders constitute the most prevalent psychiatric diseases in the west, with the highest lifetime prevalence estimates ranging from around 14 % to 29 % (Kessler et al. 2005). An anxiety disorder can be described as "an umbrella term" which can manifest in various distinct forms such as panic disorder, generalized anxiety disorder, obsessive compulsive disorder, posttraumatic stress disorder, and various phobias (APA 2000), and while distinct, these disorders have comparable cognitive, neurobiological, and behavioral components both at the clinical and subclinical levels (Moser and De Jong 2006). Anxiety disorders more often than not tend to be comorbid with other psychiatric and physical diseases (Cameron 2007). Anxiety is highly prevalent in heart disease, particularly among patients recovering from acute cardiac events (Kubzansky and Arthur 2004) and in older adults suffering from heart disease (El-Gabalawy et al. 2013). A survey of general practitioners published in the *British Journal of Cardiology* in 2006 unveiled that rates of anxiety (30 %) were higher than for depression (20 %) following myocardial infarction (Thornton et al. 2006). In patients with unstable angina and myocardial infarction, rates of anxiety appeared persistent 1 year after their acute cardiac event (Grace et al. 2004).

Anxiety also appears to precipitate heart disease. A meta-analysis of 20 studies found that the presence of anxiety at baseline was associated with a 26 % increase in risk of onset of heart disease (95 % CI, 1.15–1.38) and 48 % increase in cardiac death (95 % CI, 1.14–1.92) in a nonpsychiatric sample over a mean follow-up period of 11.2 years (Roest et al. 2010). Janszky et al. (2010) in a longitudinal study spanning 37 years found that men diagnosed with anxiety, but not depression, were more than twice as likely to develop coronary heart disease (CHD) compared with a non-anxious matched sample. This appears to be supported by Rothenbacher et al.'s (2007) earlier finding that in patients with coronary heart disease undergoing cardiac rehabilitation, anxiety is a stronger predictor of long-term prognosis of

relapse than depression. Anxiety has also been linked with an increased risk of ventricular arrhythmias (Wilkinson et al. 1998), carotid atherosclerosis (Paterniti et al. 2001), nonfatal myocardial infarction, and sudden cardiac death (Kawachi et al. 1994, 1996).

Anxiety and Stress

Stress is closely related to the development and maintenance of anxiety and its complications (Black and Garbutt 2002), and it has been associated with the risk and the occurrence of cardiac disease (Mosovich et al. 2008). Rosengren et al. (2004) reported that in the first-time myocardial infarction cohort of males and females, across different countries, there had been a high prevalence of stressful events in the 12 months preceding the acute cardiac event compared to a control group. Patients experiencing ventricular fibrillation, without previous cardiac pathology, have also described significantly greater incidence of severe to moderate stressful events in the 6–24 months preceding their acute cardiac event (Lane et al. 2005). Systematic evidence has been gathered at times of natural and man-made disasters, which strongly support the link between stress and heart disease (Leor et al. 1996; Meisel et al. 1991). Forty-eight hours after the 2001 Nisqually earthquake in Washington, USA, there was a significant increase in the number of cardiac deaths ($p = 0.02$) when compared to the number of cardiac deaths at the same time in previous years (Gold et al. 2007). Earlier, Leor et al. (1996) also reported an increase in mortality from cardiac causes as a result of the 1994 Los Angeles earthquake. Sudden cardiac death related to atherosclerotic cardiovascular disease increased from a daily average of 4.6 ± 2.1 in the preceding week to 24 on the day of the earthquake ($z = 4.41, p < 0.001$). During the six days after the earthquake, their results showed a drop in the number of sudden cardiac deaths to below baseline (Leor et al. 1996) (Fig. 1).

The effects of emotional stress in heart disease arising from "excitation" have also been researched with the 2006 Football World Cup in Germany showing a spike in incidences of cardiac emergencies having a positive correlation with the national team playing at the tournament (Mendenhall et al. 2008). The research team calculated incidence ratios for the 7 days of matches played by the German team and the 24 days of matches not involving the German team as a control. They then calculated incidence ratios for subgroups of patients, according to their final diagnosis. Their results showed a significant increase in the incidence of acute coronary syndrome and symptomatic cardiac arrhythmia when the German team played as opposed to when they did not play at the tournament. The fans' anguish over whether their team would win the match was also evident with spikes in cardiac events observed when the national team played with perceived good teams as opposed to when they played with perceived poorer teams. These studies did not examine preexisting levels of anxiety in their sample nor did they seem to account for other potential sources of cardiac risk, such as spectators being sleep deprived,

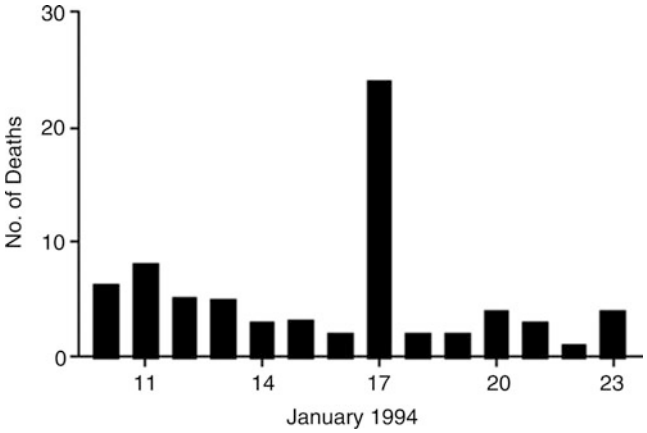


Fig. 1 Daily numbers of Sudden Deaths Related to Atherosclerotic Cardiovascular Disease from January 10 through 23, 1994

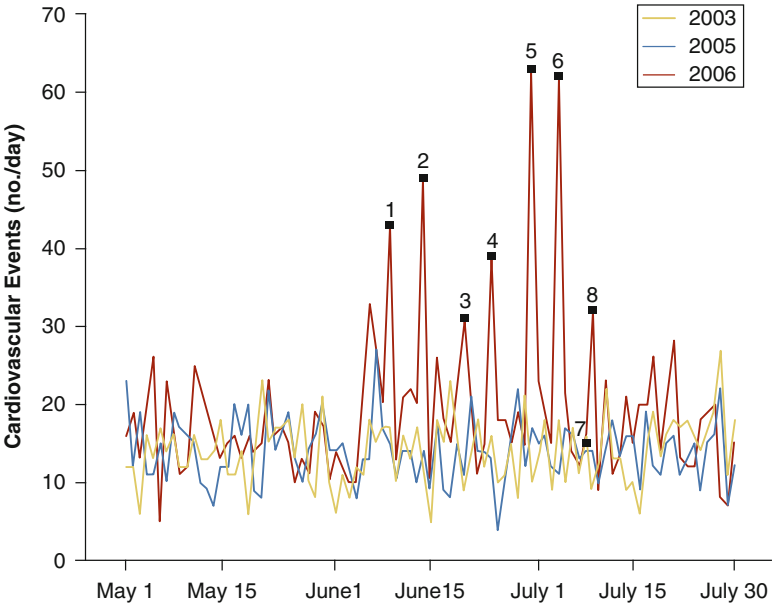


Fig. 2 Daily Cardiovascular Events in the Study Population from May 1 to July 31 in 2003, 2005, and 2006

diet during World Cup matches, or whether medication had been neglected due to preoccupation with World Cup match (Fig. 2).

A satisfactory definition of stress can of course be a complex matter, but it cannot be denied that in a significant manner sudden stress incorporates a strong element of acute anxiety.

The impact of anxiety on heart disease appears to be both a contributing factor and an obstacle to recovery, where anxiety has the potential to impede the recovery of patients who have suffered from acute cardiac events by creating a fear of physical exertion which could potentially sabotage the patient's adherence to exercise regimes (Graham 2003). It can also make these patients withdrawn (in extreme cases agoraphobic), which can lead to social disconnection and comorbid depression (Kalisch et al. 2005). An increased focus on the heart, making the patient "hyperaware" of cardiac symptomatology, can potentially lead to the experience of debilitating panic attacks (Asmundson et al. 1993). Anxiety can also affect concentration and procrastination which in turn can create difficulties when it comes to patient's adhering to rehabilitation and medication regimes (Daly et al. 2002; McGrady et al. 2009). The families of these patients can also be affected by sharing the emotional distress of the sufferer, intimacy can be compromised between partners for fear of provoking another cardiac event, and overall quality of life can diminish (Friedman 2000; Thrall et al. 2007). Failing to appreciate and effectively address the role of anxiety and its impact on the development and maintenance of heart disease might be a significant contributing factor for cardiovascular disease's staying power as the leading cause of morbidity and mortality worldwide (Mathers and Loncar 2006).

Anxiety Syndromes and Increased Cardiac Risk

Most research investigating the role of anxiety in heart disease has predominantly assessed symptom levels, and no differentiation has been made between different types of anxiety disorders making up the research samples.

Batelaan et al. (2014) undertook a study examining the differential impact of panic, phobia, and worry on a 3-year onset of nonfatal cardiovascular disease and found that generalized anxiety disorder (GAD) was strongly associated with nonfatal cardiovascular disease. Hammel et al. (2011) showed that GAD patients displayed lower inter-beat heart rate and lower heart rate variability, indicating that the worry type of anxiety disorders appears to substantially increase risk of cardiovascular disease through decreased parasympathetic activity and increased sympathetic response. Martens et al. (2010) found the presence of GAD increased the risk for subsequent major cardiac events between 61 % and 74 %, even after adjusting for comorbid depression, indices of cardiac function, medication, and physical inactivity. These findings are in keeping with previous research examining the impact of worry on coronary heart disease (Kubzansky et al. 1997) and cardiovascular mortality (Phillips et al. 2009).

Phobic disorders do not appear to be associated with increased risk of cardiovascular disease (Batelaan et al. 2014) as found in previous studies (Albert et al. 2005; Haines et al. 1987; Kawachi et al. 1994) investigating this association in men. However, Brennan et al. (2009) found an association between phobic anxiety and higher serum concentrations of leptin and inflammatory markers in

women with diabetes which indicates that there might be marked gender differences in the way anxiety impacts cardiovascular disease.

Panic-type anxiety (panic disorder, posttraumatic stress disorder) has been associated with increased cardiovascular disease risk (Alvarenga et al. 2006; Coughlin 2011; Esler et al. 2004b; Gomez-Caminero et al. 2005; Walters et al. 2008). Coryell et al. (1986) had earlier conducted a longitudinal study over 12 years and found that men with panic disorder were twice as likely to die from cardiovascular disease and suicide. Several small studies have also found a link between panic disorder and coronary artery disease and worry and coronary artery disease (Frasure-Smith et al. 1995; Herrmann et al. 2000; Moser and Dracup 1996). The prevalence of panic disorder in patients with coronary artery disease (CAD) has been estimated to lie between 10 % and 50 % (Fleet et al. 2000). In some instances this association may represent the secondary development of panic disorder in people with existing cardiac disease. Longitudinal studies, however, do show that panic anxiety acts also as an antecedent risk factor for CVD (Coryell et al. 1986; Kawachi et al. 1996). Panic disorder sufferers are exposed to a range of cardiac complications which can occur, including triggered cardiac arrhythmias, recurrent emergency room attendances with angina and electrocardiographic changes of ischemia, and coronary artery spasm, in some cases complicated by coronary thrombosis (Mansour et al. 1998; Esler 1998; Goldstein et al. 2002). Indeed, panic anxiety has been proposed as a better predictor of coronary artery disease than depression (Zafar et al. 2010).

The Normative Aging Study (Kawachi et al. 1996) explored the relationship between anxiety and cardiac death and found that psychogenic mortality was not associated with increased risk of myocardial infarction; rather, it was associated to sudden cardiac death. However, significantly high levels of anxiety have been found after acute myocardial infarction (Moser and De Jong 2006), which has been associated with longer hospital stays in the cardiac care unit, as well as increased medical service utilization and lower quality of life (Chiou et al. 1997; Mayou et al. 2000; Lane et al. 2001). It has to be noted that these studies have mostly focused on men, while anxiety disorders are more prevalent among women (APA 2000). Current American Heart Foundation figures show that since the mid-1980s, the number of cardiovascular disease deaths in females has exceeded that of men (AHF 2014).

Anxiety and Long QT

Long QT syndrome is a congenital disorder characterized by a prolongation of the QT interval and a propensity to ventricular tachyarrhythmias, which may lead to syncope, cardiac arrest, or sudden death (Sovari et al. 2008). The condition is usually uncovered after the patient presents with a cardiac complaint, and an electrocardiogram is carried out (Heidenreich 2003). Long QT has a chronic presentation and has been identified as significantly higher in patients with panic disorder (Yeragani et al. 2000) and torsade de pointes associated with takotsubo

cardiomyopathy (Ahn et al. 2011). Anxiodepressive disorders and chronic stress have been identified as being involved in the pathophysiology of takotsubo cardiomyopathy (Delmas et al. 2013). Kawachi et al. (1994) identified a link between anxiety and fatal coronary heart disease, particularly sudden cardiac death. The experience of high QT variability is associated with risk of life-threatening arrhythmias (Crotti et al. 2008) which can result in sudden cardiac death (Berger et al. 1997; Atiga et al. 2000).

The first line of treatment in long QT is the use of beta-blockers, such as propranolol. Beta-blockers antagonize the effects of sympathetic nerve stimulation by inhibiting or locking excitatory neurotransmitters secreted during time of emotional arousal and physical activity. The use of magnesium sulfate is also promising (Purvis et al. 2009).

Heart Rate Variability

In addition to increased QT interval variability, decreased beat-to-beat heart rate variability (HRV) has also been associated with increased cardiac mortality (Malik and Camm 1990; Malliani et al. 1991; Atiga et al. 1998). Decreased HRV is also an important marker of sudden cardiac death in patients with cardiac disease as well as normal subjects (Bigger et al. 1992; Molgaard et al. 1991). Episodes of worry and prolonged worry duration have been linked with decreased HRV (Brosschot et al. 2007; Pieper et al. 2007). GAD patients have shown abnormal HRV (Hammel et al. 2011), and panic disorder has been associated with low HRV (cardiac vagal function) and an increase in sympathetic nervous system activity (Alvarenga et al. 2006; Yeragani et al. 1993, 2000; Radhakrishna and Yeragani 2001) as well. Indeed, it has been proposed that ventricular arrhythmias (abnormally rapid heart rhythms originating in the lower chambers of the heart) might be the mechanism involved in the anxiety–cardiac death link (Esler et al. 2004b), which is in keeping with the evidence in panic disorder sufferers reporting reduced heart rate variability (HRV). Indeed, a decrease in HRV is associated with the development of clinical endpoints of coronary heart disease, suggesting that low HRV might be considered an independent marker of mortality risk.

Ventricular Arrhythmias

In other clinical contexts, most notably in patients with heart failure, activation of the sympathetic outflow to the heart can also lead to the development of ventricular arrhythmias and sudden death. The risk of fatal CAD events which has been shown to increase during acute stressful events, such as fright during natural disasters, can be attributed to the influence of the preferential activation of the cardiac sympathetic outflow which occurs with acute mental stress (Esler et al. 2004b).

During the classic "fight-or-flight" stress response, sympathetic nervous system activation leads to catecholamine release, which increases heart rate and

contractility, resulting in enhanced cardiac output through stimulation of the beta-adrenergic receptors in the heart (Esler 2000) leading to activation of calcium channels, causing an influx of calcium into the neuron (Bers 2002). Calcium in the cell enhances nerve firing and the contraction of cardiac muscle, facilitating the release of catecholamines which can promote platelet aggregation (Nesbitt et al. 2003) and inflammation (Thomsen et al. 2010). Inflammation is probably an initial event very early on in plaque formation leading to calcification and ischemic heart disease (Ridker 2007). Steptoe et al. (2013) found a longitudinal association of increased white cell count but not C-reactive protein during adverse cardiac events in a sample of 216 cardiac patients. Clearly, the direct role of anxiety on inflammatory processes and overall cardiopathogenesis requires further exploration, which might most likely involve scrutiny of the renin–angiotensin pathway (Saavedra et al. 2011; Khoury et al. 2012).

Sympathetic Nervous System Activation in Anxiety

Increased sympathetic nervous system stimulation as a mechanism for increased cardiac risk has received a lot of attention in the literature. Panic disorder, in particular, has served as an ideal model to research the relationship between anxiety, as mediated by stress, and increased risk of heart disease (Esler 1998; Esler et al. 2004a, 2006, 2008). People with PD usually describe cardiac symptoms as a part of their syndrome. Indeed, panic disorder sufferers often fear that they have heart disease because of the nature of their symptoms.

Stressful emotions such as anxiety can create a chain reaction in the body, most likely mediated by the sympathetic nervous system, and culminate in the sensitization of cardiac sympathetic nerves (Esler 2000). Consistent (and chronic) experience of these emotions can predispose to disturbances of cardiac rhythm and risk of coronary artery spasm, which can eventually lead to morbidity and mortality from cardiovascular events in the context of sympathetic nervous system overstimulation or hyperresponsivity (Esler 2000).

Rozanski et al. (1999) described sympathetic nervous system hyperresponsivity (also known as cardiovascular reactivity) as:

> a dispositional tendency to exhibit exaggerated heart rate and blood pressure responses when encountering behavioural stimuli as engaging, challenging or aversive. (Rozanski et al. 1999, p. 2207)

Individuals whose sympathetic nervous system response to stress is more substantial would be more prone, over time, to the development of atherosclerosis and subsequent coronary artery disease (Matthews et al. 1998).

Several studies have reported that in panic disorder patients, there is heightened sympathetic nervous system activity during the experience of acute stress (Esler 1998; Esler et al. 2004a, 2008; Alvarenga et al. 2006).

Panic Disorder and Cardiovascular Disease

In a study examining the neurobiology of psychogenic heart disease, organ-specific sampling measures of brain noradrenaline and serotonin turnover in PD patients were undertaken (Esler et al. 2004). The measures obtained were based on the overflow into the internal jugular veins of noradrenaline and its major metabolites, 3-methoxy-4-hydroxyphenylglycol (MHPG) and 3,4-dihydroxyphenylglycol (DHPG), and of the principal brain serotonin metabolite, 5-HIAA, which were carried out to calculate sympathetic nervous system activity through an analysis of brain catecholamine turnover as well as cardiac sympathetic nervous system function. In untreated patients with PD, the process of neuronal reuptake of noradrenaline after its release from cardiac sympathetic nerves was found to be impaired (Alvarenga et al. 2006). Clearance and extraction rates across the cardiac noradrenaline transport (NET) system were abnormal, indicating that the sympathetic neural signal magnified sympathetically mediated responses. In the heart, particularly, noradrenaline inactivation is so dependent on neuronal reuptake, causing a "sensitization" of the heart that leads to increased cardiac symptomatology, which could be predisposing to the development of panic disorder.

A link between NET dysfunction and anxiety sensitivity (Reiss et al. 1986) was also found, suggesting that augmentation of sympathetic nerve firing in the heart by an impairment of neuronal noradrenaline reuptake may lead to perceptions which are potentially threatening in people with PD and thus leading to fear of autonomic arousal (i.e., anxiety sensitivity). This raises the suggestion that there may be a biological basis for high anxiety sensitivity, which predisposes to the development of PD, and that measures of anxiety sensitivity might provide an accurate indication of a PD sufferer's level of cardiac reactivity (Alvarenga 2006).

A sensitized heart, one which is prone to respond with hyperreactivity to perceived or actual stimuli, appears to elegantly exemplify the anxiety–heart disease link, where anxiety can be explained in terms of cognitive and emotional over-reactivity resulting from cardiac sensitivity signaling. This is in keeping with reports that during a panic attack, heart rate and blood pressure increase and secretion of adrenaline increases two- to sixfold (Esler 1998).

The experience of panic attacks is accompanied by surges of adrenaline secretion, which is continuously co-released with noradrenaline in the interim periods between attacks (Esler et al. 2008). Such adrenaline co-release could also lead to the development of cardiac arrhythmias. Further sympathetic nervous system arousal in PD has been demonstrated by an increase in firing fibers as well as the size of multi-fiber sympathetic electrical bursts, when recorded directly by microneurography (Lambert et al. 2006).

It should be noted that not all PD patients are at risk of CVD and that not all PD patients suffer from cardiac complications even if they experience a cardiac event. Indeed, it has been argued in the past whether PD constitutes a discrete syndrome, that is, whether people with PD represent a homogeneous group or whether PD is an umbrella term encompassing distinct subcategories of panic. Indeed, there have been attempts to subdivide PD into its clusters on the basis of localized body system symptomatology (Kircanski et al. 2009), but further research is needed in this area.

Conclusions

The perception of threat and the development of chronic anxiety expressed either as generalized anxiety disorder, panic disorder, or posttraumatic stress disorder appear on the basis of a great deal of evidence to pose a real and severe danger to life through their impact on the cardiovascular system. Anxiety in one clinical form or another has been found to be associated with coronary artery disease and sudden cardiac death, but not myocardial infarction, indicating that anxiety's impact on the heart might be both formative (as evidenced by its association with coronary artery disease) and more abrupt and deadly than the impact of other psychosocial factors, such as depression. The evidence documenting these associations is now sufficiently well established and well accepted that there can be no doubt of a role for anxiety in understanding at least some aspects of CVD. The psychobiology of this link is also now well established and understood, giving greater credence to a claim of causality as opposed to a simpler association explaining anxiety as more a reaction to the experience of a serious physical condition (CVD). Anxiety in those with already manifest CVD should certainly warrant appropriate psychological management. However, the evidence reviewed in this chapter also quite clearly underscores the need to take CVD as a potential sequel to clinical anxiety in some identified patients and to implement targeted and evidence-based psychological interventions in this light.

References

AHF. (2014). *Heart disease and stroke statistics – 2014 update: A report from the American Heart Association*. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Dallas, Texas, United States.

Ahn, J. H., Park, S. H., Shin, W. Y., & Lee, H. M. J. Y. (2011). Long QT syndrome and Torsade de Pointes associated with Takotsubo cardiomyopathy. *Journal of Korean Medical Sciences., 26*, 959–961.

Albert, C. M., Chae, C. U., Rexrode, K. M., Manson, J. E., & Kawachi, I. (2005). Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation, 111*, 480–487.

Alvarenga, M. E., Richards, J. C., Lambert, G., & Esler, M. D. (2006). Psychophysiological mechanisms in panic disorder: A correlative analysis of noradrenaline spillover, neuronal noradrenaline reuptake, power spectral analysis of heart rate variability and psychological variables. *Psychosomatic Medicine, 68*, 8–16.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Association (text rev.).

Asmundson, G. J., Sandler, L. S., Wilson, K. G., & Norton, G. R. (1993). Panic attacks and interoceptive acuity for cardiac sensations. *Behaviour Research and Therapy, 31*(2), 193–197.

Atiga, W. L., Calkins, H., Lawrence, J. H., Tomaselli, G. F., Smith, J. M., & Berger, R. D. (1998). Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death. *Journal of Cardiovascular Electrophysiology, 9*, 899–908.

Atiga, W. L., Fananapazir, L., McAreavey, D., Calkins, H., & Berger, R. D. (2000). Temporal repolarization lability in hypertrophic cardiomyopathy caused by β-myosin heavy-chain gene mutations. *Circulation, 101*, 1237–1242.

Barlow, D. H. (2002). *Anxiety and its disorders. The nature and treatment of anxiety and panic* (2nd ed.). New York: Guilford Press.

Batelaan, N. M., ten Have, M., van Balkom, A. J. L. M., Tuithof, M., & de Graff, R. (2014). Anxiety disorders and onset of cardiovascular disease: The differential impact of panic, phobias and worry. *Journal of Anxiety Disorders, 28*, 252–258.

Berger, R. D., Kasper, E. K., Baughman, K. L., Marban, E., Calkins, H., & Tomaselli, G. F. (1997). Beat to beat QT internal variability: Novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation, 96*, 1557–1565.

Bers, D. M. (2002). Cardiac excitation contraction coupling. *Nature, 415*, 198–205.

Bigger, J. T., Fleiss, J. L., Steinman, R. C., Rolnitzky, L. M., Kleiger, R. E., & Rottman, J. N. (1992). Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation, 85*(1), 164–171.

Black, P. H., & Garbutt, L. D. (2002). Stress, inflammation and cardiovascular disease. *Journal of Psychosomatic Research, 52*(1), 1–23.

Brennan, A. M., Fargnolli, J. L., Li, T., Williams, C. J., Willett, W., Kawachi, I., Qi, L., Hu, F. B., & Mantzoros, C. S. (2009). Phobic anxiety is associated with higher serum concentrations of adipokines and cytokines in women with diabetes. *Diabetes Care, 32*(5), 926–931.

Brosschot, J. F., Van Dijk, E. & Thayer, J. F. (2007). Daily worry is related to low heart rate variability during waking and the subsequent nocturnal sleep period. *International Journal of Psychophysiology 63*, 39–47.

Brunner, L. S., Suddarth, D. S., & O'Connell Smeltzer, S. C. (2004). *Brunner & Suddarth's textbook of medical-surgical nursing*. Philadelphia: Lippincott Williams & Wilkins.

Bunker, S. J., Colquhoun, D. M., Esler, M. D., Hickie, I. B., Hunt, D., Jelinek, V. W., Oldenburg, B. F., Peach, H. G., Ruth, D., Tennant, C. C., & Tonkin, A. M. (2003). "Stress" and coronary heart disease: Psychosocial risk factors. *Medical Journal of Australia, 178*(6), 272–276.

Cameron, O. G. (2007). Understanding comorbid depression and anxiety. *Psychiatric Times, 24* (14), 51–56.

Chiou, A., Potempa, K., & Buschmann, M. B. (1997). Anxiety, depression and coping methods of hospitalized patients with myocardial infarction in Taiwan. *International Journal of Nursing Studies, 34*(4), 305–311.

Coryell, W., Noyes, R., & House, D. (1986). Mortality among outpatients with anxiety disorders. *American Journal of Psychiatry, 143*(4), 508–510.

Coughlin, S. S. (2011). Posttraumatic stress disorder and cardiovascular disease. *The Open Cardiovascular Medicine Journal, 5*, 164–179.

Crotti, L., Celano, G., Dagradi, F., & Schwartz, P. J. (2008). Congenital long QT syndrome. *Orphanet Journal of Rare Diseases, 3*, 18.

Da Costa, J. M. (1871). Art. 1. On irritable heart; a clinical study of a form of functional cardiac disorder and its consequences. *American Journal of Medical Sciences, 121*(1), 2–52.

Daly, J., Sindone, A. P., Thompson, D. R., Hancock, K., Chang, E., & Davidson, P. (2002). Barriers to participation in and adherence to cardiac rehabilitation programs: A critical literature review. *Progress in Cardiovascular Nursing, 17*(1), 8–17.

Delmas, C., Lairez, O., Mulin, E., Delmas, T., Boudou, N., Dumonteil, N., Biendel-Picquet, C., Roncalli, J., Elbaz, M., Galinier, M., & Carrie, D. (2013). Anxiodepressive disorders and chronic psychological stress are associated with Tako-Tsubo cardiomyopathy- new physio-pathological hypothesis. *Circulation Journal, 77*(1), 175–180.

Descartes, R. (1649). *Le Passiones de L'Alme* (passions of the soul) (trans: Voss, S. H.). Indianapolis: Hackett, 1989.

El-Gabalawy, R., Mackenzie, C. S., Thibodeau, M. A., Asmund, G. L., & Sareen, J. (2013). Health anxiety disorders in older adults: Conceptualizing complex conditions in late life. *Clinical Psychology Review, 33*(8), 1096–1105.

Esler, M. D. (1998). Mental stress, panic disorder and the heart. *Stress Medicine, 14*, 237–243.

Esler, M. (2000). The sympathetic system and hypertension. *American Journal of Hypertension, 13*(2), 99S–105S.

Esler, M., Alvarenga, M., Kaye, D., Lambert, G., Thompson, J., Hastings, J., Schwarz, R., Morris, M., & Richards, J. (2004a). Panic disorder. In D. Robertson, P. A. Low, G. Burnstock, & I. Biaggioni (Eds.), *Primer of the autonomic nervous system*. Amsterdam: Elsevier.

Esler, M., Alvarenga, M., Lambert, G., Kaye, D., Hastings, J., Jennings, G., Morris, M., Schwarz, R., & Richards, J. (2004b). Cardiac sympathetic nerve biology and brain monoamine turnover in panic disorder. *Annals of the New York Academy of Science, 1018*, 505–514.

Esler, M., Alvarenga, M., Pier, C., Richards, J., El-Osta, A., Barton, D., Haikerwal, D., Kaye, D., Schlaich, M., Guo, L., Jennings, G., Socratous, F., & Lambert, G. (2006). The neuronal noradrenaline transporter, anxiety and cardiovascular disease. *Journal of Psychopharmacology, 20*(4), 60–66.

Esler, M., Schwarz, R., & Alvarenga, M. (2008). Mental stress is a cause of cardiovascular diseases: From scepticism to certainty. *Stress and Health, 24*, 175–180.

Fleet, R., Lavoie, K., & Beitman, B. D. (2000). Is panic disorder associated with coronary artery disease? A critical review of the literature. *Journal of Psychosomatic Research, 48*, 347–356.

Fox, K., Ford, I., Steg, P. G., Tendera, M., Robertson, M., & Ferrari, R. (2008). Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A subgroup analysis of a randomised controlled trial. *Lancet, 6372*(9641), 817–821.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1995). The impact of negative emotions on prognosis following myocardial infarction: Is it more than depression? *Health Psychology, 14*(5), 388–398.

Friedman, S. (2000). Cardiac disease, anxiety and sexual functioning. *American Journal of Cardiology, 86*(2 Suppl 1), 46–50.

Gold, L. S., Kane, L. B., Sotoodehnia, N., & Rea, T. (2007). Disaster events and the risk of sudden cardiac death: A Washington State investigation. *Prehospital Disaster Medicine, 22*(4), 313–317.

Goldstein, D. S., Robertson, D., Esler, M. D., Straus, S., & Eisenhofer, G. (2002). Dysautonomias: Clinical disorders of the autonomic nervous system. *Annals of Internal Medicine, 137*(9), 753–763.

Gomez-Caminero, A., Blumentals, W. A., Russo, L. J., Brown, R. R., & Castilla-Puentes, R. (2005). Does panic disorder increase the risk of coronary heart disease? A cohort study of a national managed care database. *Psychosomatic Medicine, 67*(5), 688–691.

Grace, S. L., Abbey, S. E., Irvine, J., Shnek, Z. M., & Stewart, D. E. (2004). Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events. *Psychotherapy and Psychosomatics, 73*(6), 344–352.

Graham, H. (2003). A conceptual map for studying long-term exercise in a cardiac population. *Rehabilitation Nursing, 28*(3), 80–86.

Haines, A. P., Imeson, J. D., & Mease, T. W. (1987). Phobic anxiety and ischaemic heart disease. *British Medical Journal, 295*, 297–299.

Hammel, J. C., Smitherman, T. A., McGlynn, D., Mulfinger, A. M. M., Lazarte, A., & Gothard, K. D. (2011). Vagal influence during worry and cognitive challenge. *Anxiety, Stress and Coping: An International Journal, 24*(2), 121–136.

Heidenreich, W. F. (2003). Assessment for congenital long QT syndrome. *Journal of Insur Med, 35*(3–4), 196–200.

Heikkila, J., Paunonen, M., Laippala, P., & Virtanen, V. (1998). Nurses' ability to perceive patients' fears related to coronary arteriography. *Journal of Advanced Nursing, 28*(6), 1225–1235.

Herrmann, C., Brand-Driehorst, S., Buss, U., & Rüger, U. (2000). Effects of anxiety and depression on 5-year mortality in 5057 patients referred for exercise testing. *Journal of Psychosomatic Research, 48*(4–5), 455–462.

James, W. (1892). *The stream of consciousness* (Psychology). Cleveland/New York: H.Holt, Chapter XI.

Janszky, I. S., Ahnve, S., Lundber, I., & Hemmingsson, T. (2010). Early onset depression, anxiety, and risk of subsequent coronary heart disease: 37 year follow up of 49,321 young Swedish Men. *Journal of American Cardiology, 56*(1), 31–37.

Kalisch, R., Wiech, K., Critchley, H. D., Seymour, B., O'Doherty, J. P., Oakley, D. A., Allen, P., & Dolan, R. J. (2005). Anxiety reduction through detachment: Subjective, physiological, and neural effects. *Journal of Cognitive Neuroscience, 17*(6), 874–883.

Kannel, W. B., Cupples, L. A., & D'Agostino, R. B. (1987). Sudden death risk in overt coronary heart disease: The Framingham study. *American Heart Journal, 113*(3), 799–804.

Kawachi, I., Sparrow, D., Vokonas, P. S., & Weiss, S. T. (1994). Symptoms of anxiety and risk of coronary heart disease: The normative aging study. *Circulation, 90*, 2225–2229.

Kawachi, I., Colditz, G. A., Ascherio, A., Rimm, E. B., Giovannucci, E., Stampfer, M. J., & Willett, W. C. (1996). A prospective study of social networks in relation to total mortality and cardiovascular disease in men in the USA. *Journal of Epidemiology & Community Health, 50* (3), 245–5.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, R., & Walters, E. E. (2005). Lifetime prevalence of age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593–602.

Khoury, N., Marvar, P. J., Gillespie, C. F., Wingo, A., Schwartz, A., Bradley, B., Kramer, M., & Ressler, K. J. (2012). The renin-angiotensin pathway in PTSD: ACE inhibitor and ARB medications are associated with fewer traumatic stress symptoms. *Journal of Clinical Psychiatry, 73*(6), 849–855.

Kircanski, K., Craske, M. G., Epstein, A. M., & Wittchen, H. U. (2009). Subtypes of panic attacks: A critical review of the empirical literature. *Depression and Anxiety, 26*, 878–887.

Kolloch, R., Legler, U. F., Champion, A., Cooper-Dehoff, R. M., Handberg, E., et al. (2008). Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: Findings from the INternational VErapamil-SR/trandolapril STudy (INVEST). *European Heart Journal, 29*, 1327–1334.

Kotseva, K., Wood, D., De Backer, G., De Bacquer, D., Pyörälä, K., & Keil, U. (2009). Cardiovascular prevention guidelines in daily practice: A comparison of EUROASPIRE I, II and III surveys in eight European countries. *The Lancet, 373*(9667), 929–940.

Kubzansky, L. D., & Arthur, C. M. (2004). Anxiety, heart disease and mortality. In N. Anderson (Ed.), *Emotional longevity*. New York: Viking.

Kubzansky, L. D., Kawachi, I., Spiro, A., III, Weiss, S. T., Vokonas, P. T., & Sparrow, D. (1997). Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the normative aging study. *Circulation, 95*(4), 818–824.

Lambert, E., Hotchkin, E., Alvarenga, M., Pier, C., Richards, J., Barton, D., Dawood, T., Esler, M., & Lambert, G. (2006). Single-unit analysis of sympathetic nervous discharges in patients with panic disorder. *Journal of Physiology, 570*(3), 637–643.

Lane, D., Carroll, D., Ring, C., Beevers, D. G., & Lip, G. Y. (2001). Predictors of attendance at cardiac rehabilitation after myocardial infarction. *Journal of Psychosomatic Research, 51*, 497–501.

Lane, R. D., Laukes, C., Marcus, F. I., et al. (2005). Psychological stress preceding idiopathic ventricular fibrillation. *Psychosomatic Medicine, 67*, 359–365.

Leor, J., Poole, W. K., & Kloner, R. A. (1996). Sudden cardiac death triggered by an earthquake. *The New England Journal of Medicine, 334*, 413–419.

Malik, M., & Camm, A. J. (1990). Heart rate variability. *Clinical Cardiology, 13*, 570–576.

Malliani, A., Pagani, M., Lombardi, E., & Cerruti, S. (1991). Cardiovascular neural regulation explored in the frequency domain. *Circulation, 84*, 482–492.

Mansour, V. M., Wilkinson, D. J. C., Jennings, G. L., Schwarz, R. G., Thompson, J. M., & Esler, M. D. (1998). Panic disorder: Coronary spasm as a basis for cardiac risk? *MJA, 168*, 390–392.

Martens, E., De Jonge, P., Na, B., Cohen, B., Lett, H., & Whooley, M. (2010). Scared to death? Generalised anxiety disorder and cardiovascular events in patients with stable coronary heart disease. *Archives of General Psychiatry, 67*(7), 750–758.

Mathers, C. D., & Loncar, D. (2006). Updated projections of global mortality and burden of disease, 2002–2030: Data sources, methods and results. *PLoS Med*, *3*(11):e442. Text available at http://www.who.int/healthinfo/statistics/bod_projections2030_paper.pdf

Matthews, K. A., Owens, J. F., Kuller, L. H., Sutton-Tyrrell, Lasilla, H. C., & Wolfson, S. K. (1998). Stress-induced pulse pressure changes predicts women's carotid atherosclerosis. *Stroke, 29*, 1525–1530.

Mayou, R. A., Gill, D., Thompson, D. R., et al. (2000). Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosomatic Medicine, 62*(2), 212–219.

McGrady, A., McGinnis, R., Badenhop, D., Bentle, M., & Rajput, M. (2009). Effects of depression and anxiety on adherence to cardiac rehabilitation. *Journal of Cardiopulmonary Rehabilitation & Prevention., 29*(6), 358–364.

Meisel, S. R., Kutz, I., Dayan, K. I., Pauzner, H., Chetboun, I., Arbel, Y., & David, D. (1991). Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. *Lancet, 338*(8768), 660–661.

Mendenhall, M. E., Osland, J. S., Bird, A., Oddou, G. R., & Maznevski, M. L. (2008). *Global leadership: Research, practice, and development*. London: Routledge.

Molgaard, H., Sorensen, K. E., & Bjerregaard, P. (1991). Attenuated 24-h heart rate variability in apparently healthy subjects, subsequently suffering sudden cardiac death. *Clinical Autonomic Research, 1*, 233–237.

Moser, D. K., & De Jong, M. J. (2006). Anxiety and heart disease. In E. Mollinari, A. Compare, & G. Paratti (Eds.), *Clinical psychology and heart disease*. Italia: Springer.

Moser, D. K., & Dracup, K. (1996). Is anxiety early after myocardial infarction associated with subsequent ischemic and arrhythmic events? *Psychosomatic Medicine, 58*, 395–401.

Mosovich, S. A., Boone, R. T., Reichenberg, A., Bansilal, S., Shaffer, J., Dahlman, K., Harvey, P. D., & Farkouh, M. E. (2008). New insights into the link between cardiovascular disease and depression. *International Journal of Clinical Practice, 62*, 423–432.

Nesbitt, W. S., Giuliano, S., Kulkarni, S., Dopheide, S. M., Harper, I. S., & Jackson, S. P. (2003). Intercellular calcium communication. *The Journal of Cell Biology, 160*(7), 1151–1161.

Pajak, A., Jankowski, P., Kotseva, K., Heidrich, J., De Smedt, D., & De Bacquer, D. (2013). Depression, anxiety and risk factor control in patients after hospitalisation for coronary heart disease: The EUROASPIRE III study. *European Journal of Cardiology, 20*(2), 331–340.

Paterniti, S., Zureik, M., Ducimetière, P., Touboul, P. J., Fève, J. M., & Alpérovitch, A. (2001). Sustained anxiety and 4-year progression of carotid atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 21*, 136–141.

Phillips, A. C., Batty, G. D., Gale, C. R., Deary, I. J., Osborn, D., MacIntyre, K., & Carroll, D. (2009). Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: The Vietnam experience study. *Psychosomatic Medicine, 71*(4), 395–403.

Pieper, S., Brosschot, J. F., van der Leeden, R., & Thayer, J. F. (2007). Cardiac effects of momentary assessed worry episodes and stressful events. *Psychosomatic Medicine, 69*, 901–909.

Purvis, J. A., Cunningham, E. L., McGlinchey, P. G., & Barr, S. H. (2009). Drugs, electrolytes and takotsubo cardiomyopathy: Triple aetiology of acquired long QT syndrome and torsades de pointes. *Ulster Medical Journal, 78*(3), 188–189.

Radhakrishna, R. K. A., & Yeragani, V. K. (2001). Decreased chaos and increased non-linearity of heart rate time series in patients with panic disorder. *Autonomic Neurosciences, 88*, 99–108.

Reiss, S., Peterson, R. A., Gursky, D. M., & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the predictions of fearfulness. *Behaviour Research & Therapy, 24*(1), 1–8.

Ridker, P. M. (2007). C-reactive protein and the prediction of cardiovascular events amongst those at intermediate risk: Moving an inflammatory hypothesis toward consensus. *Journal of the American College of Cardiology, 49*(21), 2129–2138.

Roest, A. M., Martens, E. J., De Jonge, P., & Denollet, J. (2010). Anxiety and risk of incident of coronary heart disease: A meta-analysis. *Journal of the American College of Cardiology, 56* (1), 38–46.

Rosengren, S., Hawkin, S., Ounpuu, S., et al. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (the INTERHEART study): Case–control study. *Lancet, 364*, 953–962.

Rothenbacher, D., Hahmann, H., Wusten, B., Koenig, W., & Brenner, H. (2007). Symptoms of anxiety and depression in patients with stable coronary heart disease: Prognostic value and consideration of pathogenic links. *European Journal Cardiovascular Preven Rehabiliation, 14* (4), 547–554.

Rozanski, A., Blumenthal, J. A., & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation, 99*, 2199–2217.

Saavedra, J., Sanchez-Lemus, E., & Benicky, J. (2011). Blockade of brain angiotensin II AT1 receptors ameliorates stress, anxiety, brain inflammation and ischemia: Therapeutic implications. *Psychoneuroendocrinology, 36*(1), 1–18.

Sovari, A. A., Cesario, D., Kocheril, A. G., & Brugada, R. (2008). Multiple episodes of ventricular tachycardia induced by silent coronary vasospasm. *Journal of Interventional Cardiology and Electrophysiology, 21*(3), 223–226.

Steptoe, A., Wikman, A., Molloy, G. J., Messerli-Burgy, N., & Kaski, J. C. (2013). Inflammation and symptoms of depression and anxiety in patients with acute coronary heart disease. *Brain, Behaviour & Immunity, 31*, 183–188.

Thomsen, S. B., Rathke, C. N., Zerahn, B., & Vestergaard, H. (2010). Increased levels of calcification marker matrix GIa protein and the inflammatory markers YKL-40 and CRP in patients with type 2 diabetes and ischemic heart disease. *Cardiovascular Diabetology, 9*, 86.

Thornton, E. W., Bundred, P., Tytherleigh, M., & Davies, A. D. M. (2006). Anxiety, depression and myocardial infarction: A survey of their impact on consultation rates before and after an acute primary episode. *British Journal of Cardiology, 13*(3), 220–224.

Thrall, G., Lip, G. Y. H. P., Carroll, D., & Lane, D. (2007). Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest, 132*(4), 1259–1264.

Thurston, R. C., Rewak, M., & Kubzansky, L. D. (2013). An anxious heart: Anxiety and the onset of cardiovascular diseases. *Progress in Cardiovascular Diseases, 55*(6), 524–537.

Uzun, S., Vural, H., Uzun, M., & Yokusoglu, M. (2008). State and trait anxiety levels before coronary angiography. *Journal of Clinical Nursing, 17*(5), 602–607.

Walters, K., Rait, G., Petersen, I., & Williams, R. (2008). Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: Cohort study using the general practice research database. *European Heart Journal, 29*(24), 2981–2988.

Wilbert-Lampen, U., Leistner, D., Greven, S., Pohl, T., Sper, S., Völker, C., Güthlin, D., Plasse, A., Knez, A., Küchenhoff, H., & Steinbeck, G. (2008). Cardiovascular events during World Cup soccer. *New England Journal of Medicine, 358*, 475–483.

Wilkinson, D. J., Thompson, J. M., Lambert, G. W., Jennings, G. L., Schwarz, R. G., Jefferys, D., Turner, A. G., & Esler, M. D. (1998). Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. *Archives of General Psychiatry, 55*(6), 511–520.

Wulsin, L. R., & Singal, B. M. (2003). Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosomatic Medicine, 65*, 201–210.

Yeragani, V. K., Pohl, R., Berger, R., Balon, R., Ramesh, C., Glitz, D., Srinivasan, K., & Weinberg, P. (1993). Decreased heart rate variability in panic disorder patients: A study of power spectral analysis of heart rate. *Psychiatry Research, 46*(1), 89–103.

Yeragani, V. K., Pohl, R., Jampala, V. C., Balon, R. R., & Srinivasan, K. (2000). Increased QT variability in patients with panic disorder and depression. *Psychiatry Research, 1093*(3), 225–235.

Zafar, M. U., Paz-Yepes, M., Shimbo, D., Vilahur, G., Burg, M. M., Chaplin, W., Fuster, V., Davidson, K. W., & Badimon, J. J. (2010). Anxiety is a better predictor of platelet reactivity in coronary artery disease patients than depression. *European Heart Journal, 31*(13), 1573–1582.

Posttraumatic Stress Disorder and Risk of Cardiovascular Disease

Viola Vaccarino and J. Douglas Bremner

Contents

Abstract

PTSD is a disabling mental disorder with health consequences that reach far beyond the neuropsychiatric domain. Growing evidence links PTSD to increased risk of cardiovascular conditions including ischemic heart disease and

V. Vaccarino (✉)
Department of Epidemiology, Rollins School of Public Health, Department of Medicine, School of Medicine, Emory University, Atlanta, GA, USA
e-mail: viola.vaccarino@emory.edu

J.D. Bremner
Emory University School of Medicine, Atlanta, GA, USA

Mental Health Research, Atlanta VAMC, Decatur, GA, USA

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA
e-mail: jdbremn@emory.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_14

thromboembolic stroke. Emerging data also suggest that PTSD may be a consequence, in addition to a cause, of acute, life-threatening cardiovascular events. Individuals with PTSD are more likely to engage in adverse lifestyle behaviors, which may predispose to cardiovascular risk factors such as obesity, diabetes, and hypertension. PTSD is also frequently comorbid with other psychiatric conditions which may affect cardiovascular risk, such as depression and substance abuse. However, additional plausible mechanisms exist that go beyond these associated conditions and risk factors. An emerging model of cardiovascular risk in PTSD is that neurobiology plays a role. Specifically, mechanisms such as repeated and heightened physiological activation in association with intrusive memories in PTSD could lead to cumulative long-term damaging effects on the cardiovascular system. This could be mediated through vascular, immune, or other mechanisms. This chapter will review the existing evidence linking PTSD to major cardiovascular disorders, discuss potential underlying pathophysiology, and provide suggestions for future research.

Keywords

Posttraumatic stress disorder • Cardiovascular disease • Stress • Myocardial ischemia • Stroke • Acute coronary syndromes

Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder characterized by a persistent maladaptive reaction to a traumatic event (Dohrenwend et al. 2006). It is a common condition, occurring in about 10–12 % of women and 5–6 % of men in the general population (Kessler et al. 1994), and is especially prevalent in military personnel exposed to combat. Among veterans serving in Southeast Asia during the Vietnam War, 15–19 % have developed PTSD; the estimated prevalence of PTSD is even higher in service members from the recent Iraq and Afghanistan conflicts (Hoge et al. 2007). However, in absolute terms, combat trauma is not the most frequent cause of PTSD, since in the general population, noncombat trauma is much more common than combat trauma. In many patients the disorder continues to manifest many years after the initial trauma exposure (Dohrenwend et al. 2006).

PTSD has well-known devastating effects on the mental health and functioning of affected individuals; however, the health consequences of PTSD reach far beyond the neuropsychiatric domain (Glaesmer et al. 2011; Hoge et al. 2007; Qureshi et al. 2009). Particular attention has been given to a possible link between PTSD and major forms of cardiovascular disease (CVD), including ischemic heart disease (IHD) and thromboembolic stroke (Boscarino 2012; Coughlin 2011; Wentworth et al. 2013). It is well established that PTSD increases the risk for many adverse health behaviors, such as smoking, alcohol abuse, and sedentary lifestyle, which in turn predispose to chronic conditions such as obesity, diabetes, hypertension, and hyperlipidemia (Coughlin 2011). PTSD is also often comorbid with other psychiatric conditions that have been related to CVD, especially depression.

While these associated conditions and risk factors are likely to play a significant role in the observed link between PTSD and CVD, other plausible mechanisms exist, mostly related to the peculiar neurobiological features of this psychiatric disorder. There are also emerging data to suggest that PTSD may be a consequence, in addition to a cause, of acute coronary syndromes or acute stroke events, due to the intense stress associated with these life-threatening episodes (Edmondson et al. 2012, 2013).

Definition and Diagnosis of PTSD

A PTSD diagnosis requires, as a fundamental criterion, exposure to severe psychological stress or trauma. A traumatic event has been traditionally defined as a threat to one's life or self- integrity, accompanied by intense fear, horror, or helplessness. It may include, for example, rape, assault, motor vehicle accidents, or childhood abuse, in addition to combat trauma (Reed et al. 2012). More than half of Americans will experience a traumatic event at some time in their lives; for women the most common type of trauma is sexual abuse or assault, and for men it is physical assault (Reese et al. 2012). In about half of cases, PTSD becomes a chronic condition that can last for years. Persons with PTSD may suffer severe functional impairment, including difficulties with employment and relationships and increased rates of depression and substance abuse.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, which have been used in clinical practice and research for almost two decades, PTSD is characterized by three major symptom clusters, intrusions, avoidance, and hypervigilance, lasting for at least 1 month and resulting in significant impairment in work and/or social function. *Intrusion symptoms* include recurrent memories of the traumatic event that the patient cannot control or nightmares about the event. *Avoidance symptoms* include avoiding situations that would remind the person of the trauma and avoiding thinking of the trauma, for example, having trouble remembering an important aspect of the traumatic event, feeling detached or cutoff from others, or feeling emotionally numb. As part of their avoidance, PTSD patients might feel uncomfortable in crowds and may have trouble just getting out of the house. *Hypervigilance* symptoms include trouble falling or staying asleep, irritability, outbursts of anger, and difficulty concentrating. An increased startle response, for instance, being jumpy with loud noises, is another symptom of hypervigilance. In the recently released DSM-5, symptoms of PTSD have remained mostly the same, but the trauma definition no longer requires feelings of fear, helplessness, or horror in conjunction with the trauma (American Psychiatric Association 2013). In addition, new qualifying symptoms were added. These include a new criterion of *negative alterations in cognition and mood* which comprises many different symptoms, including new ones such as a persistent and distorted blame of self or others and a persistent negative emotional state. A new symptom of reckless or destructive behavior was also added as part of the hyperarousal symptom cluster. The DSM-5 has overall loosened the criteria for

PTSD, so that a much larger proportion of the population is expected to meet criteria for PTSD under the new definition.

PTSD and Incidence of Ischemic Heart Disease

In the past several decades, a wealth of studies have documented many physical health problems in PTSD, especially cardiac symptoms (Wentworth et al. 2012). However, until recently most of these studies have used a cross-sectional design, which has limited the ability to infer a temporal relationship between PTSD and cardiac conditions such as IHD (Qureshi et al. 2009; Vaccarino and Bremner 2013). Studies that have used self-report assessments of cardiac symptoms are especially problematic. There could be recall bias, and in fact PTSD patients tend to report more symptoms and medical problems in general, not just IHD, compared with persons without PTSD (Qureshi et al. 2009). There could be reverse causation, since PTSD can be a consequence, in addition to a cause, of a heart attack (Edmondson et al. 2012). Selection bias is also a potential problem, since many studies have relied on clinical samples of self-referred patients who may have a higher prevalence of medical problems compared with PTSD cases from the general population.

In the past 10 years, a number of longitudinal studies have been published linking PTSD symptoms or a PTSD diagnosis to IHD incidence (Boscarino 2006, 2008; Dirkzwager et al. 2007; Kang et al. 2006; Kubzansky et al. 2007, 2009; Scherrer et al. 2010). All these studies have shown significant associations, although many have lacked validated measures of IHD outcomes and have relied, in several instances, on death certificate codes or administrative records. More recent investigations that used objective measures of coronary atherosclerosis or myocardial ischemia, however, have confirmed these observations (Ahmadi et al. 2011; Turner et al. 2013; Vaccarino et al. 2013). These recent studies have found substantial evidence of increased coronary artery disease or myocardial perfusion abnormalities in individuals with PTSD compared to those without PTSD. Ahmadi et al. studied veterans who underwent clinically indicated computed tomography for evaluation of coronary artery calcification, a marker of coronary atherosclerosis, and found that PTSD patients had twice the odds of coronary artery calcification than those without PTSD (Ahmadi et al. 2011). In another veteran sample from the Veteran Health Administration outpatient clinics, Turner et al. found about twice the prevalence of myocardial ischemia assessed by exercise electrocardiography (ECG) in patients with PTSD than those without PTSD (Turner et al. 2013). These studies provide important new evidence for a link between PTSD and IHD, but a remaining concern is possible selection bias because they were based on clinical samples from medical encounters. Compared with persons without PTSD, those with PTSD may differ in their likelihood to seek care, or to be referred for, medical evaluation, or treatments for CVD, since they tend to report more symptoms and health problems in general (Qureshi et al. 2009). Thus, PTSD patients selected from hospitals or clinics may have an increased likelihood to be

diagnosed with IHD than it would be found in individuals with PTSD from the community or patients without PTSD.

A recent twin study of PTSD and IHD was able to address this concern since it was based on a registry of twins (Vaccarino et al. 2013). The study followed a sample of 562 military veteran twins from the Vietnam Era who did not report a previous history of IHD at baseline, when PTSD was measured with the Diagnostic Interview Schedule (Robins et al. 1981) and when the mean age of the twins was 43 years. After an average follow-up of 13 years, IHD was measured. Assessment included the occurrence of clinical events (myocardial infarction, other hospitalizations for IHD, and coronary revascularization) by self-report, in conjunction with objective measures of IHD using myocardial perfusion imaging with N-13 ammonia positron emission tomography (PET). Twins with PTSD were greater than twofold more likely to report hospitalizations or revascularization procedures for IHD over the follow-up compared with twins without PTSD (23 % vs. 9 %). The association was robust to adjustment for lifestyle factors, IHD risk factors, and even depression (adjusted odds ratio, 2.2, 95 % CI, 1.2–4.1). PET measures of coronary perfusion and myocardial blood flow supported the self-reported results. A quantitative measure of perfusion defects, the stress total severity score (STSS), was significantly higher (+95 %, $p = 0.001$) in twins with PTSD than those without, denoting almost twice as many myocardial perfusion abnormalities. PET-measured coronary flow reserve was also lower in twins with PTSD compared to those without PTSD ($-0.21, p = 0.02$), denoting worse coronary microvascular function. In addition, there was a graded association with increasing PTSD symptom quartiles for both IHD events and STSS. Associations were only mildly attenuated within 117 twin pairs discordant for PTSD, even after adjusting for traditional IHD risk factors, health behaviors, depression, and other psychiatric diagnoses. Figure 1 shows a representative twin pair discordant for PTSD. The co-twin design that compares brothers within twin pairs controls for unmeasured genetic and familial confounders that could be shared between PTSD and cardiovascular diseases and lends further support to a possible causal relationship between PTSD and IHD (McGue et al. 2010).

PTSD and Incidence of Stroke

In addition to IHD, there is also evidence that severe stress increases the risk of stroke even after many years from the original exposure (Thurston et al. 2014; Wilson et al. 2012), but data related specific to PTSD are limited. In a study of former World War II prisoners of war (POWs), those with PTSD had an almost twofold, albeit not statistically significant, increased risk of stroke, 13 % (20 of 158) vs. 8 % (24 of 317), relative risk = 1.7, and 95 % confidence interval 0.95–2.9 (Brass and Page 1996). The small number of stroke events and the similarity of exposures between POWs with and without PTSD are limitations of this study. This study did find a sevenfold difference in stroke between POW and non-POW veterans. In a cross-sectional survey of female veterans who received care at the

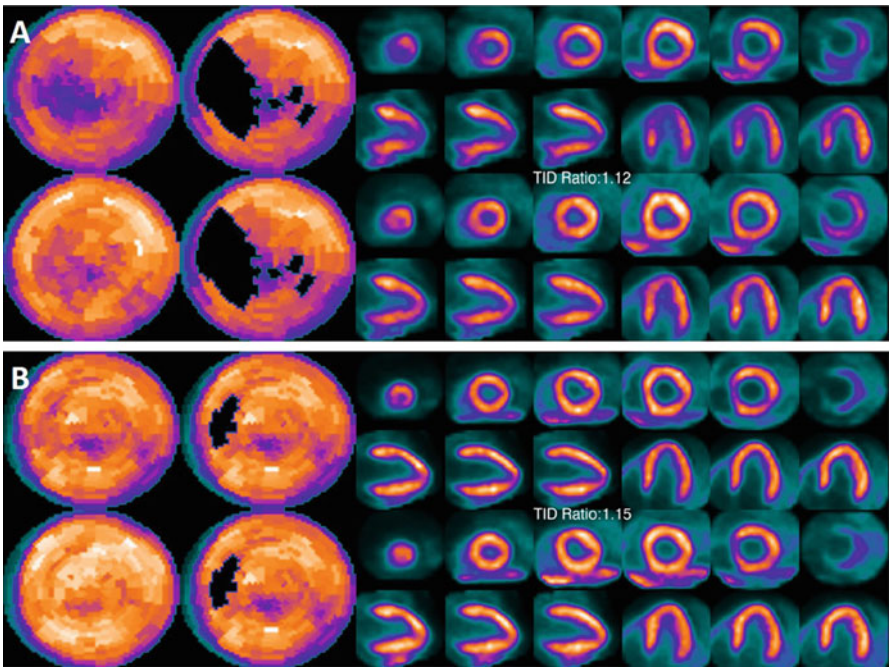


Fig. 1 Positron emission tomography myocardial perfusion scan in a representative twin pair. (**a**) Twin with PTSD. (**b**) Twin without PTSD. In the polar maps on the left, the extent of hypoperfusion is shown as *blackout*. The severity of hypoperfusion was quantified by a stress total severity score (*STSS*) that measured the total number of standard deviations below the mean for the entire extent of the abnormality compared to a normal database

VA Puget Sound Health Care System, there was an association between PTSD and self-reported history of stroke, although, again, the number of stroke events was small. Of the female veterans with PTSD, 5 % (13 of 256) reported a history of stroke as compared with 3 % (28 of 905) of those without PTSD (age-adjusted odds ratio = 2.9, 95 % confidence interval 1.4–6.0) (Dobie et al. 2004). A study of trauma and PTSD among 3,171 men and women from a German community sample found that those with a history of trauma or PTSD had higher odds of self-reported stroke, as well as of other cardiovascular diseases, compared with those without trauma, after adjusting for demographic factors, CVD risk factors, and lifestyle factors (Spitzer et al. 2009). Thus, although more data are needed, the overall evidence points to a possible increase in stroke risk associated with PTSD.

PTSD as a Consequence of Acute Cardiovascular Events

Some patients may develop PTSD as a consequence of acute, life-threatening cardiovascular events such as a heart attack or stroke. According to a recent meta-analysis, clinically significant PTSD symptoms occur on average in

approximately 12 % of patients hospitalized for acute coronary syndromes, or one in every eight patients, but there is substantial heterogeneity in various studies, with prevalence rates ranging from 0 % to 32 % (Edmondson et al. 2012). Although few studies assessed a psychiatric diagnosis of PTSD using a clinical interview, 4 % of the patients on average met full diagnostic criteria for the disorder. Younger patient age is associated with greater likelihood of developing PTSD following an acute cardiac event; in some studies, female sex, ethnic minority status, low socioeconomic status, and previous history of psychiatric disorders were related to the development of PTSD (Roberge et al. 2010; Wikman et al. 2008). Additionally, experiencing intense fear, lack of control or helplessness, and perceived life threat during the acute cardiac event have all been reported as predictors of PTSD. However, clinical severity of the cardiac event appears to be unrelated to PTSD.

PTSD secondary to acute coronary syndromes is associated with approximately doubled risk for recurrent cardiac events and mortality (Edmondson et al. 2012). No study to date has been sufficiently large to assess potential mechanisms for the relationship between PTSD induced by acute coronary syndromes and adverse clinical outcomes. However, since both acute coronary syndromes and PTSD are associated with noradrenergic activation and elevated proinflammatory cytokines (as discussed below), there could be synergistic adverse effects on inflammatory and procoagulant processes that may increase the risk of recurrent cardiac events or mortality.

PTSD may also be a consequence of acute cerebrovascular accidents such as stroke or transient ischemic attacks (TIA). In a recent meta-analysis, the prevalence of PTSD among stroke survivors was estimated at 23 % (95 % confidence interval, 16–33 %) within 1 year of the stroke or TIA and 11 % (95 % confidence interval, 8–14 %) after 1 year (Edmondson et al. 2013). Thus, stroke-induced PTSD is relatively common, with approximately one in four stroke patients experiencing PTSD in the first year after the event and one in nine experiencing chronic PTSD over a year later. It is currently unknown whether PTSD after stroke is associated with poorer survival.

PTSD is even more common among survivors of an out-of-hospital cardiac arrest, with a prevalence ranging from 27 % to 38 % (Gamper et al. 2004; Ladwig et al. 2008). In a study of patients with an implantable cardioverter defibrillator, a significant proportion of whom survived a cardiac arrest or a myocardial infarction, PTSD was associated with a threefold increased risk of subsequent mortality (Ladwig et al. 2008).

Potential Mechanisms

The mechanisms behind the relationship between PTSD and CVD incidence or recurrence are not entirely clear and are likely to be multifactorial. It is believed that acute CVD events are triggered by a confluence of several factors including biological, environmental, and emotional factors, like a “perfect storm” (Arbab-Zadeh et al. 2012). Maladaptive behaviors are likely to be important contributors,

such as smoking, substance abuse, sedentary lifestyle, medication nonadherence, and sleep disturbances, which are all prevalent in persons with PTSD (Breslau et al. 2003). In most studies, however, adjusting for these factors did not explain away the relationship between PTSD and CVD, suggesting that they are not sufficient mechanisms in themselves. Similarly, comorbidity of PTSD with other psychiatric disorders, such as depression, did not explain the association with CVD (Ahmadi et al. 2011; Kubzansky et al. 2009; Turner et al. 2013; Vaccarino et al. 2013).

Even the link between PTSD and traditional CVD risk factors such as hypertension, obesity, and diabetes is not entirely clear. Although several studies have described such associations, others have not (Ahmadi et al. 2011; Kubzansky et al. 2007, 2009; Vaccarino et al. 2013, 2014). Some reports have even found a paradoxically *lower* total cholesterol or LDL cholesterol level in persons with PTSD than those without PTSD (Ahmadi et al. 2011; Vaccarino et al. 2013). Furthermore, when these risk factors were adjusted for in the analysis, the relationship between PTSD and CVD usually persisted. Thus, pathways other than traditional CVD risk factors are likely to be involved in the link between PTSD and CVD.

A current conceptual model is that neurobiological features characteristic of PTSD could play a role in increasing the risk of CVD in this population. Specifically, heightened and repeated physiological activation with reexperiencing symptoms and intrusive memories in PTSD could result in cumulative long-term damaging cardiovascular effects through vascular and immune mechanisms (Fig. 2) (Vaccarino and Bremner 2013).

Neurobiology of PTSD

PTSD is characterized by chronic dysregulation of neurohormonal systems involved in the two main arms of the physiological stress response, namely, the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis (Bremner and Charney 2010; Yehuda 2002). Disturbances in the SNS and other aspects of the autonomic nervous system are evidenced by the fact that heart rate variability (HRV) and baroreflex function, both established markers of autonomic imbalance and inflexibility, tend to be abnormal in individuals with PTSD compared with controls (Hughes et al. 2007; Shah et al. 2013). Autonomic inflexibility measured by these and other indices is a well-known indicator of increased CVD risk and an adverse prognostic factor. In a study where 24-h HRV was measured in 459 middle-aged male twins who served in the military during the Vietnam Era, current PTSD was inversely associated with very-low-frequency HRV and low-frequency HRV both in individual twins and within 20 twin pairs discordant for current PTSD. Twins with current PTSD had a 49 % lower

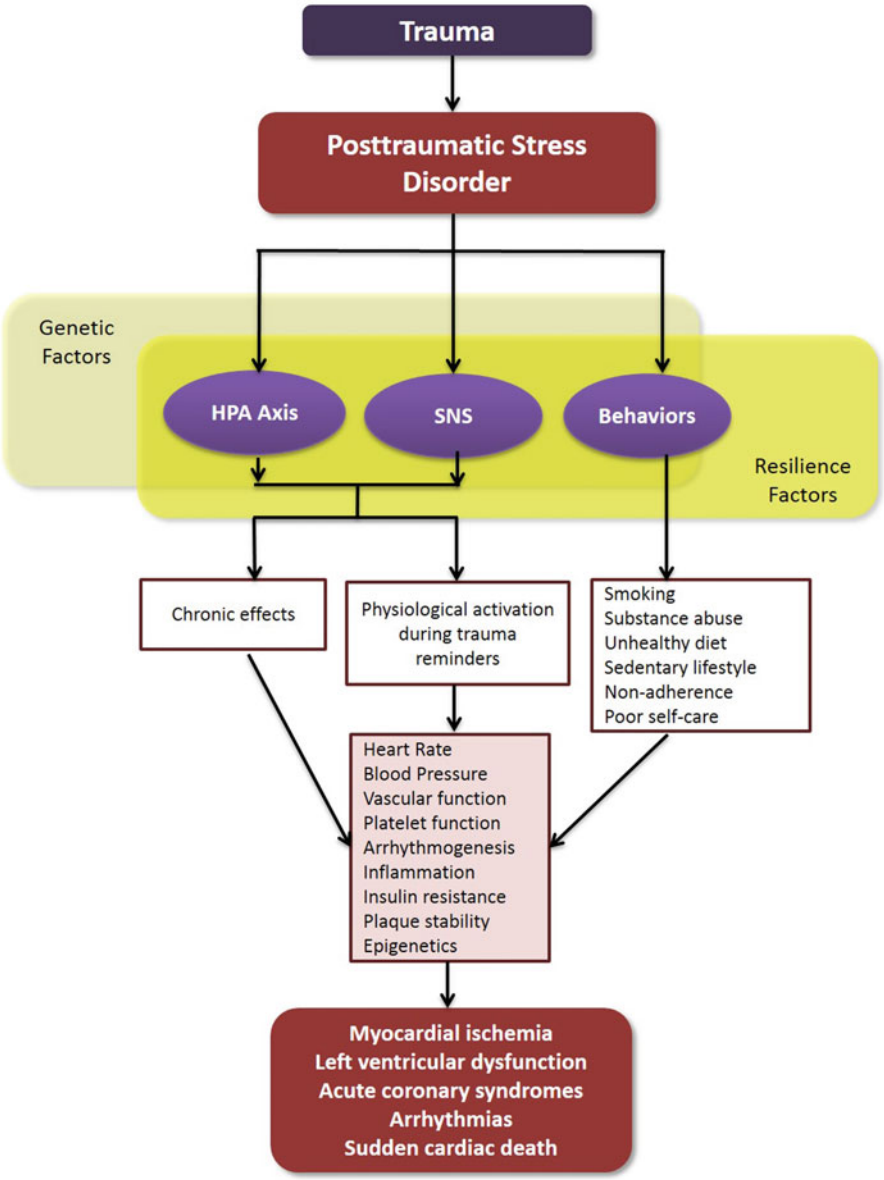


Fig. 2 Schematic representation diagram illustrating potential mechanisms linking PTSD to coronary heart disease. HPA, hypothalamic-pituitary-adrenal; SNS, sympathetic nervous system (From Vaccarino V, & Bremner JD. Biol Psychiatry 2013;74:790-792. Reproduced with publisher's permission)

low-frequency HRV than their brothers without PTSD ($p < 0.001$). Remitted PTSD was not associated with HRV. Results were robust to adjustment for depression and other risk factors. These data suggest that PTSD, especially current PTSD, is associated with autonomic inflexibility indices previously shown to be prognostic and that this effect might reverse with remission of PTSD (Shah et al. 2013).

One of the biological hallmarks of PTSD is enhanced sensitivity of the noradrenergic system resulting in heightened SNS activity, particularly during trauma reminders (Bremner and Charney 2010; Yehuda 2002; Zoladz and Diamond 2013). For example, combat veterans with PTSD, compared with controls, exhibit an increase in catecholamines, heart rate, and other physiological parameters in response to reminders of trauma such as sound of gunfire, combat slides, or scripts of their traumatic experiences (Blanchard et al. 1982; Pitman et al. 1987). They also show altered brain function (especially decreased frontal lobe function) compared to non-PTSD subjects in response to traumatic reminders (Bremner and Charney 2010). Most of these responses are not observed when using neutral stressors such as mental arithmetic (Blanchard et al. 1982).

In addition to dysfunction of the autonomic nervous system, PTSD is characterized by dysregulation of the HPA axis. Overall, individuals with PTSD show enhanced negative feedback sensitivity of the glucocorticoid receptors, as evidenced by increased corticotrophin-releasing factor and decreased peripheral cortisol concentrations at rest, suggesting that the HPA system may be downregulated (Bremner and Charney 2010; Yehuda 2002; Zoladz and Diamond 2013). However, there is enhanced cortisol release with reminders of the trauma in PTSD compared with controls. For example, women with abuse-related PTSD listening to traumatic scripts had a fourfold salivary cortisol response than women with abuse without PTSD (Elzinga et al. 2003). PTSD patients also show increased cortisol response to the type of cognitive mental stress challenge used in studies of patients with CVD (Bremner et al. 2003). Patients with PTSD, however, have lower serial cortisol levels throughout the day and a blunted effect of dexamethasone on declarative memory function.

Stress Reactivity in PTSD and IHD

A commonly endorsed pathway for the increased CVD risk in PTSD is neuroendocrine, hemodynamic, and immune hyperreactivity during psychological stress, which has been related to cardiovascular risk factors such as hypertension and to CVD events (Chida and Steptoe 2010; Treiber et al. 2003). PTSD patients subjected to a stress challenge in the laboratory involving personalized trauma scripts show higher increases in blood pressure, heart rate, and other indicators of activated SNS compared with controls (Bremner et al. 1999). Patients with depression and CVD and a history of childhood abuse (many of whom had comorbid PTSD) showed an increase in myocardial ischemia in response to mental stress relative to patients with CVD without depression or abuse (Bremner et al. 2009). This suggests that early abuse may play a role in sensitizing patients to stress-induced myocardial

ischemia in adulthood. It is plausible that these responses result in a cumulative long-term increase in cardiovascular risk, but whether this is true needs further investigation.

Vascular and Immune Effects

Heightened physiological stress activation during reexperiencing episodes in PTSD, such as it was described above, could have cumulative and enduring effects that directly or indirectly impact the endothelium, the myocardium, immune function, platelet activity, and vascular repair processes. These in turn may affect vascular function and plaque stability and may result in acute cardiac events through pathways that are independent of traditional risk factors and even independent of atherosclerotic plaque burden (Bhattacharyya and Steptoe 2007; Strike et al. 2006). For example, catecholamines have direct adverse effects on the myocardium, the cardiac conduction system, the endothelium, and platelet function and have also been implicated in the development of heart failure and cardiac ischemia (Brotman et al. 2007).

Vascular Function. SNS activation during stress, through the neurohormone epinephrine, can cause peripheral vasoconstriction. This has been demonstrated in acute stress studies in the laboratory (mental stress testing), where peripheral vasoconstriction was measured noninvasively (Hassan et al. 2009b; Ramadan et al. 2013a). In addition, enhanced SNS activation could lead to microvascular and endothelial dysfunction, early precursors of IHD. It has been shown that even a brief period of mental stress induced in the laboratory may result in prolonged peripheral vascular endothelial dysfunction (Ghiadoni et al. 2000).

Peripheral vasoconstriction during mental stress could lead to myocardial ischemia because of a sudden increase in cardiac afterload or because it correlates with coronary vascular dysfunction. Indeed, noninvasively measured peripheral vasoconstriction predicts mental stress-induced myocardial ischemia (Burg et al. 2009; Hassan et al. 2009a, b). In a study of 384 cardiac patients, peripheral vascular tone was measured noninvasively using a device which recorded the pulse wave amplitude of vascular flow in the microvessels of the fingers, deriving a ratio of amplitude during mental stress over the amplitude at rest (Ramadan et al. 2013b). This ratio was lower in those who developed mental stress ischemia during a speech task compared with those who did not, indicating greater digital microvascular constriction. Notably, this measure did not correlate with angiographic severity of coronary artery disease and was a better predictor of mental stress ischemia than angiographically measured coronary disease. It is possible that these vascular effects occur in subjects with PTSD during episodes of intrusive memories associated with marked SNS activation, and thus, they may predispose some individuals to acute myocardial ischemia.

Inflammation and Immunity. There have been many reports that persons with PTSD have higher levels of inflammatory biomarkers and evidence of immune dysregulation (Gill et al. 2009). Recently, PTSD has also been associated with

cellular adhesion molecules and other endothelium-derived circulating proteins, including ICAM-1, VCAM-1, selectins (von Kanel et al. 2010), and some clotting factors (von Kanel et al. 2006, 2008). In a twin study, there was a robust association between PTSD and ICAM-1, within a panel of inflammatory markers including CRP, IL-6, fibrinogen, and white blood cells, in addition to ICAM-1 and VCAM-1 (Plantinga et al. 2013). In within-pair analyses of twin pairs discordant for PTSD, ICAM-1 was the only biomarker that was significantly associated with PTSD.

Circulating adhesion molecules are especially relevant here because they are markers of inflammation but also of endothelial injury and predict IHD risk (Blann et al. 2003; Hope and Meredith 2003a, b). ICAM-1, in particular, increases during acute stress and was found to go up about 12 % more in PTSD subjects than those without PTSD under stress conditions (von Kanel et al. 2010). ICAM-1 is associated with remarkably higher risk of IHD in prospective studies, while VCAM-1 is not as good of a predictor (Hwang et al. 1997; Luc et al. 2003). The endothelial adhesion molecule E-selectin and the platelet adhesion molecule P-selectin have also been associated with IHD (Blann et al. 2003; Hwang et al. 1997).

Although the mechanisms underlying immune dysfunction in PTSD are not clear, they may be related to neurobiological features of PTSD characterized by a hyperactive noradrenergic system and lower basal cortisol levels and/or to protracted activation of stress systems during stressful reexperiencing episodes (Bremner 2010; Bremner and Charney 2010; Garakani et al. 2011). Glucocorticoids and catecholamines affect the immune system in many ways (Elenkov and Chrousos 2002). Psychosocial stress directly triggers inflammation through norepinephrine-dependent activation of the transcription factor NF-κB in circulating monocytes (Bierhaus et al. 2003). During mental stress, the concentration of several circulating inflammatory molecules goes up within 90–120 min, with most consistent increases for interleukin (IL)-6 and IL-1β, and marginal effects for C-reactive protein (CRP) (Steptoe et al. 2007). It is important to remember that inflammatory processes promote a hypercoagulable state and endothelial dysfunction, which are mechanisms of IHD and could lead to plaque instability, plaque disruption, or superimposed thrombus, which could lead to myocardial ischemia.

Clinical Implications

PTSD is a common condition in the general population and in patients with CVD. It is associated with considerable disability and impaired quality of life and is now emerging as an important risk factor and prognostic factor for CVD. Nonetheless, PTSD symptoms are often overlooked in general clinical practice. Clinicians who care for patients in primary care settings or in cardiology clinics should be aware that PTSD may have adverse effects on the cardiovascular system including increased risk of adverse cardiovascular events and mortality.

In the United States alone, about one million patients are discharged each year with a diagnosis of acute coronary syndrome (Go et al. 2014); of these, over 100,000 patients could develop clinically significant PTSD symptoms. In addition,

about 800,000 people experience a new or recurrent stroke each year, which may translate into approximately 180,000 patients with PTSD secondary to stroke. To these numbers, one should add PTSD cases that preexisted the onset of CVD. It follows that PTSD could contribute substantially to repeat hospitalization, mortality, and an increase in healthcare costs associated with acute cardiovascular disease.

Effective pharmacological and psychotherapy approaches for the treatment of PTSD and ameliorating symptomatic distress are available (Bandelow et al. 2012; Sullivan and Neria 2009), but whether such treatments also reduce CVD risk is currently unknown. Similarly untested is whether reducing symptoms of PTSD would improve adherence and other health behaviors in PTSD patients. The advantages and disadvantages of routinely screening for PTSD symptoms in cardiac patients are also unknown. Several primary care centers within the Veterans Health Administration in the United States routinely screen for PTSD using questionnaires such as the four-item Primary Care PTSD Screen (PC-PTSD). Although this approach may be useful to detect undiagnosed PTSD in high-risk populations, its utility for CVD prevention or treatment is unknown, and there are currently no guidelines for screening in the nonveteran population at large.

In order to optimize clinical outcomes of patients with comorbid PTSD and CVD, the cardiologist or primary care physician should seek psychiatric consultation as needed, which may also be helpful if associated problems are present, such as depression and substance abuse. In addition, some medications for the treatment of PTSD, especially the older tricyclic medications, may adversely affect cardiovascular function, and thus drug treatment, if needed, should be carefully evaluated within the overall management of the patient.

Conclusion

Research in the past decade has accumulated compelling evidence to support an association between PTSD and incident CVD and is beginning to show a similar relationship between PTSD and recurrent CVD events. However, more longitudinal studies, using established, objective measures of CVD, are needed to definitely prove this link. Additionally, the underlying mechanisms are unclear and are likely to be complex and multifactorial. Better understanding of the underlying pathophysiology will help identify effective management and preventive modalities. PTSD appears to be a pro-inflammatory, procoagulant condition through hyperactivity of the noradrenergic system and downregulation of the HPA axis. Autonomic imbalance is reflected by an exaggerated catecholamine response to stressful circumstances which may contribute to CVD through a multitude of pathways related to inflammation, coagulation, vascular function, and repair processes. Adverse health behaviors are common in PTSD, such as cigarette smoking and substance abuse related to self-medication. At this time, not one causal pathway has been identified and ultimately multiple pathways may be involved. Thus, future research efforts will require wider approaches with rigorous study designs and sufficiently large sample sizes.

It will also be of interest to identify risk factors for susceptibility to both PTSD and CVD, such as whether there are specific exposures, or genetic backgrounds, that might increase individual predisposition to both disorders. Furthermore, it will be important to clarify predisposing factors that might make patients more vulnerable to develop PTSD after an acute cardiovascular event. Finally, research should be directed toward the identification of effective treatments that may help reduce cardiovascular risk and improve prognosis among persons with PTSD. As the scientific community will continue to discover the most important mechanisms underlying the link between PTSD and CVD, clues can be derived about the most promising targets for reducing CVD risk in PTSD. New trials of pharmacologic and behavioral treatments for PTSD should examine the effects of PTSD symptom reduction on these potential mechanisms and on CVD outcomes.

References

Ahmadi, N., Hajsadeghi, F., Mirshkarlo, H. B., Budoff, M., Yehuda, R., & Ebrahimi, R. (2011). Post-traumatic stress disorder, coronary atherosclerosis, and mortality. *American Journal of Cardiology, 108*(1), 29–33. doi:10.1016/j.amjcard.2011.02.340.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington: American Psychiatric Association.

Arbab-Zadeh, A., Nakano, M., Virmani, R., & Fuster, V. (2012). Acute coronary events. *Circulation, 125*(9), 1147–1156. doi:10.1161/CIRCULATIONAHA.111.047431.

Bandelow, B., Sher, L., Bunevicius, R., Hollander, E., Kasper, S., Zohar, J., & Moller, H. J. (2012). Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *International Journal of Psychiatry in Clinical Practice, 16*(2), 77–84. doi:10.3109/13651501.2012.667114.

Bhattacharyya, M. R., & Steptoe, A. (2007). Emotional triggers of acute coronary syndromes: Strength of evidence, biological processes, and clinical implications. *Progress in Cardiovascular Diseases, 49*(5), 353–365.

Bierhaus, A., Wolf, J., Andrassy, M., Rohleder, N., Humpert, P. M., Petrov, D., . . . Nawroth, P.P. (2003). A mechanism converting psychosocial stress into mononuclear cell activation. *Proceedings of the National Academy of Sciences of the United States of America, 100*(4), 1920–1925.

Blanchard, E. B., Kolb, L. C., Pallmeyer, T. P., & Gerardi, R. J. (1982). A psychophysiological study of post-traumatic stress disorder in Vietnam veterans. *Psychiatric Quarterly, 54*, 220–229.

Blann, A. D., Nadar, S. K., & Lip, G. Y. (2003). The adhesion molecule P-selectin and cardiovascular disease. *European Heart Journal, 24*(24), 2166–2179.

Boscarino, J. A. (2006). Posttraumatic stress disorder and mortality among U.S. Army veterans 30 years after military service. *Annals of Epidemiology, 16*(4), 248–256.

Boscarino, J. A. (2008). A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: Implications for surveillance and prevention. *Psychosomatic Medicine, 70*(6), 668–676. doi:PSY.0b013e31817bccaf[pii] 10.1097/PSY.0b013e31817bccaf.

Boscarino, J. A. (2012). PTSD is a risk factor for cardiovascular disease: Time for increased screening and clinical intervention. *Preventive Medicine*. doi:10.1016/j.ypmed.2012.01.001.

Brass, L. M., & Page, W. F. (1996). Stroke in former prisoners of war. *Journal of Stroke and Cerebrovascular Diseases, 6*(2), 72–78.

Bremner, J. D. (2010). Imaging in CNS disease states: PTSD. In D. Borsook, L. Beccera, E. Bullmore, & R. Hargreaves (Eds.), *Imaging in CNS drug discovery and development: Implications for disease and therapy* (pp. 339–360). Basel: Springer.

Bremner, J. D., & Charney, D. S. (2010). Neural circuits in fear and anxiety. In D. J. Stein, E. Hollander, & B. O. Rothbaum (Eds.), *Textbook of anxiety disorders* (2nd ed., pp. 55–71). Arlington: American Psychiatric Publishing.

Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., McGlashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *American Journal of Psychiatry, 156*(11), 1787–1795.

Bremner, J. D., Vythilingam, M., Vermetten, E., Adil, J., Khan, S., Nazeer, A., . . . Charney, D. S. (2003). Cortisol response to a cognitive stress challenge in posttraumatic stress disorder (PTSD) related to childhood abuse. *Psychoneuroendocrinology, 28*, 733–750.

Bremner, J. D., Cheema, F. A., Ashraf, A., Afzal, N., Fani, N., Reed, J., . . . Vaccarino, V. (2009). Effects of a cognitive stress challenge on myocardial perfusion and plasma cortisol in coronary heart disease patients with depression. *Stress and Health, 25*, 267–278.

Breslau, N., Davis, G. C., & Schultz, L. R. (2003). Posttraumatic stress disorder and the incidence of nicotine, alcohol, and other drug disorders in persons who have experienced trauma. *Archives of General Psychiatry, 60*(3), 289–294.

Brotman, D. J., Golden, S. H., & Wittstein, I. S. (2007). The cardiovascular toll of stress. *Lancet, 370*(9592), 1089–1100. doi:10.1016/S0140-6736(07)61305-1.

Burg, M. M., Graeber, B., Vashist, A., Collins, D., Earley, C., Liu, J., . . . Soufer, R. (2009). Noninvasive detection of risk for emotion-provoked myocardial ischemia. *Psychosomatic Medicine, 71*(1), 14–20. doi:10.1097/PSY.0b013e318187c035.

Chida, Y., & Steptoe, A. (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: A meta-analysis of prospective evidence. *Hypertension, 55*(4), 1026–1032. doi:10.1161/HYPERTENSIONAHA.109.146621.

Coughlin, S. S. (2011). Post-traumatic stress disorder and cardiovascular disease. *Open Cardiovascular Medicine Journal, 5*, 164–170. doi:10.2174/1874192401105010164.

Dirkzwager, A. J., van der Velden, P. G., Grievink, L., & Yzermans, C. J. (2007). Disaster-related posttraumatic stress disorder and physical health. *Psychosomatic Medicine, 69*(5), 435–440. doi:10.1097/PSY.0b013e318052e20a.

Dobie, D. J., Kivlahan, D. R., Maynard, C., Bush, K. R., Davis, T. M., & Bradley, K. A. (2004). Posttraumatic stress disorder in female veterans: Association with self-reported health problems and functional impairment. *Archives of Internal Medicine, 164*(4), 394–400. doi:10.1001/archinte.164.4.394.

Dohrenwend, B. P., Turner, J. B., Turse, N. A., Adams, B. G., Koenen, K. C., & Marshall, R. (2006). The psychological risks of Vietnam for U.S. Veterans: A revisit with new data and methods. *Science, 313*(5789), 979–982.

Edmondson, D., Richardson, S., Falzon, L., Davidson, K. W., Mills, M. A., & Neria, Y. (2012). Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: A meta-analytic review. *PLoS ONE, 7*(6), e38915. doi:10.1371/journal.pone.0038915.

Edmondson, D., Richardson, S., Fausett, J. K., Falzon, L., Howard, V. J., & Kronish, I. M. (2013). Prevalence of PTSD in survivors of stroke and transient ischemic attack: A meta-analytic review. *PLoS ONE, 8*(6), e66435. doi:10.1371/journal.pone.0066435.

Elenkov, I. J., & Chrousos, G. P. (2002). Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Annals of the New York Academy of Sciences, 966*, 290–303.

Elzinga, B. M., Schmahl, C. S., Vermetten, E., van Dyck, R., & Bremner, J. D. (2003). Higher cortisol levels following exposure to traumatic reminders in abuse-related PTSD. *Neuropsychopharmacology, 28*(9), 1656–1665.

Gamper, G., Willeit, M., Sterz, F., Herkner, H., Zoufaly, A., Hornik, K., . . . Laggner, A.N. (2004). Life after death: Posttraumatic stress disorder in survivors of cardiac arrest – prevalence, associated factors, and the influence of sedation and analgesia. *Critical Care Medicine, 32*(2), 378–383. doi:10.1097/01.CCM.0000108880.97967.C0.

Garakani, A., Murrough, J., Mathew, S.J., Charney, D. S., & Bremner, J. D. (2011). The neurobiology of anxiety disorders. In D. S. Charney & E. J. Nestler (Eds.), *Neurobiology of mental illness*, Oxford University Press, New York, NY.

Ghiadoni, L., Donald, A. E., Cropley, M., Mullen, M. J., Oakley, G., Taylor, M., . . . Deanfield, J. E. (2000). Mental Stress Induces Transient Endothelial Dysfunction in Humans. *Circulation, 102*(20), 2473–2478.

Gill, J. M., Saligan, L., Woods, S., & Page, G. (2009). PTSD is associated with an excess of inflammatory immune activities. *Perspectives in Psychiatric Care, 45*(4), 262–277. doi:10.1111/j.1744-6163.2009.00229.x.

Glaesmer, H., Brahler, E., Gundel, H., & Riedel-Heller, S. G. (2011). The association of traumatic experiences and posttraumatic stress disorder with physical morbidity in old age: A German population-based study. *Psychosomatic Medicine, 73*(5), 401–406. doi:10.1097/PSY.0b013e31821b47e8.

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Blaha, M. J., . . . Stroke Statistics, S. (2014). Heart disease and stroke statistics – 2014 update: A report from the American Heart Association. *Circulation, 129*(3), e28–e292. doi:10.1161/01.cir.0000441139.02102.80.

Hassan, M., Quyyumi, A. A., & Sheps, D. S. (2009a). A noninvasive clinically useful predictor for mental stress-induced ischemia. *Psychosomatic Medicine, 71*(1), 21–22. doi:PSY.0b013e3181967c3d [pii] 10.1097/PSY.0b013e3181967c3d.

Hassan, M., York, K. M., Li, H., Li, Q., Lucey, D. G., Fillingim, R. B., & Sheps, D. S. (2009b). Usefulness of peripheral arterial tonometry in the detection of mental stress-induced myocardial ischemia. *Clinical Cardiology, 32*(9), E1–E6. doi:10.1002/clc.20515.

Hoge, C. W., Terhakopian, A., Castro, C. A., Messer, S. C., & Engel, C. C. (2007). Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq war veterans. *The American Journal of Psychiatry, 164*(1), 150–153. doi:164/1/150 [pii] 10.1176/appi.ajp.164.1.150.

Hope, S. A., & Meredith, I. T. (2003a). Cellular adhesion molecules and cardiovascular disease. Part I. Their expression and role in atherogenesis. *Internal Medicine Journal, 33*(8), 380–386.

Hope, S. A., & Meredith, I. T. (2003b). Cellular adhesion molecules and cardiovascular disease. Part II. Their association with conventional and emerging risk factors, acute coronary events and cardiovascular risk prediction. *Internal Medicine Journal, 33*(9–10), 450–462.

Hughes, J. W., Dennis, M. F., & Beckham, J. C. (2007). Baroreceptor sensitivity at rest and during stress in women with posttraumatic stress disorder or major depressive disorder. *Journal of Traumatic Stress, 20*(5), 667–676. doi:10.1002/jts.20285.

Hwang, S. J., Ballantyne, C. M., Sharrett, A. R., Smith, L. C., Davis, C. E., Gotto, A. M., Jr., & Boerwinkle, E. (1997). Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: The Atherosclerosis Risk in Communities (ARIC) study. *Circulation, 96*(12), 4219–4225.

Kang, H. K., Bullman, T. A., & Taylor, J. W. (2006). Risk of selected cardiovascular diseases and posttraumatic stress disorder among former world war II prisoners of war. *Annals of Epidemiology, 16*(5), 381–386. doi:S1047-2797(05)00098-0 [pii] 10.1016/j.annepidem.2005.03.004.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., . . . Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Archives of General Psychiatry, 51*, 8–19.

Kubzansky, L. D., Koenen, K. C., Spiro, A., 3rd, Vokonas, P. S., & Sparrow, D. (2007). Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the normative aging study. *Archives of General Psychiatry, 64*(1), 109–116.

Kubzansky, L. D., Koenen, K. C., Jones, C., & Eaton, W. W. (2009). A prospective study of posttraumatic stress disorder symptoms and coronary heart disease in women. *Health Psychology, 28*(1), 125–130. doi:2009-00026-006 [pii] 10.1037/0278-6133.28.1.125.

Ladwig, K. H., Baumert, J., Marten-Mittag, B., Kolb, C., Zrenner, B., & Schmitt, C. (2008). Posttraumatic stress symptoms and predicted mortality in patients with implantable

cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. *Archives of General Psychiatry, 65*(11), 1324–1330. doi:10.1001/archpsyc.65.11.1324.

Luc, G., Arveiler, D., Evans, A., Amouyel, P., Ferrieres, J., Bard, J.M., . . . Group, P.S. (2003). Circulating soluble adhesion molecules ICAM-1 and VCAM-1 and incident coronary heart disease: The PRIME Study. *Atherosclerosis, 170*(1), 169–176.

McGue, M., Osler, M., & Christensen, K. (2010). Causal inference and observational research: The utility of twins. *Perspectives on Psychological Science, 5*(5), 546–556. doi:10.1177/1745691610383511.

Pitman, R. K., Orr, S. P., Forgue, D. F., de Jong, J. B., & Claiborn, J. M. (1987). Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. *Archives of General Psychiatry, 44*(11), 970–975.

Plantinga, L., Bremner, J. D., Miller, A. H., Jones, D. P., Veledar, E., Goldberg, J., & Vaccarino, V. (2013). Association between posttraumatic stress disorder and inflammation: A twin study. *Brain, Behavior, and Immunity, 30*, 125–132. doi:10.1016/j.bbi.2013.01.081.

Qureshi, S., Pyne, J., Magruder, K., Schulz, P., & Kunik, M. (2009). The link between post-traumatic stress disorder and physical comorbidities: A systematic review. *Psychiatric Quarterly, 80*(2), 87–97.

Ramadan, R., Sheps, D., Esteves, F., Zafari, A. M., Bremner, J. D., Vaccarino, V., & Quyyumi, A. A. (2013a). Myocardial ischemia during mental stress: Role of coronary artery disease burden and vasomotion. *Journal of the American Heart Association, 2*(5), e000321. doi:10.1161/JAHA.113.000321.

Ramadan, R., Sheps, D., Esteves, F., Zafari, A. M., Bremner, J. D., Vaccarino, V., & Quyyumi, A. A. (2013b). Myocardial ischemia during mental stress: Role of coronary artery disease burden and vasomotion. *Journal American Heart Association, 2*(5), e000321. doi:10.1161/JAHA.113.000321.

Reed, R. V., Fazel, M., & Goldring, L. (2012). Post-traumatic stress disorder. *BMJ, 344*, e3790.

Reese, C., Pederson, T., Avila, S., Joseph, K., Nagy, K., Dennis, A., . . . Bokhari, F. (2012). Screening for traumatic stress among survivors of urban trauma. *Journal of Trauma and Acute Care Surgery, 73*(2), 462–467. Discussion 467–468. doi:10.1097/TA.0b013e31825ff713.

Roberge, M. A., Dupuis, G., & Marchand, A. (2010). Post-traumatic stress disorder following myocardial infarction: Prevalence and risk factors. *Canadian Journal of Cardiology, 26*(5), e170–e175.

Robins, L. N., Helzer, J. E., Croughan, J., & Ratcliff, K. S. (1981). National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. *Archives of General Psychiatry, 38*(4), 381–389.

Scherrer, J.F., Chrusciel, T., Zeringue, A., Garfield, L.D., Hauptman, P.J., Lustman, P.J., . . . True, W.R. (2010). Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans administration patients. *American Heart Journal, 159*(5), 772–779. doi:10.1016/j.ahj.2010.02.033.

Shah, A. J., Lampert, R., Goldberg, J., Veledar, E., Bremner, J. D., & Vaccarino, V. (2013). Posttraumatic stress disorder and impaired autonomic modulation in male twins. *Biological Psychiatry, 73*(11), 1103–1110. doi:10.1016/j.biopsych.2013.01.019.

Spitzer, C., Barnow, S., Volzke, H., John, U., Freyberger, H. J., & Grabe, H. J. (2009). Trauma, posttraumatic stress disorder, and physical illness: Findings from the general population. *Psychosomatic Medicine, 71*(9), 1012–1017. doi:10.1097/PSY.0b013e3181bc76b5.

Steptoe, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain, Behavior, and Immunity, 21*(7), 901–912.

Strike, P. C., Magid, K., Whitehead, D. L., Brydon, L., Bhattacharyya, M. R., & Steptoe, A. (2006). Pathophysiological processes underlying emotional triggering of acute cardiac events. *Proceedings of the National Academy of Sciences of the United States of America, 103*(11), 4322–4327.

Sullivan, G. M., & Neria, Y. (2009). Pharmacotherapy in post-traumatic stress disorder: Evidence from randomized controlled trials. *Current Opinion in Investigational Drugs, 10*(1), 35–45.

Thurston, R. C., Chang, Y., Derby, C. A., Bromberger, J. T., Harlow, S. D., Janssen, I., & Matthews, K. A. (2014). Abuse and subclinical cardiovascular disease among midlife women: The study of women's health across the nation. *Stroke, 45*(8), 2246–2251. doi:10.1161/STROKEAHA.114.005928.

Treiber, F. A., Kamarck, T., Schneiderman, N., Sheffield, D., Kapuku, G., & Taylor, T. (2003). Cardiovascular reactivity and development of preclinical and clinical disease states. *Psychosomatic Medicine, 65*(1), 46–62.

Turner, J. H., Neylan, T. C., Schiller, N. B., Li, Y., & Cohen, B. E. (2013). Objective evidence of myocardial ischemia in patients with posttraumatic stress disorder. *Biological Psychiatry*. doi:10.1016/j.biopsych.2013.07.012.

Vaccarino, V., & Bremner, J. D. (2013). Traumatic stress is heartbreaking. *Biological Psychiatry, 74*(11), 790–792. doi:10.1016/j.biopsych.2013.10.002.

Vaccarino, V., Goldberg, J., Rooks, C., Shah, A.J., Veledar, E., Faber, T. L., . . . Bremner, J. D. (2013). Post-traumatic stress disorder and incidence of coronary heart disease: A twin study. *J Am Coll Cardiol, 62*(11), 970–978. doi:10.1016/j.jacc.2013.04.085.

Vaccarino, V., Goldberg, J., Magruder, K. M., Forsberg, C. W., Friedman, M. J., Litz, B. T., . . . Smith, N. L. (2014). Posttraumatic stress disorder and incidence of type-2 diabetes: A prospective twin study. *Journal of Psychiatric Research, 56*, 158–164. doi:10.1016/j.jpsychires.2014.05.019.

von Kanel, R., Hepp, U., Buddeberg, C., Keel, M., Mica, L., Aschbacher, K., & Schnyder, U. (2006). Altered blood coagulation in patients with posttraumatic stress disorder. *Psychosomatic Medicine, 68*(4), 598–604. doi:10.1097/01.psy.0000221229.43272.9d.

von Kanel, R., Hepp, U., Traber, R., Kraemer, B., Mica, L., Keel, M., . . . Schnyder, U. (2008). Measures of endothelial dysfunction in plasma of patients with posttraumatic stress disorder. *Psychiatry Research, 158*(3), 363–373. doi:10.1016/j.psychres.2006.12.003.

von Kanel, R., Abbas, C. C., Begre, S., Saner, H., Gander, M. L., & Schmid, J. P. (2010). Posttraumatic stress disorder and soluble cellular adhesion molecules at rest and in response to a trauma-specific interview in patients after myocardial infarction. *Psychiatry Research, 179*(3), 312–317. doi:10.1016/j.psychres.2009.06.005.

Wentworth, B. A., Stein, M. B., Redwine, L. S., Xue, Y., Taub, P. R., Clopton, P., . . . Maisel, A. S. (2012). Post-traumatic stress disorder: A fast track to premature cardiovascular disease? *Cardiology in Review*. doi:10.1097/CRD.0b013e318265343b.

Wentworth, B. A., Stein, M. B., Redwine, L. S., Xue, Y., Taub, P. R., Clopton, P., . . . Maisel, A. S. (2013). Post-traumatic stress disorder: A fast track to premature cardiovascular disease? *Cardiology in Review, 21*(1), 16–22. doi:10.1097/CRD.0b013e318265343b.

Wikman, A., Bhattacharyya, M., Perkins-Porras, L., & Steptoe, A. (2008). Persistence of posttraumatic stress symptoms 12 and 36 months after acute coronary syndrome. *Psychosomatic Medicine, 70*(7), 764–772. doi:10.1097/PSY.0b013e3181835c07.

Wilson, R. S., Boyle, P. A., Levine, S. R., Yu, L., Anagnos, S. E., Buchman, A. S., . . . Bennett, D. A. (2012). Emotional neglect in childhood and cerebral infarction in older age. *Neurology, 79*(15), 1534–1539. doi:10.1212/WNL.0b013e31826e25bd.

Yehuda, R. (2002). Post-traumatic stress disorder. *New England Journal of Medicine, 346*, 108–114.

Zoladz, P. R., & Diamond, D. M. (2013). Current status on behavioral and biological markers of PTSD: A search for clarity in a conflicting literature. *Neuroscience and Biobehavioral Reviews, 37*(5), 860–895. doi:10.1016/j.neubiorev.2013.03.024.

Natural Disasters and the Risk of Cardiovascular Disease

Julie Zarifeh and Roger Mulder

Contents

Abstract

Cardiovascular events are a major cause of morbidity and mortality worldwide. Such events can be triggered by both acute and chronic mental stress caused by a number of known stressors, one of these being natural disasters. Triggering of

J. Zarifeh
Consultation-Liaison Service, Christchurch Public Hospital, Christchurch, New Zealand
e-mail: julie.zarifeh@cdhb.health.nz; julie.zarifeh@otago.ac.nz

R. Mulder (✉)
Department of Psychological Medicine, University of Otago, Christchurch, New Zealand
e-mail: roger.mulder@otago.ac.nz

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_19

acute mental stress results in increased sympathetic output, disturbed endothelial function, and the creation of a hypercoagulable state. There is then the potential for vulnerable plaque to be ruptured, resulting in thrombosis, and subsequent myocardial infarction, or even death. Chronic mental stress contributes to the atherosclerotic process through increased allostatic load, and related chronic risk factors.

This chapter summarizes what is known about the relationship between natural disasters and cardiovascular disease. A review of the literature relating cardiovascular risk to natural disasters was undertaken and proposed underlying mechanisms of this relationship examined. The review then examines potential management of cardiovascular risk related to natural disasters, particularly focusing on psychological implications and strategies for management of both individual and population health.

Keywords

Acute myocardial infarction (AMI) • Coronary artery disease (CAD) • Cardiopulmonary arrest (CPA) • Coronary heart disease (CHD) • Cardiovascular disease (CVD) • Pulmonary embolism (PE) • Posttraumatic stress disorder (PTSD) • Sympathetic nervous system (SNS)

Search Categories and Selection

PubMed, Cinahl, and Embase were searched for relevant articles published between 1990 and 2014. Only articles in English and published in journals were examined using the search terms: natural disaster/earthquake, cardiovascular disease, stress, and posttraumatic stress disorder. Further searches were made for authors published in this field, and the bibliographies of all papers retrieved were hand- searched for relevant articles also.

Introduction

Despite advances in prevention and treatment, cardiovascular disease (CVD) remains the leading cause of death worldwide (Turner et al. 2013). CVD can be thought of as a continuum that commences with the presence of cardiovascular risk factors continuing via progressive vascular disease to organ damage, organ failure, and, ultimately, death (Dahlof 2010). Only half of the causes in CVD are accounted for by traditional cardiac risk factors, with psychosocial factors explaining much of the remaining risk (Turner et al. 2013). Most research has focused on long-term outcome, reporting that exposure to psychosocial risk factors is associated with accelerated atherosclerosis and higher risks of coronary heart disease. However it has become increasingly recognized that emotional factors might also contribute to cardiovascular disease through the stimulation of acute cardiac events such as

myocardial infarction (MI), unstable angina, or sudden cardiac death (Steptoe and Brydon 2009).

Acute physical and psychological stress, induced by catastrophic events such as natural disasters, can contribute to CVD morbidity and mortality (Watanabe et al. 2008). The apparent growing number of natural disasters, their ramifications, and increasing urbanization imply that health services must be prepared and resourced to manage large numbers of patients with (acute and) chronic cardiovascular disease symptoms in disaster situations (Miller and Arquilla 2008).

Epidemiology of Cardiovascular Effects Related to Natural Disaster

Earthquakes

Several observational studies have been carried out on populations affected by natural disasters, establishing what is now sometimes called disaster epidemiology (Norwood et al. 2000; Peleg et al. 2002). There is consistent evidence that earthquakes are associated with adverse cardiovascular events (Bartels and VanRooyen 2012). Earthquakes are unique disasters in that they occur with no warning and are then followed by a series of aftershocks which engender more uncertainty, ambiguity, and anxiety. "Of course such disasters have an adverse effect on psychiatric morbidity, but what happens to the heart?" (Dimsdale 2008).

Trevisan et al. (1986) reported on a longitudinal study of cardiovascular disease (CVD) risk factors (the Olivetti Study). They noted that participants screened a few weeks after a major earthquake had a higher heart rate and higher serum cholesterol and serum triglyceride levels than matched participants screened before the earthquake. They concluded that the acute stress associated with a major disaster can influence risk factors for CVD. Furthermore, because of disruptions to the social environment, risk factors in those affected could remain permanently elevated, thus contributing to the long-term adverse effect on CVD mortality that had started to be alluded to in literature. A threefold increase in cardiac deaths was observed following the 1978 earthquake in Thessaloniki, Greece (Trichopoulos et al. 1983), and a 2.5-fold increase in cardiac deaths, (compared with the number from other diseases), following the 1981 Athens 6.7 magnitude earthquake. Leor et al. (1996) reported a modest yet significant increase in hospital admissions for acute myocardial infarction (AMI), 2 weeks after the 1994 earthquake in Northridge, Los Angeles (from 149 to 201, a 35 % increase). This increase was especially noticeable in the hospitals closest to the epicenter, with the rates of sudden cardiac death also observed to have risen, from a daily average of 4.6 (SD = 2.1) in the preceding week to 24 on the day of the earthquake. Suzuki et al. (1997) reported a 3.5-fold increase in the number of admissions for AMI on the day of the Hanshin-Awaji disaster, Japan (1995), suggesting that the acute traumatic event had caused cardiac diseases in people who were vulnerable to acute coronary syndrome (ACS). This increased cardiovascular mortality persisted for up to 8 weeks.

Watanabe et al. (2008) reported on the marked incidence of pulmonary embolism (PE) with relatively high mortality following the October 23, 2004 earthquake in central Niigata, Japan (and several significant aftershocks). It was speculated that physical and psychological stress, as well as prolonged immobilization in automobiles following displacement, may increase the risk of PE and sudden death.

Chan et al. (2013) examined the effects of the two recent Christchurch, New Zealand earthquakes (4.36 am, 4 September 2010, magnitude 7.1 and 12.51 pm, 22 February 2011, magnitude 6.3) on acute cardiac presentations to Christchurch Hospital. They reported a significant increase in overall admissions, ST elevation myocardial infarction, and noncardiac chest pain in the first 2 weeks following the early morning September earthquake. This pattern was not replicated following the early afternoon February earthquake. Instead there were a large number of stress cardiomyopathy (SCM) admissions (21 cases) over 4 days. (There had been six stress cardiomyopathy cases after the September earthquake.)

Chan et al.'s (2013) data suggests that earthquakes occurring late in the morning and in the afternoon are less likely to precipitate MI than those occurring in the early hours of the morning. Similar findings on increased rates of AMI were reported in the Northridge earthquake (4.31 am, magnitude 6.7) (Leor and Kloner 1996) and the Hanshin-Awaji earthquake (5.46 am, magnitude 6.8) (Suzuki et al. 1997). Chan et al. (2013) also raised the possibility of circadian variation in response to stress cardiomyopathy (SCM). The Christchurch February 2011 earthquake at 12.51 pm while of less magnitude than the September 2010 earthquake at 4.36 am resulted in three times the rate of of SCM cases. Watanabe et al. (2008 found 25 cases of SCM in the 4 weeks following the 2004 13.01 pm Niigata earthquake compared with only one case reported in the 4 weeks previously and none in the 2 years before. As with all earthquake studies, Chan et al.'s (2013) was retrospective although it reports on a single-center experience; hence the researchers were studying the same population exposed to two different earthquakes in a 6-month time period.

Aoki et al. (2012) investigated "mid-term" occurrences of cardiovascular diseases after the Great East Japan earthquake disaster in the Miyagi Prefecture (population 2.3 million people) of 11 March 2011. This catastrophe was the second largest earthquake ever recorded in Japan; it generated a large tsunami, numerous aftershocks, and a nuclear power accident. For the 12 weeks following the earthquake, the weekly occurrences of cardiovascular diseases (heart failure, acute coronary syndrome (ACS), stroke, and cardiopulmonary arrest) were all significantly increased when compared with the previous 3 years.

Wilbert-Lampen and Steinbeck (2012) claim to be the first authors who have demonstrated a marked and prolonged increase in heart failure following an earthquake, but other researchers have criticized their methodology. They noted that diagnoses were not well defined and that no information was available about individual's disease history or medications. Nonetheless, high rates of heart failure resulted in the authors speculating that either the stressor had persisted for weeks (because of frequent aftershocks) or the noted increase in cardiovascular disease is

caused "in a complex way by the consequences of the humanitarian catastrophe: the trauma, the breakdown of lifelines (water, food, electricity, traffic, the emergency system), evacuation, temperature changes and aspiration pneumonia" (Wilbert-Lampen and Steinbeck 2012).

Whatever the mechanisms, it seems clear that the ramifications of a catastrophe such as a large earthquake is a challenge to any healthcare system which is forced to deal with increased cardiovascular disease, not only for the initial days, but for months and possibly years afterward.

On the other hand, the data has not always been consistent when investigating the impact of earthquakes on CVD. Brown (1999) reported that the 1989 magnitude 7.0 Loma Prieta earthquake in San Francisco, California, was not associated with an increase in AMI. Similarly, no increase in acute myocardial infarction onset due to physical and psychological stress was noted following the 5.6 magnitude earthquake in Newcastle, Australia, in 1989 (Dobson et al. 1991). These inconsistent findings may be due to "the size and region of the earthquakes, the time of day that the earthquakes occurred, the length of the study observation period, the number of injuries/deaths, and the rates of recognition of cases" (Tsai et al. 2004).

A number of conditions may cause decompensation of preexistent chronic cardiovascular disease or contribute to the onset of new CVD. Older age, poor nutrition, infection, injury, and physical and mental stress were conditions discussed as exacerbating risk of CVD by Sofia et al. (2012). Kako et al. (2014) reviewed all research regarding disaster health following the Great East Japan earthquake in 2011. They also highlighted the vulnerability of older people and discussed the environmental stress and the psychological and physical stress of dislocation and demobilization. A limitation of the observational, population-based studies is that the circumstances surrounding each cardiac event are not well defined, and analyses usually take place weeks, months, or even years after the trauma. Information about how the individuals who were affected specifically experienced the trauma is seldom collected, making it difficult to prove a causal link or to rule out alternative explanations of associations between disasters and increased cardiovascular risk.

Other Natural Disasters

Tsunami

Prior to 2011 no study had investigated the impact of tsunamis on the incidence of cardiovascular disease. Nakamura et al. (2012) reported that following the March 2011 tsunami which affected the northeastern coast of Japan, the number of patients with acute decompensated heart failure in the tsunami area was around twice the number compared to the pre-disaster period. They concluded that large and sudden changes in daily life and the trauma associated with a devastating tsunami have a significant impact on the incidences of acute decompensated heart failure.

Hurricanes

Hendrickson et al. (1997) compared the incidence of injury, cardiovascular disease, and asthma for a 2-week period following Hurricane Iniki – a class III/IV storm that passed directly over Kauai in September 1992. They reported that medical visits for cardiovascular disease nearly trebled in the 'post-Iniki' period. A more recent study by Peters et al. (2014) attempted to determine the prolonged effect of Hurricane Katrina on the incidence and timing of AMI in the city of New Orleans. The authors reported a more than threefold increase in the number of admissions for AMI during the 6 years after Hurricane Katrina and also significantly higher rates of psychiatric comorbidities. They hypothesized that increases in acute psychosocial risk factors (unemployment, substance abuse, psychiatric problems) as well as traditional risk factors such as smoking and hyperlipidemia led to the persistence of increased AMI admissions seen after Hurricane Katrina.

Terrorist Attacks

While not strictly fulfilling the definition of a natural disaster, terrorist attacks have many similar features; they occur with little or no warning and are associated with much physical and psychological distress. Chi et al. (2003) investigated the relationship between the terrorist attacks of September 11, 2001 in the USA and cardiac morbidity and mortality. They reported no acute increases in hospitalizations for cardiac events after the September 11 attacks in the NYC hospitals they studied. The authors speculated that cardiac events that occurred inside the World Trade Center may have been masked by deaths, from crush or burn injuries, or that exposure to an emotional or a psychological stressor may have to be direct to trigger an adverse response. In contrast Goldberg et al. (2005) and Steinberg et al. (2004) reported increased rates of AMI and ventricular arrhythmias, respectively, in patients living in NYC. Their reports however were limited by small sample sizes and failure to correct for seasonal variation in ventricular arrhythmias. Jordan et al. (2011) reported that 9/11-related PTSD was associated with elevated heart disease risk several years after the disaster.

Mechanisms

Therefore we can conclude that there is reasonably consistent data reporting an increased cardiovascular risk after natural disasters. However the mechanisms underlying this association are less clear. "The idea that 'acute' emotional stress can trigger a heart attack, or that a person can die of a broken heart has a large pedigree both in fiction and in historical anecdote" (Bhattacharyya and Steptoe 2007).

Pathophysiological mechanisms underlying the relationship between psychological factors and coronary artery disease can be divided into:

i. Direct pathophysiological mechanisms
ii. Behavioral mechanisms – whereby psychosocial conditions contribute to a higher frequency of adverse health behaviors

Given the emergency conditions surrounding large earthquakes, it is difficult to conduct fine-grained experimental or epidemiological studies. Data collected is typically retrospective using two broad strategies: population-based studies or studies investigating an individual's emotional experience. Nonetheless the evidence generally supports an association between exposure to population-based traumatic events and heightened rates of cardiovascular disease.

The methodology to study emotional triggers has improved over recent years. A trigger can be defined as a stimulus or activity that produces an acute physiological or pathophysiological change leading directly to the onset of acute cardiovascular disease. The pathophysiological process underlying emotional triggers is not fully elucidated but appears to occur predominantly through sympathetic nervous symptom activation and potentiation of acute risk factors (blood pressure increase, endothelial cell dysfunction, increased blood viscosity, and platelet and hemostatic activation). As noted previously, these inflammatory responses, when associated with plaque disruption, can promote myocardial ischemia, cardiac dysrhythmia, and thrombosis formation (Fig. 1).

Stressful events are also thought to influence this pathogenesis via negative emotional states. Feelings of anxiety and depression may exert direct effect on biological patterns and processes that influence disease risk. Thereafter, behavioral changes that occur as adaptation or responses to stressors such as increased smoking, poor sleep, and poor adherence to medical regimes provide a further pathway through which stressors influence disease risk, probably in the medium to long term.

Individual Vulnerability

In humans there are substantial differences in the perception of stress and in the subsequent physiological processes with inconsistent consequences across individuals. Although stressors are often associated with illness, the majority of individuals confronted with a traumatic event will remain disease-free. Therefore, there has been considerable interest in identifying individual differences in vulnerability to the potential pathogenic effects of stress with emphasis on genetic and psychological factors (Cohen et al. 2007). One consistent difference reported is a stronger association of emotional distress with AMI in women. This relationship extends to traumatic events like earthquakes (Culic 2007) and suggests that the

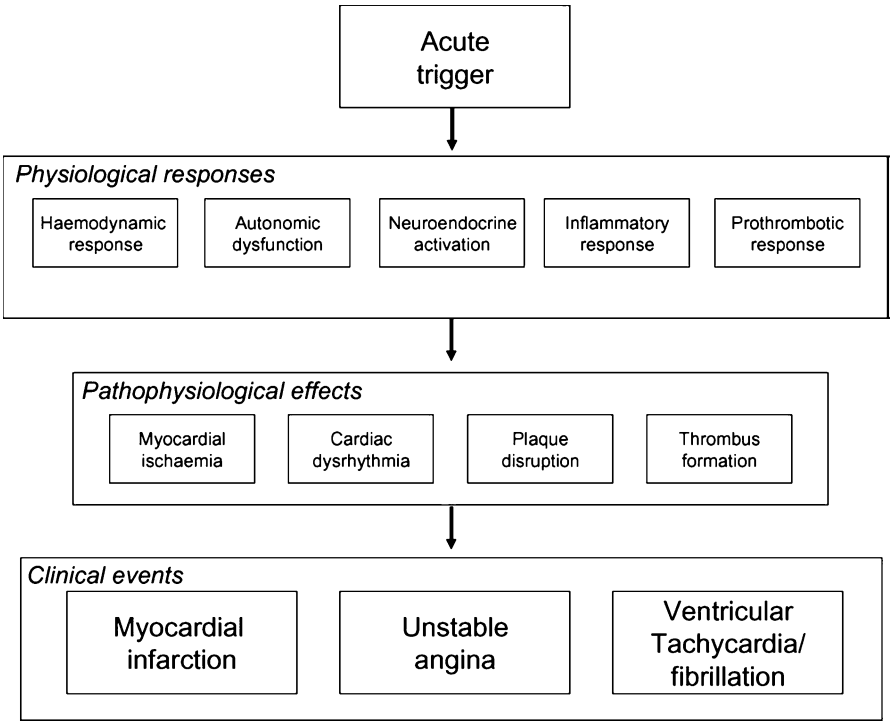


Fig. 1 Hypothesized links between acute emotional triggers and clinical cardiac events, mediated through physiological responses and their pathophysiological consequences (Adapted from Bhattacharyya and Steptoe 2007)

pathophysiological mechanism of triggering AMI by emotional stress may be different for men and women (Tofler and Muller 2006).

Kario et al. (2003) discussed the "allostatic load model" which can be applied to evaluate individual differences in response to stress. "Allostasis" refers to the ability to achieve stability through change (Fig. 2).

An event is perceived as being stressful if it is reported as being a threat to an individual's environment. This can induce a variety of negative emotional responses, of which fear is likely to be the predominant one after a natural disaster. In addition, loss, poverty, excessive physical exertion, changes in diet, and smoking may further modify the behavioral responses and have an additional effect on the physiological response to stress.

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy is a fascinating and potentially rapid fatal physical illness that appears to be triggered by emotional stress (Zarifeh et al. 2012). Symptoms mimic that of AMI but takotsubo cardiomyopathy has characteristic

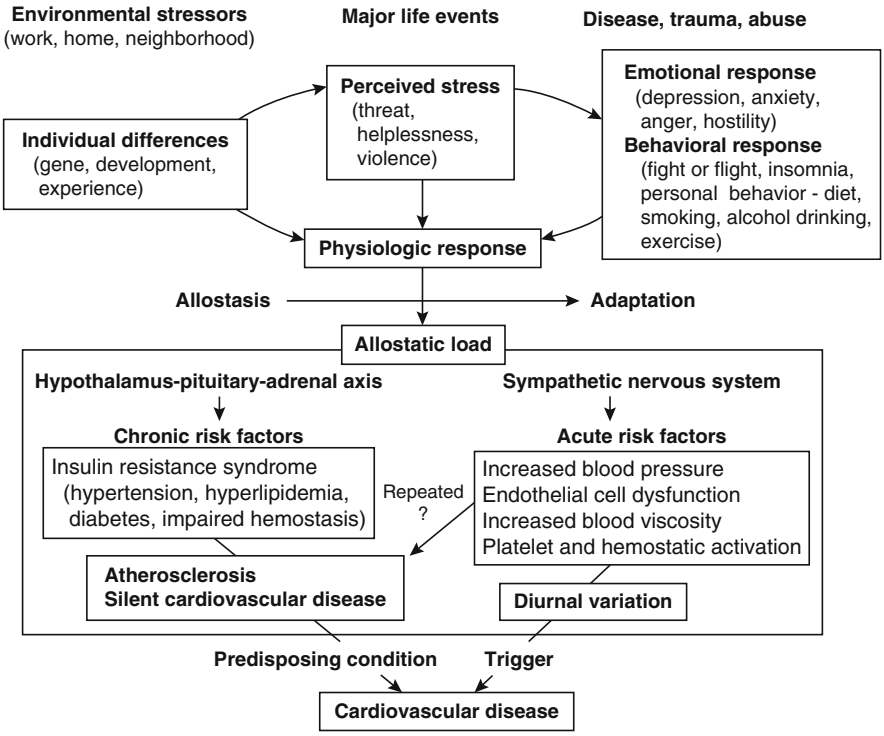


Fig. 2 Mechanism of stress-associated cardiovascular disease (Kario et al. 2003)

clinical findings including female predominance and infrequent history of existing heart disease. Takotsubo is rare and the majority of cases resolve spontaneously with supportive care. As many as 80 % of patients with takotsubo cardiomyopathy report a precipitant major identifiable stressful event. Watanabe et al. (2005), Sharkey (2013), Gianni et al. (2006), Summers et al. (2010), Leor et al. (1996), Wittstein (2008), Chan et al. (2013), and Zarifeh et al. (2012) have all reported that a major earthquake has dramatically increased the incidence of takotsubo cardiomyopathy in their exposed population. The pathophysiology of takotsubo is unknown but believed to be related to a combination of elevated catecholamines (Sharkey et al. 2010) and both acute (as a trigger) and chronic and psychological stresses (Summers et al. 2010), although a recent study by Zarifeh et al. (2012) failed to find evidence of psychological predisposition or exposure to more psychological stress in patients with takotsubo.

Further research into stress cardiomyopathy may lead to better understanding about the relationship between acute stress and cardiovascular disease.

In summary, further studies are needed to elucidate the mechanisms of disaster-related CVD (Aoki et al. 2012). The study of emotional triggers provides an important insight into the timing of acute cardiac events and opens up possibilities for new methods of clinical management. “It is possible in the future that if

characteristic biological stress responses are identified in patients susceptible for emotional triggers, then some form of risk stratification could be carried out" (Tofler and Muller 2006).

> The advantage of the emotions is that they lead us astray, and the advantage of science is that it is not emotional.
>
> (Oscar Wilde, The Picture of Dorian Gray, 1981)

The Association of Posttraumatic Stress Disorder and Cardiovascular Disease

There is overwhelming evidence both for the deleterious effects of stress on the heart and for the fact that vulnerability and resilience factors play a role in amplifying or dampening the effects of stress (Dimsdale 2008). Posttraumatic stress disorder (PTSD) is the most studied and probably the most frequent and debilitating disorder that occurs after traumatic events and disasters (Galea et al. 2005). PTSD has been defined as an anxiety disorder initiated by exposure to a traumatic event, characterized by intrusive thoughts about the event, attempts to avoid reminders of the event (cognitive and behavioral), and heightened physiological arousal. Studies report that regardless of the study population, the type of stressor exposure, or the cardiovascular measures used, there is an association between PTSD and the onset of CVD.

Epidemiology of PTSD and CVD

There have been nearly 100 disease studies conducted and published in the aftermath of a natural disaster, many noting an association between CVD and PTSD (Kubzansky and Koenen 2009; Coughlin 2011; Boscarino et al. 2004). Substantial rates of PTSD (ranging from approximately 5 % to 60 %) have been reported, with rates differing according to length of exposure to trauma, and whether people have been directly affected or less directly exposed.

Edmondson and Cohen (2013) summarized the findings of five prospective cohort studies (with a total of 401,712 participants) – estimating the association between PTSD with incident CVD and/or mortality. These studies adjusted for multiple demographic, clinical, and psychosocial factors including depression. They followed up participants from 1 to 30 years. The effect sizes reported range from a hazard ratio for incident CVD and/or cardiac mortality of 1.46–3.28. Another prospective study by Jordan et al. (2011) using 39,324 World Trade Center Health Registry participants reported that men and women with PTSD at study enrolment had significantly elevated risk of heart disease and that this risk had a dose-response relationship with PTSD symptoms.

As well as exposure to an event, there are also a number of risk factors for PTSD which increase the rate of PTSD across multiple studies. More vulnerable are women, persons with preexisting or concurrent psychiatric comorbidity or previous

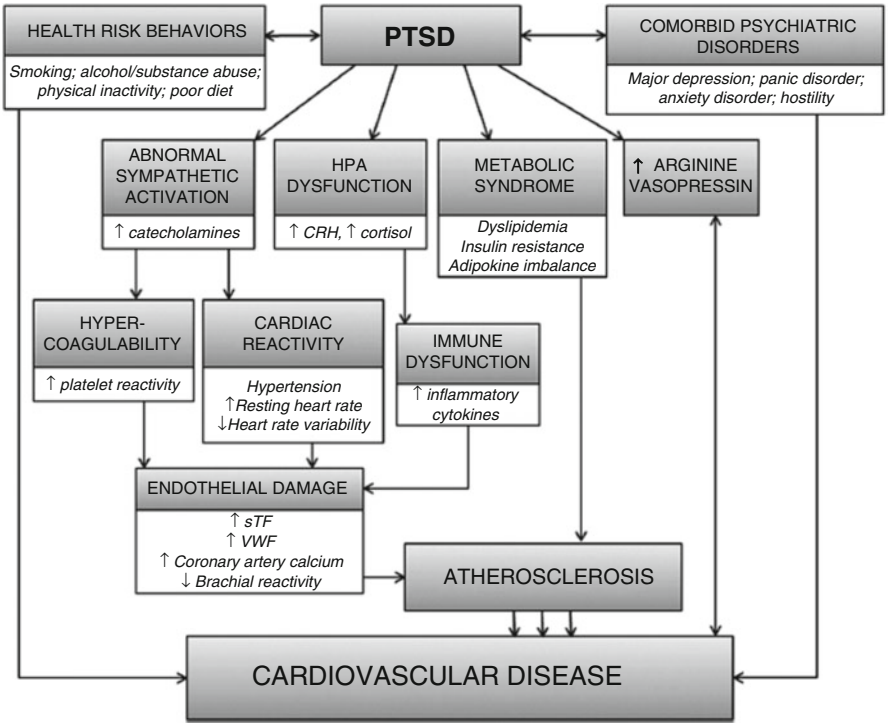


Fig. 3 Potential paths to cardiovascular disease in PTSD. *PTSD* indicates posttraumatic stress disorder, *HPA* hypothalamic-pituitary-adrenal, *CRH* corticotropin-releasing hormone, sTF, *vWF* von Willebrand factor (Adapted from Wentworth et al. 2013)

exposure to traumatic events, people of lower SES, those from an ethnic minority, and those of older age (Galea et al. 2005; Bartels and VanRooyen 2012). Given the consistent findings of these studies on PTSD and CVD, attention has turned to understanding the pathologic mechanisms that connect these two disorders.

Mechanisms

There is no single causal pathway explaining the association between PTSD and CVD, and it is likely to involve multiple pathways including behavioral risk factors (Boscarino 2011).

Edmondson and Cohen (2013) classified potential mechanisms relating CVD and PTSD into three categories. The first was biological risk factors, namely, dysregulation of the hypothalamic-pituitary- adrenal (HPA) axis, autonomic nervous system dysfunction, and increased inflammation. The authors commented on how PTSD arises in response to overwhelming external stress, but simultaneously generates ongoing internal distress. The second mechanism was behavioral risk factors including medication nonadherence, substance abuse, decreased physical

activity, obesity, and sleep disturbance. Sedentary behavior, in particular, is important as it is strongly connected to other cardiac risk factors such as increased blood pressure, insulin resistance, cholesterol levels, non-medication adherence, and sleep disturbances which are now recognized as strong risk factors for the progression of CVD. Thirdly, comorbid psychological disorders and impairment in social functioning may also increase CVD risk in patients with PTSD. These include such factors as mood disturbance, anger, hostility, social isolation, and lowered socioeconomic status.

A model recently provided by Wentworth et al. (2013) summarizes these concepts (Fig. 3).

"It is expected that multiple mechanisms will contribute in a complex, interacting way to the association between PTSD and physical health" (Turner et al. 2013). Given this body of research, the question now is not if there is a link between PTSD and cardiovascular disease but rather why this association exists and can this outcome be prevented (Boscarino 2011).

Implications for Management

Pragmatic

The response to natural disasters is generally that during the early phases attention is focused on the care and prevention of primary illnesses, such as traumatic injuries. However secondary illnesses comprise a sizeable disease burden (Miller and Arquilla 2008). Negative effects on the cardiovascular system, if left untreated, may be long lasting and possibly irreversible, resulting in permanent elevation of CVD risk.

The identification of individuals at higher risk of becoming ill (Kurita et al. 2001) is the essential first step in prevention programs aimed at reducing the adverse effects of major disaster on health. Given the known risks associated with the development of CVD following a natural disaster, there are some general principles of prevention (Kurita et al. 2001). These include minimizing coronary risk factors, regular physical examination of those patients with structural heart disease (cardiomyopathy, congenital heart disease), avoidance of temperature fluctuations and heavy physical activity, and monitoring of and adherence to prescribed medications.

Ford et al. (2006) have promoted a behavioral risk factor surveillance system (BRFSS) measure as a way of providing useful baseline information about the number of people with cardiovascular and other chronic diseases and the treatment that they receive. This may be useful to help assess the needs of already vulnerable people after disasters and assist in planning relief efforts.

To better triage for disaster-associated cardiovascular events, Kario et al. (2011) developed a web-based disaster cardiovascular prevention (DCAP) network and have begun to implement it with survivors of the 2011 Japan disaster. The DCAP system uses a risk score to identify survivors at higher risk of

Table 1 Management of disaster-associated cardiovascular risk (From Kario et al. 2005)

Sleep quality	Turn off lights in shelters at night
	Ensure privacy in shelters
Blood pressure	Measure morning blood pressure levels at home or in shelter
	Frequent BP assessment (every 2 weeks) and antihypertensive medication
	Reduce salt intake and increase high potassium-containing diet (green vegetables, fruits, and seaweeds)
Thrombotic tendency	Increase water intake (ensure access to temporary restroom facilities)
	Encourage physical activity (regular walking)
	Frequent assessment of anticoagulation activity in patients treated with warfarin
Infection	Distribute gauze masks
	Ensure a hygienic environment
Lipid profile	Reduce lipid-rich diet
Blood sugar	Reduced intake of sugar and carbohydrate
	Frequent assessment glucose in diabetics and those with glucose intolerance

cardiovascular events (based on a number of behavioral measures) and to promote preventative behaviors.

In situations immediately following a disaster, stress reduction by improving the conditions of the post-disaster environment and management of stress-induced potentiation of risk factors may reduce prolonged increase in CVD events for the surviving population (Table 1).

Pharmacological

The goal of pharmacological protection is to attempt to reduce the link between acute risk factors and their pathologic consequences. In a prospective analysis of 1,384 patients with AMI (Culic 2007), it was reported that triggered MIs and morning-related MIs (each of which results from increased sympathetic activity) were significantly less likely in patients who had taken beta-blockers, calcium, antagonists, or nitrates. Another study of patients with AMI reported that patients taking beta-blockers were less likely to report an emotional or physical trigger (Tofler et al. 1990). Schwartz et al. (2012) commented that: triggered plaque rupture might be prevented by utilization of such medication prescribed routinely to modify cardiovascular risk factors but may possibly be especially beneficial in the settling of a cardiovascular trigger. Therefore the possibility that B Blockers and other relevant medications may reduce myocardial vulnerability may help direct future research and improve the understanding of relationships among psychological process, autonomic balance, and triggering. Until more is known about the inhibition of internal triggering mechanisms, pharmacological protection in coronary patients should probably cover the morning risk. However, "possible additional modification may depend on the characteristics of the individual's disease,

and exposure to a particular external trigger – but at present precise recommendations cannot be given" (Culic 2007, p. 268).

In addition to recommendations around the use of medications, a list of essential medications consistent with the predicted burden of chronic disease could be developed and used in planning for provision of chronic maintenance medications following disasters. Furthermore, the establishment of electronic health records and the coordinated allocation of these medication and medical supplies may provide substantial benefit in terms of medication availability and access to health information in the wake of a disaster (Kario et al. 2011).

Psychosocial

Cardiovascular disease has a complex etiology. Psychosocial factors contribute to CVD although the importance of their contribution remains unclear (Dimsdale 2008). No randomized controlled trials comparing psychosocial interventions following natural disasters have been reported so there is no good evidence to guide psychosocial management of CVD risk following earthquakes, tsunamis, and other natural disasters. We can however extrapolate and generalize from what we do know of the link between psychosocial factors and CVD, in general terms.

Because acute forms of psychosocial stress are ubiquitous and frequently unavoidable, it could be argued that the best protection from their potential deleterious effects is the targeted prevention and treatment of cardiovascular disease risk before any natural disaster occurs. Furthermore, because chronic forms of psychosocial stress are subject to clinical modification, their contribution to the underlying development of CVD might potentially be reduced by interventions designed to treat these factors.

Rozanski et al. (2005) discussed the reasons that cardiologists should be interested and skilled in recognizing and managing psychosocial risk factors in clinical practice. It is appropriate to extend the observations of these authors to psychosocial management of individuals and communities following natural disasters. Acute psychological distress can shape the course of cardiac disease, commonly presents as symptoms of cardiac disease, and tends to cluster with adverse behaviors that further promote CVD. Possibly the first diagnosis to screen for, especially in middle- to older-aged women presenting with cardiac symptoms following a natural disaster, is takotsubo cardiomyopathy, given the high rates of occurrence discussed earlier in this chapter. In the Christchurch February 2011 earthquake, for example, around 50 % of postmenopausal women who presented with symptoms consistent with an AMI actually have takotsubo cardiomyopathy (Chan et al. 2013).

Following a natural disaster, cardiologists can also increase the detection of psychosocial risk factors by systematic screening. Screening can take place by way of structured interviews incorporating questions about psychosocial risk factors (depression, anxiety, chronic stressors, and somatic complaints) and adjunctive

self-administered and objectively scored questionnaires. Studies conducted by Boscarino et al. (Boscarino 2011, 2012) suggest that PTSD screening can be effectively conducted among at-risk populations. These researchers reported that those who received counseling shortly after the terrorist attacks in NYC not only had better PTSD outcomes but also had improved outcomes in a number of different clinical areas. Consideration of the features of the post-disaster environment that may influence the burden of PTSD could guide interventions aimed at improving the mental and physical health of individuals and populations following natural disasters Galea et al. (2005).

After identification and screening of psychological distress in cardiac populations following natural disasters, appropriate referral to an available network of specialists might be indicated. Stress effects are potentially modifiable, if not by cardiologists themselves then by colleagues who help patients change their behaviors and cognitions. Historically, cardiologists have been accustomed to managing lifestyle behaviors such as overeating and physical activity but are less likely to assess and treat psychosocial risk factors, perhaps because of their limited familiarity with effective strategies and recommendations. While it is not the function of the cardiologists to serve as mental health professionals, the strong and robust relationship between psychosocial risk factors and CVD suggest that cardiologists, who commonly treat patients who have experienced life-threatening events such as natural disasters and who might be receptive at that point in time to medical advice, are ideally positioned to initiate these interventions. Furthermore Shah et al. (2014) reported the results of a recent study showing that depression is particularly harmful to the hearts of young women. Their conclusion was that it is also important for psychiatrists to remind patients not to forget about looking after their heart health as well as mental health.

Current management of psychological distress and in particular PTSD addresses the psychiatric parameters of the condition primarily via the use of cognitive behavioral therapy, in conjunction with anxiolytics, antidepressant, and antipsychotic medication, all of which only partially reduce symptoms. Efforts are also underway to lower susceptibility to PTSD through greater stress resilience training aimed at reducing its incidence and severity (and thus possibly reduce cardiovascular risk) via immediate posttraumatic psychological interventions.

A meta-analysis of more than 20 controlled trials that evaluated the impact of psychosocial treatment directed at reducing distress-related factors among cardiac patients indicates that patients receiving psychosocial treatment show greater reduction when compared to controls, not only psychosocial distress but also in BP, heart rate, serum cholesterol levels, morbidity, and mortality data (Linden et al. 1996). Blumenthal et al. (1997) reported that a stress management program reduced the risk of a cardiovascular event by nearly three quarters over 3 years of follow-up. Their study included patients with coronary artery disease and documented ischemic change. Compared with usual care, the stress management patients demonstrated improved treadmill times, improved lipid profiles, and greater weight loss. Compared with usual care and exercise training, the stress management group also demonstrated less severe heart wall motion abnormalities,

fewer ischemic episodes during ECG monitoring, and fewer cardiovascular events during follow-up (Blumenthal et al. 1997).

Transcendental meditation has also been widely studied in the scientific literature with results supporting its usefulness for treating a variety of cardiovascular diseases and risk factors (Schneider et al. 2006). Data pooled from two randomized trials with overall mean follow-up of 7–6 ± 3.5 years show reduced all-cause and cardiovascular mortality with transcendental meditation compared with combined control groups (Walton et al. 2004).

Diverse and effective intervention programs have been tested in heart patients that provide formal psychotherapy, psychotropic medications, time management training, progressive relaxation training, meditation, and regular exercise. The majority of these intervention programs improve patient morale and functioning and decrease suffering. Therefore it would seem appropriate to study such treatment programs for individuals and populations demonstrating signs and symptoms of psychosocial stress following a natural disaster. It may be time to develop and implement guidelines for both short- and long-term care before, during, and in the immediate aftermath of natural disasters (Mokdad et al. 2005).

Conclusion

An association between natural disasters and cardiovascular disease is generally accepted, in particular PTSD and CVD outcomes. Further studies are needed to explore the complex relationship between natural disasters and acute cardiac events. Studies of this association need to be multidisciplinary – using unfamiliar concepts derived from disciplines other than cardiology and medicine. Cardiologists may therefore benefit from clarification of some of the key concepts and issues in this area.

The mechanisms by which stressors trigger AMI and sudden cardiac death need to be better understood. Research is also necessary to determine whether some patients with coronary artery disease are more susceptible to sudden death from cardiac causes after a stressful event and what triggers might be involved. Identifying these high-risk patients and defining potential triggers may assist the development of strategies to prevent sudden death due to cardiac causes. We must also develop a better understanding of the mechanisms linking PTSD and CVD to try and develop targeted interventions to reduce cardiovascular events and mortality in patients with PTSD.

While our understanding of pathophysiological processes linking psychosocial risk factors and CAD has improved, the development of effective therapeutic interventions for the modification and reduction of the impact of psychosocial risk factors in CAD remains a challenge. Studies suggest that there is a need to monitor the short- and long-term physical health of the affected population following a natural disaster. Establishing a comprehensive understanding of the acute and chronic psychological and medical needs following an emergency may assist health

professionals in preparing for the medical care of people with both acute and chronic diseases after a disaster.

The field of behavioral cardiology would benefit from the development of practical interventions since the etiologic links between psychosocial risk factors, behavioral risk factors, and CVD are now consistently reported. Cardiologists will regularly encounter patients with psychological distress and unhealthy behaviors in their clinical practice. Therefore the development of interventions that may reduce the behavioral and biological sequelae of natural disasters and the testing of their efficacy in randomized clinical trials would provide important data to help people following these very traumatic events.

References

Aoki, T., Fukumoto, Y., Yasuda, S., Sakata, Y., Ito, K., Takahashi, J., et al. (2012). The Great East Japan Earthquake Disaster and cardiovascular diseases. *European Heart Journal, 33*(22), 2796–2803. doi:10.1093/eurheartj/ehs288.

Bartels, S. A., & VanRooyen, M. J. (2012). Medical complications associated with earthquakes [Review]. *Lancet, 379*(9817), 748–757. doi:10.1016/S0140-6736(11)60887-8.

Bhattacharyya, M. R., & Steptoe, A. (2007). Emotional triggers of acute coronary syndromes: Strength of evidence, biological processes, and clinical implications [Research Support, Non-U.S. Gov't Review]. *Progress in Cardiovascular Diseases, 49*(5), 353–365.

Blumenthal, J. A., Jiang, W., Babyak, M. A., Krantz, D. S., Frid, D. J., Coleman, R. E., et al. (1997). Stress management and exercise training in cardiac patients with myocardial ischemia. Effects on prognosis and evaluation of mechanisms [Clinical Trial Randomized Controlled Trial. Research Support, U.S. Gov't, P.H.S.]. *Archives of Internal Medicine, 157*(19), 2213–2223.

Boscarino, J. A. (2011). Post-traumatic stress disorder and cardiovascular disease link: Time to identify specific pathways and interventions [Comment letter]. *The American Journal of Cardiology, 108*(7), 1052–1053. doi:10.1016/j.amjcard.2011.07.003.

Boscarino, J. A. (2012). PTSD is a risk factor for cardiovascular disease: Time for increased screening and clinical intervention [Letter]. *Preventive Medicine, 54*(5), 363–364. doi:10.1016/j.ypmed.2012.01.001. author reply 365.

Boscarino, J. A., Figley, C. R., Adams, R. E., Galea, S., Resnick, H., Fleischman, A. R., et al. (2004). Adverse reactions associated with studying persons recently exposed to mass urban disaster [Research Support, U.S. Gov't, P.H.S.]. *The Journal of Nervous and Mental Disease, 192*(8), 515–524.

Brown, D. L. (1999). Disparate effects of the 1989 Loma Prieta and 1994 Northridge earthquakes on hospital admissions for acute myocardial infarction: Importance of superimposition of triggers [Comparative Study Multicenter Study]. *American Heart Journal, 137*(5), 830–836.

Chan, C., Elliott, J., Troughton, R., Frampton, C., Smyth, D., Crozier, I., et al. (2013). Acute myocardial infarction and stress cardiomyopathy following the Christchurch earthquakes. *PLoS One, 8*(7), e68504. doi:10.1371/journal.pone.0068504.

Chi, J. S., Speakman, M. T., Poole, W. K., Kandefer, S. C., & Kloner, R. A. (2003). Hospital admissions for cardiac events in New York City after September 11, 2001. *American Journal of Cardiology, 92*(1), 61–63.

Cohen, S., Janicki-Deverts, D., & Miller, G. E. (2007). Psychological stress and disease. *JAMA, 298*(14), 1685–1687.

Coughlin, S. S. (2011). Post-traumatic stress disorder and cardiovascular disease. *The Open Cardiovascular Medicine Journal, 5*, 164–170. doi:10.2174/1874192401105010164.

Culic, V. (2007). Acute risk factors for myocardial infarction [Review]. *International Journal of Cardiology, 117*(2), 260–269.

Dahlof, B. (2010). Cardiovascular disease risk factors: Epidemiology and risk assessment [Research Support, Non-U.S. Gov't Review]. *The American Journal of Cardiology, 105* (1 Suppl), 3A–9A. doi:10.1016/j.amjcard.2009.10.007.

Dimsdale, J. E. (2008). Psychological stress and cardiovascular disease [Research Support, N.I.H., Extramural Review]. *Journal of the American College of Cardiology, 51*(13), 1237–1246. doi:10.1016/j.jacc.2007.12.024.

Dobson, A. J., Alexander, H. M., Malcolm, J. A., Steele, P. L., & Miles, T. A. (1991). Heart attacks and the Newcastle earthquake [Comparative Study Research Support, Non-U.S. Gov't]. *Medical Journal of Australia, 155*(11-12), 757–761.

Edmondson, D., & Cohen, B. E. (2013). Posttraumatic stress disorder and cardiovascular disease [Research Support, N.I.H., Extramural Review]. *Progress in Cardiovascular Diseases, 55*(6), 548–556. doi:10.1016/j.pcad.2013.03.004.

Ford, E. S., Mokdad, A. H., Link, M. W., Garvin, W. S., McGuire, L. C., Jiles, R. B., et al. (2006). Chronic disease in health emergencies: In the eye of the hurricane. *Preventing Chronic Disease, 3*(2), A46.

Galea, S., Nandi, A., & Vlahov, D. (2005). The epidemiology of post-traumatic stress disorder after disasters [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S. Review]. *Epidemiologic Reviews, 27*, 78–91.

Gianni, M., Dentali, F., Grandi, A. M., Sumner, G., Hiralal, R., & Lonn, E. (2006). Apical ballooning syndrome or takotsubo cardiomyopathy: A systematic review [Review]. *European Heart Journal, 27*(13), 1523–1529.

Goldberg, R. J., Spencer, F., Lessard, D., Yarzebski, J., Lareau, C., & Gore, J. M. (2005). Occurrence of acute myocardial infarction in Worcester, Massachusetts, before, during, and after the terrorists attacks in New York City and Washington, DC, on 11 September 2001 [Research Support, U.S. Gov't, P.H.S.]. *American Journal of Cardiology, 95*(2), 258–260. doi:10.1016/j.amjcard.2004.08.094.

Hendrickson, L. A., Vogt, R. L., Goebert, D., & Pon, E. (1997). Morbidity on Kauai before and after Hurricane Iniki [Research Support, U.S. Gov't, P.H.S.]. *Preventive Medicine, 26*(5 Pt 1), 711–716. doi:10.1006/pmed.1997.0196.

Jordan, H. T., Miller-Archie, S. A., Cone, J. E., Morabia, A., & Stellman, S. D. (2011). Heart disease among adults exposed to the September 11, 2001 World Trade Center disaster: Results from the World Trade Center Health Registry. *Preventive Medicine, 53*(6), 370–376. doi:10.1016/j.ypmed.2011.10.014.

Kako, M., Arbon, P., & Mitani, S. (2014). Disaster health after the 2011 great East Japan earthquake [Review]. *Prehospital and Disaster Medicine, 29*(1), 54–59. doi:10.1017/S1049023X14000028.

Kario, K., McEwen, B. S., & Pickering, T. G. (2003). Disasters and the heart: A review of the effects of earthquake-induced stress on cardiovascular disease [Research support, Non-U.S. Gov't research support, U.S. Gov't, P.H.S. Review]. *Hypertension Research: Official Journal of the Japanese Society of Hypertension, 26*(5), 355–367.

Kario, K., Shimada, K., & Takaku, F. (2005). Management of cardiovascular risk in disaster: Jichi Medical School (JMS) proposal 2004. *Japan Medical Association Journal, 48*(7), 363–376.

Kario, K., Nishizawa, M., Hoshide, S., Shimpo, M., Ishibashi, Y., Kunii, O., et al. (2011). Development of a disaster cardiovascular prevention network. *Lancet, 378*(9797), 1125–1127. doi:10.1016/S0140-6736(11)61187-2.

Kubzansky, L. D., & Koenen, K. C. (2009). Is posttraumatic stress disorder related to development of heart disease? An update [Review]. *Cleveland Clinic Journal of Medicine, 76*(Suppl 2), S60–S65. doi:10.3949/ccjm.76.s2.12.

Kurita, A., Takase, B., & Ishizuka, T. (2001). Disaster and cardiac disease [Review]. *Anadolu kardiyoloji dergisi: AKD = The Anatolian Journal of Cardiology, 1*(2), 101–106.

Leor, J., & Kloner, R. A. (1996). The Northridge earthquake as a trigger for acute myocardial infarction. *American Journal of Cardiology, 77*(14), 1230–1232.

Leor, J., Poole, W. K., & Kloner, R. A. (1996). Sudden cardiac death triggered by an earthquake. *The New England Journal of Medicine, 334*(7), 413–419. doi:10.1056/NEJM199602153340701.

Linden, W., Stossel, C., & Maurice, J. (1996). Psychosocial interventions for patients with coronary artery disease: A meta-analysis [Meta-analysis research support, Non-U.S. Gov't]. *Archives of Internal Medicine, 156*(7), 745–752.

Mokdad, A. H., Mensah, G. A., Posner, S. F., Reed E., Simoes, E. J., Engelgau, M. M. (2005). When chronic conditions become acute: Prevention and control of chronic diseases and adverse health outcomes during natural disasters. *Preventing Chronic Disease*, 2 Spec No, A04.

Miller, A. C., & Arquilla, B. (2008). Chronic diseases and natural hazards: Impact of disasters on diabetic, renal, and cardiac patients [Review]. *Prehospital and Disaster Medicine, 23*(2), 185–194.

Nakamura, M., Tanaka, F., Nakajima, S., Honma, M., Sakai, T., Kawakami, M., et al. (2012). Comparison of the incidence of acute decompensated heart failure before and after the major tsunami in Northeast Japan [Comparative Study Research Support, Non-U.S. Gov't]. *The American Journal of Cardiology, 110*(12), 1856–1860. doi:10.1016/j.amjcard.2012.08.020.

Norwood, A. E., Ursano, R. J., & Fullerton, C. S. (2000). Disaster psychiatry: Principles and practice [Review]. *Psychiatric Quarterly, 71*(3), 207–226.

Peleg, K., Reuveni, H., & Stein, M. (2002). Earthquake disasters-lessons to be learned [Review]. *Israel Medical Association Journal: IMAJ, 4*(5), 361–365.

Peters, M. N., Moscona, J. C., Katz, M. J., Deandrade, K. B., Quevedo, H. C., Tiwari, S., et al. (2014). Natural disasters and myocardial infarction: The six years after hurricane Katrina [Comparative study]. *Mayo Clinic Proceedings, 89*(4), 472–477. doi:10.1016/j.mayocp.2013.12.013.

Rozanski, A., Blumenthal, J. A., Davidson, K. W., Saab, P. G., & Kubzansky, L. (2005). The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology [Review]. *Journal of the American College of Cardiology, 45*(5), 637–651.

Schneider, R. H., Walton, K. G., Salerno, J. W., & Nidich, S. I. (2006). Cardiovascular disease prevention and health promotion with the transcendental meditation program and Maharishi consciousness-based health care. *Ethnicity & Disease, 16*(3 Suppl 4), S4–S15. 26.

Schwartz, B. G., French, W. J., Mayeda, G. S., Burstein, S., Economides, C., Bhandari, A. K., et al. (2012). Emotional stressors trigger cardiovascular events [Review]. *International Journal of Clinical Practice, 66*(7), 631–639. doi:10.1111/j.1742-1241.2012.02920.x.

Shah, A. J., Ghasemzadeh, N., Zaragoza-Macias, E., Patel, R., Eapen, D. J., Neeland, I. J., et al. (2014). Sex and age differences in the association of depression with obstructive coronary artery disease and adverse cardiovascular events [Research Support, N.I.H., Extramural]. *Journal of the American Heart Association, 3*(3), e000741. doi:10.1161/JAHA.113.000741.

Sharkey, S. W. (2013). Takotsubo cardiomyopathy: Natural history [Review]. *Heart Failure Clinics, 9*(2), 123–136. doi:10.1016/j.hfc.2012.12.006. vii.

Sharkey, S. W., Windenburg, D. C., Lesser, J. R., Maron, M. S., Hauser, R. G., Lesser, J. N., et al. (2010). Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy [Research Support, Non-U.S. Gov't]. *Journal of the American College of Cardiology, 55*(4), 333–341. doi:10.1016/j.jacc.2009.08.057.

Sofia, S., Melone, A., Manzoli, L., De Ciantis, P., Varrato, E., Di Filippo, R., et al. (2012). Cardiovascular and cerebrovascular events pre- and post-earthquake of 6 April 2009: The Abruzzo's experience [Comparative study]. *American Journal of Hypertension, 25*(5), 556–560. doi:10.1038/ajh.2012.4.

Steinberg, J. S., Arshad, A., Kowalski, M., Kukar, A., Suma, V., Vloka, M., et al. (2004). Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack [Comparative study evaluation studies]. *Journal of the American College of Cardiology, 44*(6), 1261–1264.

Steptoe, A., & Brydon, L. (2009). Emotional triggering of cardiac events [Research Support, Non-U.S. Gov't Review]. *Neuroscience & Biobehavioral Reviews, 33*(2), 63–70. doi:10.1016/j.neubiorev.2008.04.010.

Summers, M. R., Lennon, R. J., & Prasad, A. (2010). Pre-morbid psychiatric and cardiovascular diseases in apical ballooning syndrome (tako-tsubo/stress-induced cardiomyopathy): Potential pre-disposing factors? [Letter]. *Journal of the American College of Cardiology, 55*(7), 700–701. doi:10.1016/j.jacc.2009.10.031.

Suzuki, S., Sakamoto, S., Koide, M., Fujita, H., Sakuramoto, H., Kuroda, T., et al. (1997). Hanshin-Awaji earthquake as a trigger for acute myocardial infarction. *American Heart Journal, 134*(5 Pt 1), 974–977.

Tofler, g. H., Stone, P. H., Maclure, M., Edelman, E., Davis, V. G., Robertson, T., et al. (1990). Analysis of possible triggers of acute myocardial infarction (The MILIS Study). *American Journal of Cardiology, 66*, 22–27.

Tofler, G. H., & Muller, J. E. (2006). Triggering of acute cardiovascular disease and potential preventive strategies [Review]. *Circulation, 114*(17), 1863–1872.

Trevisan, M., Celentano, E., Meucci, C., Farinaro, E., Jossa, F., Krogh, V., et al. (1986). Short-term effect of natural disasters on coronary heart disease risk factors. *Arteriosclerosis, 6*(5), 491–494.

Trichopoulos, D., Katsouyanni, K., Zavitsanos, X., Tzonou, A., & Dalla-Vorgia, P. (1983). Psychological stress and fatal heart attack: The Athens (1981) earthquake natural experiment [Research support, Non-U.S. Gov't]. *Lancet, 1*(8322), 441–444.

Tsai, C.-H., Lung, F.-W., & Wang, S.-Y. (2004). The 1999 Ji-Ji (Taiwan) earthquake as a trigger for acute myocardial infarction. *Psychosomatics, 45*(6), 477–482.

Turner, J. H., Neylan, T. C., Schiller, N. B., Li, Y., & Cohen, B. E. (2013). Objective evidence of myocardial ischemia in patients with posttraumatic stress disorder [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Biological Psychiatry, 74*(11), 861–866. doi:10.1016/j.biopsych.2013.07.012.

Walton, K. G., Schneider, R. H., & Nidich, S. (2004). Review of controlled research on the transcendental meditation program and cardiovascular disease. Risk factors, morbidity, and mortality. *Cardiology in Review, 12*(5), 262–266.

Watanabe, H., Kodama, M., Okura, Y., Aizawa, Y., Tanabe, N., Chinushi, M., et al. (2005). Impact of earthquakes on Takotsubo cardiomyopathy [Letter Research Support, Non-U.S. Gov't]. *JAMA, 294*(3), 305–307.

Watanabe, H., Kodama, M., Tanabe, N., Nakamura, Y., Nagai, T., Sato, M., et al. (2008). Impact of earthquakes on risk for pulmonary embolism [Letter]. *International Journal of Cardiology, 129*(1), 152–154. doi:10.1016/j.ijcard.2007.06.039.

Wentworth, B. A., Stein, M. B., Redwine, L. S., Xue, Y., Taub, P. R., Clopton, P., et al. (2013). Post-traumatic stress disorder: A fast track to premature cardiovascular disease? [Research support, Non-U.S. Gov't review]. *Cardiology in Review, 21*(1), 16–22. doi:10.1097/CRD.0b013e318265343b.

Wilbert-Lampen, U., & Steinbeck, G. (2012). Earthquakes: Another cause of heart failure? [Comment editorial]. *European Heart Journal, 33*(22), 2759–2760. doi:10.1093/eurheartj/ehs297.

Wittstein, I. S. (2008). Acute stress cardiomyopathy [Review]. *Current Heart Failure Reports, 5*(2), 61–68.

Zarifeh, J. A., Mulder, R. T., Kerr, A. J., Chan, C. W., & Bridgman, P. G. (2012). Psychology of earthquake-induced stress cardiomyopathy, myocardial infarction and non-cardiac chest pain. *Internal Medicine Journal, 42*(4), 369–373. doi:10.1111/j.1445-5994.2012.02743.x.

Psychoses and Cardiovascular Disease: The Heart and Mind of the Matter

Peter Bosanac and David Castle

Contents

Abstract

Cardiovascular disease and its risk factors are markedly overrepresented in people suffering with psychotic disorders such as schizophrenia. Adverse sequelae of this association include heightened mortality, worsened quality of life, and course of mental illness. Of further concern are that cardiovascular disease is underreported and neglected in this population as well as low rate of metabolic screening. The relationship of cardiovascular disease to psychosis is a complex one, with core symptoms of psychosis, poor diet, smoking, sedentary lifestyle, and socioeconomic factors predisposing to cardiovascular risk. These factors act in combination with iatrogenically induced risk factors attributed to antipsychotic medication, in particular weight gain. There are also syndromes that predispose to both psychosis and cardiovascular disease, including velocardiofacial syndrome, homocystinuria, and Cushing's syndrome and possibly pro-inflammatory mechanisms. Psychotic symptoms are also

P. Bosanac (✉) • D. Castle
St Vincent's Hospital, Melbourne, VIC, Australia

University of Melbourne, Melbourne, VIC, Australia
e-mail: bosanacp@unimelb.edu; peter.bosanac@svha.org.au; david.castle@svha.org.au; djcastle@unimelb.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_15

independently associated with coronary artery bypass and valve surgery. Stress plays a role in the negative impact on both psychosis and cardiovascular disease via the hypothalamic-pituitary-adrenal axis.

Regular metabolic monitoring and intervention for identified cardiovascular risk factors in psychosis are mandatory. The latter includes education about diet, exercise, and cardiac risk factors, as well as minimization of weight gain and sedation associated with antipsychotic medication, with switching to more weight-neutral and tolerable medication options. Metformin appears to have a role in ameliorating antipsychotic-related weight gain. While there is a limited evidence base about psychological and psychotherapeutic interventions for primary or secondary prevention of cardiac disease in people with psychoses, behavioral and lifestyle interventions have emerged as showing benefit. Varenicline, a medication not without its propsychotic risks, may also complement these lifestyle interventions via facilitation of smoking cessation.

Keywords
Schizophrenia • Psychotic disorder • Cardiovascular • Metabolic monitoring • Intervention • Mortality • Lifestyle

Introduction

Cardiovascular disease and its risk factors are markedly overrepresented in people suffering with psychoses. This includes first-episode patients with psychosis (De Hert et al. 2008; Galletly et al. 2010). Comorbid cardiovascular disease in schizophrenia impacts adversely on quality of life, as well as the course and severity of the mental illness itself (Fagiolini and Goracci 2009). Mortality associated with cardiovascular disease in psychosis is two to four times that of the general population (Castillo et al. 2013), notwithstanding that there is an inherent 20 % lifespan reduction in schizophrenia compared with the general population (Hennekens et al. 2005). Alarmingly, in a large population-based survey of Australian adults with psychosis: three-quarters were overweight or obese, about half were hypertensive, two-thirds were current smokers, half had abnormal lipid profiles, a third had elevated fasting glucose, greater than half met criteria for metabolic syndrome, and the overall level of physical activity level was very low (Galletly et al. 2010). Moreover, a retrospective cohort analysis of patients in primary care found that people suffering with schizophrenia had earlier onset of cardiac risk factors and disease than those with affective psychoses and those without disabilities (McDermott et al. 2005). Concomitantly, cardiovascular disease in people with psychoses can be underreported (De Hert et al. 2011; Smith et al. 2013) or even, more disconcertingly, neglected (McNamee et al. 2013). Also, screening for the metabolic syndrome is low in this population (De Hert et al. 2011). About one in six patients with schizophrenia in a large survey across Europe reported experiencing discrimination when accessing general medical care (Harangozo et al. 2013). Of further concern, people suffering psychosis may not consider themselves to be at risk

Table 1 Metabolic monitoring in psychotic disorders (Grundy et al. 2005)

At least 6 monthly:
Fasting blood glucose (<5.6 mmol/L or <100 mg/dL)
Body mass index (<25–30 kg/m^2, i.e., overweight to obese range)
Waistline circumference (≤102 cm in men, ≤ 88 cm in women)
Blood pressure (<130/85 mmHg)
Serum lipids (cholesterol; LDL- <100 mg/dL; 2.6 mmol/L in patients at high risk,
<160 mg/dL or 4.9 mmol/L in patients at low risk for cardiovascular disease;
HDL <40 mg/dL or 1.04 mmol/L in men and <50 mg/dL or 1.3 mmol/L in women; triglycerides- <150 mg/dL or 1.7 mmol/L)
Urea and electrolytes

of cardiovascular disease and consequently do not attend for physical health monitoring (Campion et al. 2005).

The term "psychosis" broadly and nonspecifically covers a clinically significant distortion or abnormal inference of reality across a spectrum of diagnostic syndromes. On utilization of modern classification systems such as the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (APA 2013) and the International Classification of Diseases, Tenth Edition (WHO 1994), these syndromes include schizophrenia and related disorders, major depression and bipolar disorder with psychotic features, substance induction and intoxication or withdrawal states, delirium, and neuropsychiatric disorders such as dementia. Transient psychotic experiences may also occur as part of a continuum in the general population (van Os 2009) and in those with personality vulnerabilities in the setting of significant stressors. This chapter will focus on "psychosis" in the context of schizophrenia and related disorders (Table 1).

Etiology and Epidemiology

The relationship of cardiovascular disease to psychosis is indeed a complex one. The core symptoms of psychosis (Beratis et al. 2001) in combination with poor diet, smoking, sedentary lifestyle (Fusar-Poli et al. 2009; Hennekens et al. 2005; McCreadie 2003), reduced access to care (Werner et al. 2007), and socioeconomic factors all predispose to cardiovascular risk factors. The socioeconomic risk factors relate to socioeconomic status at birth and to ongoing poverty, namely, low levels of income, employment, car, and home ownership.

More specifically, the risk factors for cardiovascular disease in psychosis encompass obesity, dyslipidemia, glucose intolerance, and diabetes. On the other hand, there are iatrogenic cardiovascular risk factors in people with psychosis such as weight gain, prolonged QTc interval (QTc is the QT interval corrected for heart rate, with prolongation being significant when greater than or equal to 500 ms or with greater than or equal to 60 ms increases with psychotropic medication), and cardiac dysrhythmias secondary to antipsychotic and other psychotropic (antidepressant) medications (Haddad and Anderson 2002). In addition, there is the risk of sudden

death with antipsychotic medication (Ray et al. 2009), with ziprasidone, olanzapine, haloperidol, thioridazine, and pimozide being most associated with QT prolongation (BMJ 2010). Prolongation of the QT interval, which is associated with increased risk of potentially fatal arrhythmias, such as torsade de pointes (polymorphic ventricular arrhythmia), can occur in people presenting with acute psychosis, whether they are prescribed antipsychotic medication or not. The mechanisms of prolonged QT interval in this acute setting, apart from that associated with prescribed antipsychotic medication, include hypokalemia (Hatta et al. 2000) and increased prevalence of underlying cardiovascular disease and associated risk factors in people with schizophrenia (Haddad and Anderson 2002; Lahti et al. 2012). Although the evidence about the mortality associated with QT prolongation is conflicting, greater prolongation and underlying cardiovascular or hepatic disease increase the risk of arrhythmia (Mackin 2008).

Greater than half of people with severe mental illness, including psychosis, have metabolic syndrome (John et al. 2009). While 40 % of people in this population have impaired fasting glucose, the risk of diabetes in people with psychosis is up to six times that of the general population, with the young at greatest risk (Lambert 2011). Certain ethnic groups have greater predisposition to develop diabetes, including people from Asia, the Middle East, and the Indian subcontinent and African and Latin Americans (Lambert 2011). People in whom certain antipsychotic medications have been prescribed are at up to five times at risk of hyperlipidemia in comparison with the general population, with low levels of HDL and high triglyceride levels in greater than half of those with psychosis (John et al. 2009).

Metabolic syndrome not only increases cardiovascular risk, but also that of stroke and diabetes in people with psychosis. This is true for people with psychosis as well as the general population. Metabolic syndrome refers to the presence of at least three of the following cardiovascular risk factors: large waistline circumference (at least 102 cm in men and 89 cm in women), high triglyceride level (at least 150 mg/dL or 1.7 mmol/L), low-density lipoprotein (LDL) level (less than 100 mg/dL or 2.6 mmol/L in patients with high risk for cardiovascular disease, including established disease and diabetes, and less than 160 mg/dL or 4.9 mmol/L in patients at low risk for cardiovascular disease), high-density lipoprotein (HDL) level (less than 40 mg/dL or 1.04 mmol/L in men and 50 mg/dL or 1.3 mmol/L in women), hypertension (at least 130/85 mmHg), and high fasting glucose level (at least 5.6 mmol/L or $>$100 mg/dL) (Grundy et al. 2005).

While weight gain and metabolic dysfunction/syndrome is often secondary to certain prescribed antipsychotic medication for the treatment of psychosis, insulin resistance and hyperglycemia are also present in people suffering with psychotic disorders who are medication naive. The antipsychotic medications that are particularly prone to these metabolic sequelae are olanzapine, clozapine, and quetiapine (Ojalaa et al. 2008).

Smoking, a major risk factor for cardiovascular disease in its own right, is also overrepresented in psychoses and the most common form of substance abuse in

schizophrenia. The rate of nicotine dependence in schizophrenia is three times that of the general population, being between 75 % and 90 % in the former (Cooper et al. 2012). The frequency of smoking in schizophrenia is associated with positive symptoms (delusions, hallucinations, thought disorder), while of lesser frequency with increasing negative symptoms (amotivation, anhedonia, alogia, flattened affect, asociality) (Beratis et al. 2001).

Substance use, in general, is also overrepresented in people with psychosis. Approximately one-half of people suffering with schizophrenia also have substance use disorders (Volkow 2009), a rate that is far higher than the general population (McBride et al. 2009). Although the drugs that are misused in schizophrenia most commonly include alcohol and cannabis (Green et al. 2007), substances such as methamphetamines not only predispose to and exacerbate the severity of psychotic disorders, but also induce or worsen comorbid depressive and anxiety symptoms, suicide, and violence (Darke et al. 2008). These psychological sequelae of substance misuse in schizophrenia, in turn, lead to a vicious cycle of predisposing and exacerbating psychological factors for substance misuse in psychosis, as well as heightening the risk for blood-borne viruses (HIV, viral hepatitis). The rate of HIV infection in people with psychosis is significantly greater than the general population (Rosenberg et al. 2001) as are those of viral hepatitis (Rosenberg et al. 2001). These blood-borne infections are associated with their own risks to physical health, including cardiovascular, namely congestive cardiac failure, cardiomyopathy (Younossi et al. 2013), and neuropsychiatric conditions such as HIV-associated neurocognitive disorders (HAND). HAND encompasses asymptomatic neurocognitive impairment (ANI; impaired cognitive function, with apparently unaffected functioning of daily living), mild neurocognitive disorder (MND; impaired cognitive functioning and mildly impaired functioning of daily living), and HIV-associated dementia (HAD; markedly impaired cognition, particularly learning new information, attention, concentration, and processing of information, as well as markedly impaired functioning of daily living). Therefore the spectrum of HAND may affect problem solving, decision-making, language, attention, and memory. Although antiretroviral therapy for HIV may contribute to cardiovascular disease (Ruest 2011), HIV itself may contribute to cardiovascular disease.

In some instances, there is a predisposing etiology for both psychosis and cardiovascular disease. This holds true for velocardiofacial syndrome with chromosome 22q11 deletion (Murphy 2002); homocystinuria, an autosomal recessive disorder of methionine synthesis with elevated homocysteine (Yap et al. 2001); and Cushing's syndrome with elevated cortisol (Tang et al. 2013).

It is also possible that pro-inflammatory cytokines and their activation of tryptophan-kynurenine metabolites predispose to the development of schizophrenia via inflammation and neurotoxicity. These mechanisms, in turn, predispose to changes in glucose and lipid metabolism associated with cardiovascular illness in schizophrenia (Leonard et al. 2012).

An analysis of genome-wide association studies in schizophrenia utilizing the concept that genes may influence multiple rather than single traits (genetic pleiotropy) found shared predisposition of single nucleotide pleomorphisms to both schizophrenia and systolic blood pressure, as well as triglyceride, lipoprotein levels, body mass index, and waist-hip ratio (Andreassen et al. 2013).

Depressive symptoms can occur throughout all phases of schizophrenia, including the prodrome, acute psychotic episodes, and the post-psychotic phase (Bosanac and Castle 2012). Around a quarter of people with schizophrenia meet criteria for a depressive disorder at some time in their lives (Siris 2000). In the Australian Survey of High Impact Psychosis (SHIP), people with a psychotic illness had high rates of depressed mood, with about 80 % lifetime and about 55 % in the preceding year (Morgan et al. 2012). There is a strong body of evidence linking depression and cardiovascular morbidity, namely development and progression of coronary artery disease, recurrence of cardiac events, worse physical functioning and quality of life, and excess mortality (2–2.5-fold increase) (Celano and Huffman 2011). Depression in cardiac patients per se mediates its negative prognostic impact via poorer treatment adherence, inflammation, altered endothelial function, platelet hyperactivity, and dysfunction of the autonomic nervous system (Celano and Huffman 2011). Also, hopelessness has been associated with progression of carotid atherosclerosis, mediated by fibrinogen (Pollitt et al. 2005). But, whether such linkages of specifically adverse impact of depression, or other negative effects, generalize to cardiovascular disease in psychotic disorders has not been evaluated.

Psychotic symptoms are also independently associated with coronary artery bypass and valve surgery. In turn, these psychotic symptoms are associated with worse outcome, including length of stay in intensive care units and postoperative death. Perioperative risk factors for these cardiac operations include hypothermia, hypernatremia, renal failure, low hematocrit, hypoxia, sepsis, and stroke. While prompt identification and intervention of these operative risk factors may reduce psychotic symptoms and the aforementioned adverse outcomes, this has not been demonstrated as yet (Giltay et al. 2006).

Of concern, from a population health perspective, the healthcare costs of psychosis and cardiovascular disease, including acute and continuing healthcare costs, disengagement from workforce, disability-adjusted life years, and quality of life, have not been evaluated to date.

The broad construct of "stress," which may be psychological or physiological in origin, is defined as a state in which homeostasis is threatened or perceived to be threatened (Koolhaas et al. 2011). The response to stress is mediated via the hypothalamic-pituitary-adrenal axis and over or under activity, which may be present in people with schizophrenia, can lead to adverse cardiovascular sequelae. These sequelae include frequent increases in blood pressure accelerating atherosclerosis or precipitating myocardial ischemia; increased exposure to glucocorticoid and catecholamine activity, leading to central adiposity, diabetes mellitus, hypertension, and cardiovascular disease; smoking, alcohol, and other substance misuse; and reduced physical activity (Bradley and Dinan 2010). In addition, hypertension has been shown to have adverse neuropsychological consequences in people with

schizophrenia. The latter include worsened immediate, delayed, and recognition memory (Friedman et al. 2010).

Clinical Implications

Assessment

Unfortunately, the screening for cardiovascular risk factors in people with psychosis (Roberts et al. 2007), and the treatment of identified cardiovascular risk factors in people suffering with schizophrenia and related disorders, is far from optimal (Johnsen et al. 2011). Given the excess mortality in people suffering with psychosis, regular metabolic monitoring and intervention for identified cardiovascular risk factors is essential (Grundy et al. 2005; Organ et al. 2010).

Integrated, coordinated (e.g. recovery-focused care with a key coordinating clinician), and holistic patient-centered care (Viron et al. 2012) approaches should be the rule rather than the exception. Such care packages should entail primary care, mental health, and allied health clinicians communicating and working collaboratively. This, in turn, is more likely to be an optimal framework for healthcare in this vulnerable population, rather than a range of clinicians working in isolation from one another. But, there has not been comprehensive evaluation of the effectiveness of patient-centered care in people with psychosis, with, or at risk for cardiovascular disease.

Monitoring for cardiovascular disease and its risk factors in psychosis is best served in tandem with education about diet, exercise, and cardiac risk factors. These should occur on at least a six-month basis. The monitoring includes fasting blood glucose, body mass index, serum lipids (cholesterol, LDL, HDL, triglycerides), urea, and electrolyte and liver function tests (Grundy et al. 2005).

Disconcertingly, antipsychotic medications are associated with significant weight gain in at least half of people suffering with psychosis (Baptista 1999), including first-episode patients. This is particularly true for olanzapine and clozapine (Ohlsen 2011). The risks of weight gain with antipsychotics are mediated by significantly increased insulin levels and resistance and escalated glucose, cholesterol, triglyceride, and C-peptide levels (Lancet 2011). This is in addition to the adverse impact of these medications on histamine, dopamine, and 5HT2C blockade (Ohlsen 2011). While these effects are not significantly different across olanzapine, risperidone, sulpiride, and clozapine combined (Lancet 2011), olanzapine, clozapine, and quetiapine are associated with a heightened risk of hyperlipidemia and metabolic disturbance. The latter is lower with risperidone, aripiprazole, and ziprasidone (Muench and Hamer 2010). Consequently, monitoring for and minimizing weight gain and sedation associated with antipsychotic medication is essential in this population and expressly for those on olanzapine, clozapine, and quetiapine.

Clozapine, a dibenzodiazepine antipsychotic medication, is efficacious in people suffering with “treatment-resistant” schizophrenia, who have not had benefit with therapeutic trials of other antipsychotic medication despite adequate dosage and

medication adherence. These potential benefits over other antipsychotic medications in treatment-resistant schizophrenia include reduction in positive and negative symptoms, improvement in general psychopathology, improved cognition, and less extrapyramidal side effects (Meltzer 2012). But clozapine itself is associated with the development of potentially fatal myocarditis (Meltzer 2012), as well as cardiomyopathy and pericarditis (Layland et al. 2009). Myocarditis, although more likely in the initial weeks of treatment, and cardiomyopathy can occur at any stage of treatment with clozapine and be nonspecific in terms of symptoms (Layland et al. 2009). Although multiple mechanisms for clozapine-induced cardiotoxicity have been postulated, including IgE-mediated hypersensitivity, effects of catecholamines, cytochrome P450 1A2/1A3 enzyme deficiencies, inflammatory cytokines, calcium channel blockade, and low selenium levels, none have been firmly established (Layland et al. 2009). Moreover, the cardiotoxicity associated with clozapine prescription in psychotic disorders does not appear to be dose related (Layland et al. 2009; Meltzer 2012). Patients prescribed clozapine for schizophrenia and related disorders are also at increased risk of developing diabetes, hyperlipidemia, obesity, and hypertension and, in turn, death from cardiovascular disease (Henderson et al. 2005).

Due vigilance is also required in HIV-positive patients prescribed highly active antiretroviral therapy, for whom concomitant treatment for psychosis with atypical antipsychotic medication is necessitated. The combination of antipsychotic and antiretroviral medications may be, but not conclusively demonstrated to date, associated with worsening of lipid profile, with increased total cholesterol, LDL, and non-HDL cholesterol (Edwards et al. 2011).

Treatment and Care

Although there is a relative dearth of psychological, including cognitive-behavioral therapy (CBT) or other psychotherapeutic interventions for primary or secondary prevention of cardiac disease in people with psychoses, there is evidence from meta-analysis to support behavioral interventions. These interventions, which include setting of goals, scheduling of activities, and monitoring of self, have a demonstrable, albeit small, impact on weight gain (mean of 3 kg) associated with obesity related to antipsychotic medication (Gierisch et al. 2013). There are, emerging as yet, no family and peer-support studies of interventions to address cardiovascular risk in people with psychoses, but definitive results have not been published.

A recent systematic review did not find any study that had examined the cost-effectiveness of lifestyle interventions targeting eating behavior and physical activity on weight and body mass index of people with schizophrenia (Verhaeghe et al. 2011). Nonetheless, physical activity can improve physical health, and mitigate to some extent, positive and negative symptoms, psychological distress, as well as weight gain associated with antipsychotic medication in people with schizophrenia (McNamee et al. 2013). Concomitantly, lifestyle interventions involving exercise may improve cardiometabolic risk associated with obesity in people with schizophrenia. While

barriers to physical activity in people with schizophrenia are mediated by positive and negative psychotic symptomatology, weight gain, and other medication side effects, the specific factors in clinical practice that promote active engagement in increased physical activity in people with psychosis require further study (McNamee et al. 2013).

In terms of an emerging evidence base, a novel healthy lifestyle intervention, centered on primarily mitigating smoking and cardiovascular risk factors in people with serious mental illnesses, including psychosis, was initially evaluated as a pilot study. The pilot study found that goal setting and support for patients to modify their unhealthy lifestyle led to improvements in cardiovascular risk, smoking (with nicotine replacement therapy), weight, and physical activity. The latter was in the context of the vast majority of patients completing all sessions (Baker et al. 2009). Following on from this pilot study, the authors published a protocol for a larger-scale randomized control study, in which participants are to be randomized to either a multimodal intervention or telephone-based intervention for smoking after an initial face-to-face intervention (Baker et al. 2011). Varenicline, a partial nicotine receptor agonist, which is prescribed to reduce nicotine cravings and withdrawal, has also been utilized by this research group in a small open-label pilot study as an adjunct to a healthy lifestyle intervention in smokers with a psychotic disorder (Castle et al. 2012). The combination of varenicline and the lifestyle intervention was associated with smoking cessation of 36 % and 42 % at 3 months and 6 months, respectively. However, varenicline does carry psychotogenic risks in both people with and without (Bancila et al. 2009) a history of psychosis (Gupta et al. 2012) and needs to be used with due care and careful mental state monitoring. Also, with all such interventions, long-term sustainability is difficult.

A joint primary health and mental health initiative, involving combined clinical sessions and a shared protocol, demonstrated that the recording of cardiovascular disease risk factors in people with psychosis (hypertension, glucose, lipid status, waist circumference, smoking) significantly improved across these healthcare settings (Vinas et al. 2013).

There also appears to be a role of metformin in mitigating metabolic sequelae associated with antipsychotics (Curtis et al. 2012) and controlling glycosolated hemoglobin (HbA1c) in people with psychoses suffering with diabetes or who are prescribed antipsychotic medications (Gierisch et al. 2013). Metformin's actions in this regard include the inhibition of gluconeogenesis in the liver, improving insulin sensitivity, and the peripheral uptake of glucose (Taylor 2012). But this intervention, along with potential benefits of augmenting clozapine with aripiprazole or switching from another antipsychotic (olanzapine, quetiapine, or risperidone) to aripiprazole in tandem with a manual-based diet and exercise intervention) or adding topiramate, was counterbalanced by limited information about any potential harm (Gierisch et al. 2013).

Conclusions

The relationship of cardiovascular disease to psychosis is a complex one, with core symptoms of psychosis, poor diet, smoking, sedentary lifestyle, and socioeconomic factors predisposing to cardiovascular risk factors, in combination with

iatrogenically induced risk factors attributed to antipsychotic medication, in particular weight gain. Stress plays a role in the negative impact on both psychosis and cardiovascular disease via the hypothalamic-pituitary-adrenal axis. Blood-borne infections such as HIV are also overrepresented in psychosis, including via intravenous substance use, with their own inherent as well as iatrogenic cardiovascular risks, e.g., that associated with antiretroviral therapy. There may also be a predisposing etiology for both psychosis and cardiovascular disease e.g., velocardiofacial syndrome, homocystinuria, Cushing's syndrome, and, more speculatively, pro-inflammatory mechanisms. While depression and cardiovascular morbidity are strongly linked, such a link has not been evaluated in people with psychosis. Psychotic symptoms are also associated with coronary artery bypass and valve surgery, with resultant worse healthcare outcomes.

Nonetheless, cardiovascular disease and risk factors, including metabolic syndrome, are markedly overrepresented in people suffering with psychosis. These cardiovascular risks and endpoints, in turn, impact adversely on quality of life, as well as the course of mental illness and mortality. Worryingly, cardiovascular disease in people with psychosis is often underreported, in tandem with a low rate of metabolic screening. Joint primary health and mental health clinical sessions and shared protocols may improve identification demonstrated that of the recording of cardiovascular disease risk factors in people with psychosis.

Regular metabolic monitoring and intervention for identified cardiovascular risk factors is essential, with integrated, coordinated, and patient-centered care being an appropriate framework for this. Monitoring, in tandem with education about diet, exercise, and cardiac risk factors, should occur on a regular basis. Monitoring for and minimizing weight gain and sedation associated with antipsychotic medication is also essential, with switching to more "weight-neutral" options. In addition, metformin appears to have a role in dampening antipsychotic-related weight gain.

Although there is a limited evidence base about psychological and psychotherapeutic interventions for primary or secondary prevention of cardiac disease in people with psychoses, behavioral and lifestyle interventions have an emerging beneficial role. Varenicline, notwithstanding propsychotic risks, may complement these lifestyle interventions via smoking cessation. We are aware of no studies that have examined the cost-effectiveness of lifestyle interventions targeting eating behavior and physical activity on weight and body mass index of people with psychosis.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Association.

Andreassen, O. A., Djurovic, S., Thompson, W. K., Schork, A. J., Kendler, K. S., O'Donovan, M. C., Rujescu, D.,. . . McCarthy, M. I. International Consortium for Blood Pressure GWAS; Diabetes Genetics Replication and Meta-analysis Consortium; Psychiatric Genomics Consortium Schizophrenia Working Group. Roddey, J. C., McEvoy, L. K., Desikan, R. S., Dale, A. M. (2013). Improved detection of common variants associated with schizophrenia by leveraging

pleiotropy with cardiovascular-disease risk factors. *American Journal of Human Genetics*, *92* (2), 197–209.

Baker, A., Richmond, R., Castle, D., Kulkarni, J., Kay-Lambkin, F., Sakrouge, R., Filia, S., & Lewin, T. J. (2009). Coronary heart disease reduction intervention among overweight smokers with a psychotic disorder: Pilot trial. *Australian and New Zealand Journal of Psychiatry, 43*, 129–135.

Baker, A., Frances, J., Kay-Lambkin, F. J., Richmond, R., Filia, S., Castle, D., Williams, J., & Lewin, T. J. (2011). Study protocol: A randomised controlled trial investigating the effect of a healthy lifestyle intervention for people with severe mental disorders. *BMC Public Health, 11*, 10. doi:10.1186/1471-2458-11-10.

Bancila, V., Dallon, C., & Zullino, D. F. (2009). Varenicline may induce psychotic symptoms in subjects without previous history of psychiatric disorders. *Acta Neuropsychiatrica, 21*(5), 268–269.

Baptista, T. (1999). Body weight gain induced by antipsychotic drugs: Mechanisms and management. *Acta Psychiatrica Scandanavica, 100*, 3–16.

Beratis, S., Katrivanou, A., & Gourzis, P. (2001). Factors affecting smoking in schizophrenia. *Comprehensive Psychiatry, 42*(5), 393–402.

Bosanac, P., & Castle, D. (2012). Schizophrenia and depression. *Medical Journal of Australia, 1* (supplement 4), 36–39.

Bradley, A. J., & Dinan, T. G. (2010). A systematic review of hypothalamic–pituitary–adrenal axis function in schizophrenia: Implications for mortality. *Journal of Psychopharmacology, 24* (4 Supplement), 91–118.

British Medical Journal (BMJ). (2010). Long QT syndrome. *British Medical Journal, 340:c366*. doi: 10.1136/bmj.b4815.

Campion, G., Francis, V., Preston, A., & Wallis, A. (2005). Health behaviour and motivation to change. *Mental Health Nursing, 25*, 12–15.

Castillo, S. M., Fàbregas, E. M., Bergè, B. D., Goday, A. A., & Vallès, C. J. A. (2013). Psychosis, cardiovascular risk and associated mortality: Are we on the right track? *Clinica Investigacion en Arteriosclerosis*. doi:10.1016/j.arteri.2013.05.006.

Castle, D., Baker, A. L., Richmond, R., Filia, S. L., Harris, D., & Pirola-Merlo, A. J. (2012). Varenicline plus healthy lifestyle intervention for smoking cessation in psychotic disorders. *Annals of Clinical Psychiatry, 24*(4), 285–291.

Celano, C. M., & Huffman, J. C. (2011). Depression and cardiac disease: A review. *Cardiology Review, 19*(3), 130–142.

Cooper, J., Mancuso, S. G., Borland, R., Slade, T., Galletly, C., & Castle, D. (2012). Tobacco smoking among people living with a psychotic illness: The second Australian survey of psychosis. *Australian and New Zealand Journal of Psychiatry, 46*, 851–863.

Curtis, J., Newall, H., Shiers, D., & Samaras, K. (2012). Considering metformin in cardiometabolic protection in psychosis. *Acta Psychiatrica Scandanavica, 126*, 302–303.

Darke, S., Kaye, S., McKetin, R., & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug and Alcohol Review, 27*, 253–262.

De Hert, M., Schreurs, V., Sweers, K., Van Eyck, D., Hanssens, L., Sinko, S., Wampers M.,. . . van Winkel, R. (2008). Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: A retrospective chart review. *Schizophrenia Research*, *101*, 295–303.

De Hert, M., Cohen, D, Bobes J, Cetkovich-Bakmas M, Leucht S, Ndetei DM, Newcomer, J. W.,. . . Correll, C. U. (2011). Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. *World Psychiatry*, *10*(2), 138–151.

Edwards, K. L., Chastain, L. M., Snodgrass, L., Martin, A., Busti, A. J. (2011) Effects of combined use of antiretroviral Agents and atypical antipsychotics on lipid parameters. *Journal of Antivirals & Antiretrovirals*, *3*, 034–039.

Fagiolini, A., & Goracci, A. (2009). The effects of undertreated chronic medical illnesses in patients with severe mental disorders. *Journal of Clinical Psychiatry, 70*(Supplement 3), 22–29.

Friedman, J. I., Wallenstein, S., Moshier, E., Parrella, M., White, L., Bowler, S., Gottlieb, S.,... Davis, K. L. (2010). The effects of hypertension and body mass index on cognition in schizophrenia. *American Journal of Psychiatry*, *167*(10), 1232–1239.

Fusar-Poli, P., De Marco, L., Cavallin, F., Bertorello, A., Nicolasi, M., & Politi, P. (2009). Lifestyles and cardiovascular risk in individuals with functional psychoses. *Perspectives in Psychiatric Care, 45*(2), 87–99.

Galletly, C. A., Foley, D. L., Waterreus, A., Watts, G. F., Castle, D. J., McGrath, J. J., Mackinnon, A., & Morgan, V. A. (2010). Cardiometabolic risk factors in people with psychotic disorders: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry, 46*(8), 753–761.

Gierisch, J. M., Nieuwsma, J. A., Bradford, D. W., Wilder, C. M., Mann-Wrobel, M. C., McBroom, A. J., Wing, L.,... Williams, J. W. Jr. (2013). Interventions to improve cardiovascular risk factors in people with serious mental illness. Comparative effectiveness review No. 105. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-EHC063-EF. Rockville: Agency for Healthcare Research and Quality. April 2013. Retrieved from http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Giltay, E. J., Huijskes, R. V. H. P., Kho, K. H., Blansjaar, B. A., & Rosseel, P. M. J. (2006). Psychotic symptoms in patients undergoing coronary artery bypass grafting and heart valve operation. *European Journal of Cardio-Thoracic Surgery, 30*, 140–147.

Green, A. I., Drake, R. E., Brunette, M. F., & Noordsy, D. L. (2007). Schizophrenia and co-occurring substance use disorder. *American Journal of Psychiatry, 164*, 402–408.

Grundy, S. C., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin B. A., Gordon, D. J., ... Costa, F. (2005). AHA/NHLBI scientific statement diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*, *112*, 2735–2752.

Gupta, A., Bastiampillai, T., Adams, M., Nelson, A., & Nance, M. (2012). Varenicline induced psychosis in schizophrenia. *Australian and New Zealand Journal of Psychiatry, 46*(10), 1009.

Haddad, P. M., & Anderson, I. M. (2002). Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs, 62*(11), 1649–1671.

Harangozo, J., Reneses, B., Brohan, E., Sebes, J., Csukly, G., Lopez-Ibor, J., Sartorius, N.,... Thornicroft G. (2013). Stigma and discrimination against people with schizophrenia related to medical services. *International Journal of Social Psychiatry*. doi: 10.1177/0020764013490263.

Hatta, K., Takahashi, T., Nakamura, H., & Yonezawa, Y. (2000). Prolonged QT interval in acute psychotic patients. *Psychiatry Research, 94*(3), 279–285.

Henderson, D. C., Nguyen, D. D., Copeland, P. M., Hayden, D. L., Borba, C. P., Louie, P. M., Freundereich, O.,... Goff, D. C. (2005). Clozapine, diabetes, hyperlipidemia, cardiovascular risks and mortality. Results of a 10-year naturalistic study. *Journal of Clinical Psychiatry*, *66*(9), 1116–1121.

Hennekens, C. H., Hennekens, A. R., Hollar, D., & Casey, D. E. (2005). Schizophrenia and increased risks of cardiovascular disease. *American Heart Journal, 150*, 1115–1121.

John, A. P., Koloth, R., Dragovic, M., & Lim, S. C. (2009). Prevalence of metabolic syndrome among Australians with severe mental illness. *Medical Journal of Australia, 190*, 176–179.

Johnsen, E., Gjestad, R., Kroken, R. A., Mellesdal, L., Loberg, E.-M., & Jorgensen, H. A. (2011). Cardiovascular risk in patients admitted for psychosis compared with findings from a population-based study. *Nord Journal of Psychiatry, 65*, 192–202.

Koolhaas, J. M., Bartolomucci, A., Buwalda, B., de Boer, S. F., Flügge, G., Korte, S. M., Meerlo, P.,... Fuchs, E. (2011). Stress revisited: A critical evaluation of the stress concept. *Neuroscience & Biobehavioral Reviews*, *35*(5), 1291–1301.

Lahti, M., Tihonen, J., Wildgust, H., Beary, M., Hodgson, R., Kajantie, E., ... Eriksson, J. (2012). Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia. *Psychological Medicine*, *42*(11), 2275–2285.

Lambert, T. (2011). Managing the metabolic adverse effects of antipsychotic drugs in patients with psychosis. *Australian Prescriber, 34*, 97–99.

Lancet. (2011). No mental health without physical health. *Lancet, 377*(9766), 611.
Layland, J. L., Liew, D., & Prior, D. L. (2009). Clozapine-induced cardiotoxicity: A clinical update. *Medical Journal of Australia, 190*, 190–192.
Leonard, B., Schwarz, M., & Myint, I. M. (2012). The metabolic syndrome in schizophrenia: Is inflammation a contributing cause? *Journal of Psychopharmacology, 26*(5 Supplement), 33–41.
Mackin, P. (2008). Cardiac side effects of psychiatric drugs. *Human Psychopharmacology: Clinical and Experimental, 23*, 3–14.
McBride, O., Teesson, M., Slade, T., Hasin, D., Degenhardt, L., & Baillie, A. (2009). Further evidence of differences in substance use and dependence between Australia and the United States. *Drug and Alcohol Dependence, 100*, 258–264.
McCreadie, R. (2003). Diet, smoking and cardiovascular risk in people with schizophrenia. *British Journal of Psychiatry, 183*, 534–549.
McDermott, S., Moran, R., Platt, T., Isaac, T., Wood, H., & Dasari, S. (2005). Heart disease, schizophrenia, and affective psychoses: Epidemiology of risk in primary care. *Community Mental Health Journal, 41*(6), 747–755.
McNamee, L., Mead, G., MacGillivray, S., & Lawrie, S. M. (2013). Schizophrenia, poor physical health and physical activity: Evidence-based interventions are required to reduce major health inequalities. *British Journal of Psychiatry, 203*, 239–241.
Meltzer, H. (2012). Clozapine: Balancing safety with superior antipsychotic efficacy. *Clinical Schizophrenia & Related Psychoses, 6*(3), 134–144.
Morgan, V. A., Waterreus, A., Jablensky, A., Mackinnon, A., McGrath, J. J., Carr, V., Bush, R.,. . . Saw, S. (2012). People living with psychotic illness in 2010: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry*, *46*(8), 735–752.
Muench, J., & Hamer, A. M. (2010). Adverse effects of antipsychotic medications. *American Family Physician, 81*(5), 617–622.
Murphy, K. C. (2002). Schizophrenia and velo-cardio-facial syndrome. *Lancet, 359*(9304), 426–430.
Ohlsen, R. (2011). Schizophrenia: A major risk factor for cardiovascular disease. *British Journal of Cardiac Nursing, 6*(5), 2–6.
Ojalaa, K., Niskanenb, L., Tiihonena, J., Paavolaa, P., Putkonena, A., & Repo-Tiihonen, E. (2008). Characterization of metabolic syndrome among forensic psychiatric inpatients. *Journal of Forensic Psychiatry & Psychology, 19*(1), 33–51.
Organ, B., Nicholson, E., & Castle, D. (2010). Implementing a physical health strategy in a mental health service. *Australasian Psychiatry, 18*(5), 456–459.
Pollitt, R. A., Daniel, M., Kaufman, J. S., Lynch, J. W., Salonen, J. T., & Kaplan, G. A. (2005). Mediation and modification of the association between hopelessness, hostility, and progression of carotid atherosclerosis. *Journal of Behavioral Medicine, 28*, 53–64.
Ray, W. A., Chung, C. P., Murray, K. T., Hall, K., & Stein, C. M. (2009). Atypical antipsychotic drugs and the risk of sudden cardiac death. *New England Journal of Medicine, 360*, 225–235.
Roberts, L., Roalfe, A., Wilson, S., & Lester, H. (2007). Physical health care of patients with schizophrenia in primary care: A comparative study. *Family Practice, 24*, 34–40.
Rosenberg, S. D., Goodman, L. A., & Osher, F. C. (2001). Prevalence of HIV, hepatitis B & C in people with severe mental illness. *American Journal of Public Health, 91*, 31–37.
Ruest, C. (2011). Common adverse effects of antiretroviral therapy for HIV disease. *American Family Physician, 83*(12), 1443–1451.
Siris, S. G. (2000). Depression in schizophrenia: Perspective in the era of "atypical" antipsychotic agents. *American Journal of Psychiatry, 157*, 1379–1389.
Smith, D. J., Langan, J., McLean, G., Guthrie, B., Mercer, S. W. (2013). Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: Cross-sectional study. *British Medical Journal open*, *3*(4). pii: e002808. doi:10.1136/bmjopen-2013-002808,
Tang, A., O'Sullivan, A. J., Diamond, T., Gerard, A., & Campbell, P. (2013). Psychiatric symptoms as a clinical presentation of Cushing's syndrome. *Annals of General Psychiatry, 12*, 23.

Taylor, D. An editorial comment to Curtis J, Newall H, Shiers D, Samaras K. (2012). Considering metformin in cardiometabolic protection in psychosis. *Acta Psychiatrica Scandinavica*, *126*(4), 233–234.

van Os, J. (2009). A salience dysregulation syndrome. *British Journal Psychiatry, 194*(2), 101–103.

Verhaeghe, N., De Maeseneer, J., Maes, L., Van Heeringen, C., & Annemans, L. (2011). Effectiveness and cost-effectiveness of lifestyle interventions on physical activity and eating habits in persons with severe mental disorders: A systematic review. *International Journal of Behavioral Nutrition and Physical Activity, 8*, 28.

Vinas, C. L., Fernandez, S.-M. M. I., Martin, L. L. M., & Grupo, P. L. (2013). Effectiveness of a joint project between primary care and mental health to improve the recording of cardiovascular risk factors in patients with psychosis. *Atencion Primaria, 45*(6), 307–314.

Viron, M., Baggett, T., Hill, M., & Freudenreich, O. (2012). Schizophrenia for primary care providers: How to contribute to the care of a vulnerable patient population. *American Journal of Medicine, 125*(3), 223–230.

Volkow, D. (2009). Substance use disorders in schizophrenia—clinical implications of comorbidity. *Schizophrenia Bulletin, 35*(3), 469–472.

Werner, S., Malaspina, D., & Rabinowitz, J. (2007). Socioeconomic status at birth is associated with risk of schizophrenia: Population-based multilevel study. *Schizophrenia Bulletin, 33*(6), 1373–1378.

World Health Organisation. (1994). *International statistical classification of diseases and health related problems*. Geneva: World Health Organization.

Yap, S., Boers, G. H. J., Wilcken, B., Wilcken, D. E. L., Brenton, D. P., Lee, P. J., Walter, J. H.,. . . Naughten, E. R. (2001). Vascular outcome in patients with homocystinuria due to cystathionine β-synthase deficiency treated chronically: A multicenter observational study. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *21*, 2080–2085.

Younossi, Z. M., Stepanova, M., Nader, F., Younossi, Z., & Elsheikh, E. (2013). Associations of chronic hepatitis C with metabolic and cardiac outcomes. *Alimentary Pharmacology and Therapeutics, 37*(6), 647–652.

Occupational Stress and Cardiovascular Disease

Don Byrne and Geir Arild Espnes

Contents

This chapter presents a revised version of a paper originally published in *Stress and Health* (2008), 24, 231–238, (Wiley Interscience) by the present authors (Byrne and Espnes). The revision has been made with the permission of the publisher.

D. Byrne (✉)
ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia

ANU Medical School, Research School of Psychology, Australian National University, Acton, Canberra, ACT, Australia
e-mail: Don.Byrne@anu.edu.au

G.A. Espnes
Center for Health Promotion Research, Department of Social Work and Health Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Australian National University, Canberra, ACT, Norway
e-mail: geirae@svt.ntnu.no; geir.arild.espnes@svt.ntnu.no

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_17

Abstract

This chapter reviews the evidence relating occupational stress (OS) to risk and incidence of cardiovascular disease (CVD), from the simple notion of occupational level and type as a risk marker to the more complex and theoretically more sophisticated models of occupational stress as a determinant of cardiovascular risk and disease. It does so by mapping measures of occupational stress against the three related CVD end-points of coronary risk profiles, clinical hypertension, and diagnosed events or episodes of clinical cardiovascular disease. Taken broadly, the evidence is consistently supportive of postulated links. While the evidence from studies following established theoretical models of OS appears to be both stronger and more easily interpretable, evidence from atheoretical studies employing proxy measures of OS – work hours, shift work, or perceived discrimination in the workplace, for example – has also produced evidence which is strongly supportive of the OS/CVD link. The persuasiveness of the evidence, overall, now points to the importance of OS intervention studies in the workplace undertaken according to rigorous clinical trial methodologies as the next major focus of research.

Keywords

Occupational stress • Job strain • CVD risk • Work environment • Employment

Introduction

The importance of occupational stress to the occupational health literature has increased enormously over the past 30 years or more, to the point now where it constitutes a key area of inquiry in the search for occupational correlates and determinants of major health difficulties. Not surprisingly, the role of the occupational environment and its potentially negative psychosocial impact on those in the workforce has assumed a notable prominence in the search for the origins of cardiovascular disease (CVD). In this context, links between occupational stress and cardiovascular risk have long been asserted, though not without continued debate (Yarnell 2008).

At its most fundamental level, occupational stress (OS) is that phenomenon which is experienced when an individual is exposed to a personally significant load of stressors originating wholly (or largely) from the occupational environment. And at a slightly more nuanced level, this stressor load is seen to be of such a nature or intensity (or both) that – for whatever reason – the individual feels poorly equipped, whether personally or organizationally, to effectively cope with it. But this is to grossly oversimplify a complex biopsychosocial situation. The cumulative psychological and medical literature on OS (alternatively and synonymously called work or job stress – though this chapter will adhere to the convention of *occupational stress* or OS) is substantial both in volume and breadth. It covers domains of interest as far apart as the physical characteristics of occupational environments (e.g., heat, cold, noise, and crowding), the organizational structures and constraints within which people work (hierarchical rigidity, role ambiguities, and the like), and the

intrapersonal characteristics of those working within those structures and environments (personality, coping styles, beliefs and attitudes, and cognitive capacities). And it recognizes the interdependence of OS and other arenas of stressor exposure in the complex lives of all those engaged in the workforce.

Despite evidence for a recent decline in CVD mortality (Preis et al. 2009), CVD remains a major cause of death and disability in many Western societies. A keen interest over the last four or more decades in the nature and presence of risk factors accounting for CVD is therefore not surprising, and attempts to link the psychological characteristics of both individuals and their social environments to CVD risk have formed a good part of that research (see, e.g., Kuper et al. 2002). The historical development of such objectively defined and measured constructs as the Type A behavior pattern (see Rosenman 1990 for a historical overview) and psychosocial stress (see, e.g., Levi 1972) has added depth and scientific rigor to this search. It is inevitable then that the attention of some researchers, at least, has turned to OS as an explanatory factor in the search to address the psychosocial determinants of CVD risk and disease. This chapter seeks to examine that evidence.

Historical Evidence

Systematic research linking OS to CVD has been reported since the middle of the last century. Both Russek (1965) and French and Caplan (1970) noted significant variations in rates of CVD in relation to both occupational level and demand. Later work extended this to a distinction in risk between public and private sector workers (Kornitzer et al. 1981). Bolm-Audorff and Siegrist (1983) reported higher CVD risk among those in blue-collar than white-collar occupations, suggesting the stress attached to dull and monotonous work might account for this finding. Links between more directly measured characteristics of the occupational environment and CVD risk were first reported by Liljefors and Rahe (1970), where job demand (assessed as the number of hours worked weekly) was related to the incidence of clinical events of CVD. But simple associations such as this were not always found. An examination of data from the Framingham study reported associations between workload and CVD but only in older people (Haynes et al. 1978), where advancing age might have an impact on workload tolerance. Much of this evidence has, of course, been reviewed elsewhere (Byrne 2000) and need not be revisited here. What is clear, however, is that a good deal of the early empirical work on OS and CVD was largely intuitively driven and not strongly guided either by general theories of stress or more specific theoretical models of OS. The remainder of this chapter then focuses largely on recent theoretically driven evidence accessed through systematic interrogation of standard publication databases, and in the light of the significant volume of evidence, studies from the last 15 years were favored, except where publications were considered to be seminal to the field (since good reviews of earlier evidence already exist), as were studies with large samples, robust designs, and theory-driven measures.

Models of Occupational Stress

The structural nature of the workplace itself and the organizational challenges and constraints it places upon individuals working in it (Carlsson et al. 2014) have been seen as an important starting point in identifying the origins of OS. Most approaches to the theoretical understanding of OS, however, go beyond structural considerations alone and clearly integrate the worker/organization interaction into the explanatory equation. A review of the current literature reveals many models of OS; most however reflect more or less subtle variations on related themes, and on examination, the theoretical approaches to OS really reduce to three dominant or overarching models.

The Person-Environment Fit Model – proposing a dynamic interaction between characteristics of the occupational environment and the individual resources each person is able to mobilize in order to cope (French et al. 1982), with any significant mismatch resulting in OS. And this, of course, reflects the now classical theoretical view of stress proposed initially by Lazarus (1966).

The Demand/Control Model – which views OS arising from a tension between the demands an occupational environment imposes on an individual and the level of perceived control which the person has over that environment (Karasek and Theorell 1990), with OS resulting maximally from situations of high demand and low control. The demand/control model often refers to job strain as the descriptor of OS; however, they are, to all intents and purposes, synonymous with one another. And in an important refinement of the demand/control model, Johnson and Hall (1988) proposed that it should consider the buffering effects of social support in the workplace as a significant mediator of OS.

The Effort/Reward Imbalance Model – where OS is claimed to relate to the balance between the degree of effort put into the job and the level of reward resulting from that effort (Siegrist and Marmot 2004), with high effort and low reward associated with sustained OS.

These models – and in particular, the latter two – clearly overlap both thematically (Theorell 2003; Siegrist and Marmot 2004) and in terms of their respective capacities to predict CVD risk in occupational populations (Bosma et al. 1998). Nonetheless, they all represent conceptually strong approaches to explaining risk and incidence of CVD, and most recently in particular, both the demand/control model and the effort/reward imbalance model have been backed by a wealth of empirical evidence. Comprehensive and systematic and critical reviews (e.g., Hausser et al. 2010) would suggest, however, that the weight of that evidence comes out to favor the demand/control model in explaining the role of the occupational environment as it addresses risk or incidence of CVD.

This notwithstanding, the impact of the occupational environment on CVD risk or incidence has been inferred from a wide range of studies employing an equally wide range of research methodologies. And not all studies – and perhaps the majority – have been driven by theoretical considerations. Moreover, the nature and reliability of CVD end-points (levels of risk markers, indicators of preclinical CVD, incidence of CVD events, and the like) have varied equally widely. This

variability has somewhat obscured the capacity to make unequivocal pronouncements regarding the importance of OS as a precursor to CVD. The range of evidence must therefore be considered within these various theoretical and methodological perspectives.

Occupational Stress and CVD Risk Marker Profiles

One of the central issues surrounding the link between OS and CVD has to do with its directness – does OS directly compromise cardiovascular function and precipitate clinical events or is the link indirectly manifest through intervening factors? CVD risk is predicted by an array of recognized risk factors, prominent among which are elevated blood fats (principally cholesterol), cigarette smoking, and hypertension. CVD risk profiles have been related even to such ambiguous indices of OS as occupational class (Wamala et al. 2000) and in a manner not easily explained by such theoretical models as the demand/control framework. Therefore, while there is some argument that the OS/risk factor link may be tenuous (Siegrist and Rodel 2006), it cannot be ruled out. Relationships between OS and recognized CVD risk factors must therefore be considered.

Cigarette Smoking

Cigarette smoking poses an established and potent risk for CVD (Leone 2007). Regardless of environmental setting, the experience of stress increases cigarette consumption among established smokers (Byrne and Mazanov 2008). Associations between OS and CVD risk may therefore be mediated through cigarette smoking.

The presence of work-related stress (including high concentration demand and work dissatisfaction) predicted smoking status in middle-aged women (Jonsson et al. 2003), and OS has been associated with a broad range of smoking measures in both men and women (Ng and Jeffery 2003). Associations between OS and levels of cigarette consumption particularly have emerged (Metcalfe et al. 2003) in a manner consistent with the general evidence on stress and smoking (Byrne and Mazanov 2008). Smoking appears more prevalent among blue-collar than white-collar workers (Rose et al. 2006), with this finding related to the claimed negative effects of OS. And employed adults who perceive low procedural justice (poor involvement in decision making) in the workplace are more likely to be heavy smokers than those without such perceptions (Kouvonen et al. 2007), with this finding unaffected either by adjustments for job strain or effort/reward imbalance.

Both the demand/control and effort/reward imbalance models have also been more systematically applied to analyses of OS and smoking. High job demand has been related to heavy smoking in middle-aged rural workers, though curiously, low job control appeared to be related to lower cigarette consumption (Tsutsumi et al. 2003). Job demand has been associated with cigarette smoking irrespective of job strain (Albertsen et al. 2006). But job strain (high demand and low control)

too has been linked to smoking (John et al. 2006). And in fact both high job strain and high effort/reward imbalance have been independently associated with smoking intensity (Kouvonen et al. 2005), with lower levels of effort in the workplace also predicting ex-smoking status. Sufficient empirical evidence therefore now links OS and smoking, that it must be seen as one credible pathway through which OS influences CVD risk.

Blood Pressure

Elevated blood pressure (BP) too, particularly if it is chronic (as in hypertension), poses an established risk for CVD (Weycker et al. 2007). Possible associations between OS and BP have therefore been targeted to elucidate the link between OS and CVD. In considering this evidence, it is important to distinguish between evidence relating OS and BP *per se* (even if measured repeatedly and/or in the work situation) and evidence linking OS and diagnosed hypertension as a clinical end-point; the former may indicate future hypertension, but only the latter reliably predicts CVD.

While the idea that OS may influence blood pressure has existed for some decades (see, e.g., French and Caplan 1970), Siegrist and Klein (1990) first demonstrated a covariation between chronic OS and BP reactivity under challenge. Job strain has been specifically linked to BP, though Theorell et al. (1991) and Theorell et al. (1993) restricted this to diastolic BP and then largely in the work setting. Job strain based on both demand and control has also been associated with diastolic BP, but only in men (Tsutsumi et al. 1998) or when diastolic BP was measured at night after work (Rau et al. 2001). Relationships between OS and diastolic BP appear to hold even after controlling for such possible confounders as age, smoking, and alcohol consumption (Su et al. 2001).

By contrast, a measure of OS specific to medical practitioners was related to elevation of both diastolic and systolic BP, but maximally only during the workday (O'Connor et al. 2001). Though high job strain (OS) has been found to blunt the normally expected diurnal variation in blood pressure among both men and women with abnormally high blood pressure (Fan et al. 2013), leading to the possibility that blood pressure remains higher overall during the 24 h cycle. Elevations in both diastolic and systolic BP have also been reported in relation to job strain using ambulatory BP measures in the workplace in one study (Landsbergis et al. 2003) but not in another (Riese et al. 2004), and in the former, the association was only evident in those with low socioeconomic status. Pressure/rate product too has been related to high job strain (Bishop et al. 2003). Shift work, particularly when it alternates, has been found to relate to elevated blood pressure among Japanese men (Suwazono et al. 2008). And moving from low to high job strain occupations significantly elevates systolic BP (Cesana et al. 2003), while the same effect has been observed to persist over time where high job strain prevails (Guimont et al. 2006).

BP in the workplace has been related to occupational overcommitment, independent of job control (Steptoe et al. 2004), and to expressions of workplace anger (Bongard and al'Absi 2005). And very recently it has been reported that job strain may actually interact with a genetic factor (I/D polymorphism in the adrenergic alpha2B-receptor) to elevate both systolic and diastolic BP (Ohlin et al. 2007).

At the wider level of the population, a very large study ($N = 122{,}816$ participants) of OS and resting blood pressure (Wiernik et al. 2013) found that self-perceived reports of OS were strongly related to both diastolic and systolic blood pressure – but the association disappeared when adjustment was made for occupational status. This led the authors to conclude that studies of OS and blood pressure should always take account of the potential interaction with occupational status.

Broad and abundant evidence therefore links OS with BP, largely through the experience of job strain. The evidence indicates an effect of OS on both cardiac output (systolic BP) and peripheral resistance (diastolic BP) and may possibly be mediated through a genetic interaction. And gender differences in OS/BP relationships must be considered (Cesana et al. 2003). But elevated BP is not clinical hypertension, and only the latter constitutes an established risk for CVD.

Hypertension

A combination of high effort and low reward in the workplace has been clearly associated with a diagnosis of clinical hypertension in middle managers (Peter and Siegrist 1997) and shift workers (Peter et al. 1999). Job strain too has been related to the prevalence of clinical hypertension, but curiously one study reported this only in men (Tsutsumi et al. 2001) and another only in women (Alfredsson et al. 2002).

However, beyond the strict confines of theoretical models of OS, the prevalence of clinical hypertension has also been associated, and in some cases conspicuously, with the general experience of occupational stress (Djindjic et al. 2012). At a finer level of detail, hypertension has been statistically associated with a range of proxy measures of OS, including organizational job constraints (Radi et al. 2005), excessive work hours (Yang et al. 2006), job insecurity, and low occupational prestige, but only in men – low work status predicted hypertension in women (Levenstein et al. 2001), covert (but not overt) coping with unfair treatment at work, but only in men (Theorell et al. 2000), perceived job barriers and job intensity (Greiner et al. 2004), BP reactivity to acute stressors in the workplace (Ming et al. 2004), and race-related workplace stress (Din-Dzietham et al. 2004).

This last issue is of particular psychosocial concern since it identifies a significant aspect of social inequality – still apparently endemic in many workplaces – which constitutes, over and above the serious personal distress it clearly causes, an identified risk for hypertension (Dolezsar et al. 2014).

The evidence implicating OS in the genesis of clinical hypertension is therefore persuasive though much of it goes beyond the framework of established theoretical

models. The capacity for OS to influence CVD risk through the intermediary effects of hypertension must therefore be seriously contemplated.

Blood Lipids

Levels of blood lipids, and particularly levels of LDL fractions of cholesterol, have long been associated with elevated CVD risk (Campbell et al. 2007). Recent studies have established reliable links between OS and this component of CVD risk. An early alert to this link (Siegrist et al. 1988) examined chronic OS in middle-aged men, measured as an interaction between objective (job instability and shift work) and subjective (perceived job insecurity and increased workload) factors; after controlling for such confounds as age, weight, and cigarette smoking, OS was significantly associated with elevated LDL cholesterol.

More recently however, OS conceptualized specifically within the demand/control model has been linked with elevated blood lipids. Curiously though, elevated cholesterol was related only to low decision latitude (control) and not to job strain. The composite index of job strain has been related to elevated lipids (Tsutsumi et al. 1998), but only in working females.

Turning to the effort/reward imbalance model, the most impressive link between OS and blood lipids probably comes from the WOLF (work, lipids, and fibrinogen) study (Peter et al. 1998). Examination of baseline data from employed males and females aged between 30 and 55 years showed that in men, effort/reward imbalance was significantly related both to high total cholesterol and to a total cholesterol: HDL ratio indicating CVD risk. In women, high effort was related both to increased LDL levels and to a cholesterol: LDL ratio indicating CVD risk. Westerlund et al. (2004) extended analyses of the WOLF study data to include indices of organizational (employment) stability, reporting elevated cholesterol among employees of companies where instability was evident either as change and growth, economic threat, or because of small size.

The evidence associating OS with potentially harmful levels of blood lipids therefore is well established. Given the recognized link between blood lipids and coronary atherosclerosis, it is interesting to note that in one study at least (Hintsanen et al. 2005), an association between job strain and the extent of early and nonsymptomatic atherosclerosis was evident in both young men and women.

Metabolic Syndrome

An interesting and recent extension of this work focuses on OS and the metabolic syndrome (Melamed et al. 2006). Diagnosis of metabolic syndrome, which has been reliably linked with CVD risk (Salsberry et al. 2007) is defined by obesity (waist circumference) along with any two of elevated triglycerides, low HDL levels, hypertension, and elevated plasma glucose (Hildrum et al. 2007). Job strain is strongly associated with rates of metabolic syndrome, and this relationship

appears to follow a dose-response function (Chandola et al. 2006). A study of working hours among Japanese men also indicated a clear relationship between work intensity and the existence of metabolic syndrome (Kobayashi et al. 2012). However, not all evidence has unequivocally supported the link. Women with low long-term job strain were reported to have high levels of metabolic syndrome, whereas men with high long-term job strain showed low levels of metabolic syndrome (Kinnunen et al. 2006). Hwang and Lee (2014) also reported gender discrepancies in relationships between OS and levels of metabolic syndrome. High OS and risk perception predicted the metabolic syndrome in men, whereas low OS and low social support appeared to be more important in predicting the metabolic syndrome in women. And at least one recent study found no relationship between job strain (OS) and metabolic syndrome (Demiral et al. 2006). This area must therefore be considered to require further exploration, but it is exploration worth pursuing given the promise of metabolic syndrome as a predictor of CVD.

Fibrinogen

While the evidence here is by no means uncontested, plasma fibrinogen has been implicated as a predictor of CVD (Woodward et al. 2007), and it has been suggested that this too may mediate a link between OS and CVD risk (Theorell 2002). A number of well-conducted studies have indeed reported associations between plasma fibrinogen and low job control generally (Clays et al. 2005), low job control in female workers only (Tsutsumi et al. 1999), job strain in males but not females (Kittel et al. 2002), and both occupational burnout in women and occupation-related depression in men (Toker et al. 2005). Unsupportive evidence however (Alfredsson et al. 2002) indicates that some caution needs to be exercised in regard to OS and fibrinogen until further corroborative evidence is available.

Occupational Stress and Incidence of Clinical CVD

Both the demand/control (Theorell and Karasek 1996) and effort/reward imbalance (Siegrist 2005; van Vegchel et al. 2005) models of OS have figured prominently in studies of OS and clinical CVD, and the evidence linking both to clinical CVD is impressive. Largely atheoretical constructs have also driven many studies in this area, and while the evidence is somewhat more difficult to interpret unequivocally, it is also persuasive. And both case-control and prospective studies are available in support of the view that OS directly relates to CVD morbidity and mortality.

Case-Control Studies (Theoretically Based)

An early study utilizing job strain as the index of OS in the workplace found it to be related to a significant elevation in clinical CVD incidence among middle-aged

men, independent of other CVD risk factors (Alfredsson and Theorell 1983); a strenuous occupation also elevated CVD risk. Evidence of a synergistic interaction between demands and decision latitude further strengthened associations between job strain and clinical CVD risk (Hallqvist et al. 1998). A more recent study of job strain strongly associated it with heart disease in a large sample of men, again independent of other CVD risk factors; however, heart disease as a clinical end-point here was largely self-reported (Sacker et al. 2001). The relationship, however, was also evident in a sample of men who had survived a clinically diagnosed CVD event (Malinauskiene et al. 2005). Overcommitment to work, the intrinsic part of effort/reward imbalance, was strongly related to the likelihood of clinical CVD in women occupying male-dominated jobs (Peter et al. 2006). And interestingly, recent work suggests that a combination of the demand/control and effort/reward imbalance models even further strengthens the capacity of OS to predict clinical events of CVD (Peter et al. 2002).

Case-Control Studies (Atheoretical)

Chronic high workload arising from the structural characteristics of the occupational situation has long been associated with the prevalence of clinical CVD (Siegrist et al. 1982). So too has both shift work and monotonous work (Alfredsson et al. 1982), but not hectic work unless it was also associated with low decision latitude in the workplace. The causal significance of shift work for CVD risk has, however, been queried (Frost et al. 2009). Self-reported OS, again focusing on the workplace structure, significantly predicted risk of clinical CVD in a large sample of patients having experienced their first clinical event (Panagiotakos et al. 2003). And general but essentially work-related life events were reported to act as "triggers" to the onset of a clinical episode of CVD in middle-aged men and women (Moller et al. 2005). Moreover, the experience of unfairness in the workplace has been linked with an elevated risk of clinical incidents of CVD (De Vogli et al. 2007).

Prospective Studies (Theoretically Based)

While prospective studies are clearly more difficult to conduct than retrospective or case-control studies, and they therefore appear less frequently in the literature, they are crucial to exploring hypothesized links between OS and clinical CVD since they give greater insights into possible causality than other research designs (Kivimaki et al. 2006a). In that light, Lee et al. (2002) found no evidence to causally associate job strain with the emerging incidence of clinical CVD in a large sample of women followed over 4 years. By contrast, a more than 25-year follow-up of a large and initially healthy sample of both men and women found OS, evident as both job strain and effort/reward imbalance, to significantly predict risk of CVD mortality (Kivimaki et al. 2002). High demand and low decision latitude also predicted the

incidence of clinical CVD, again in a large sample of both men and women free from CVD at outset and followed over 11 years (Kuper and Marmot 2003). And in a large general population cohort ($N = 6070$) of Swedish men followed over several decades, OS (again conceptualized and measured as job strain) clearly predicted CVD risk – but not risk of stroke (Toren et al. 2014). In women, job strain has been linked to progression of coronary atherosclerosis over a 3-year period (Wang et al. 2007), and while atherosclerosis does not constitute a clinical event of CVD, it is a clear precursor of that outcome.

Prospective Studies (Atheoretical)

A prospective study examining job dissatisfaction as an index of OS found it to be only slightly associated with age-adjusted CVD risk in men but not in women, and there was no evidence linking it with increased CVD mortality over time in either men or women (Heslop et al. 2002). An examination of high perceived justice in the workplace, however, tied this to a lower risk of incident CVD in a large sample of men followed up over more than 8 years (Kivimaki et al. 2005).

Conclusions

This has been a selective review, and it has focused largely (though not exclusively) on published research material from the past 15 years. Moreover, the review is essentially descriptive – formal comparative procedures such as meta-analyses have not been used. Nonetheless, a large volume of empirical evidence from well-conducted studies with robust research designs can be brought to bear on the issue of OS and CVD. Studies relating OS and CVD risk factors are particularly supportive of a link, albeit an indirect one, between OS and ultimate clinical CVD – and evidence focusing on BP and hypertension is strong in this regard. Evidence from both case-control and prospective studies also persuasively supports a link between OS and clinical events of CVD, though prospective studies are understandably fewer in number since they are more logistically difficult to undertake. Both the demand/control (job strain) and effort/reward imbalance models appear to offer powerful conceptual frameworks linking OS with CVD, and incorporating a combination of the two into research designs achieves useful synergies in predicting CVD. However, even atheoretical approaches provide convincing evidence of a link between OS and CVD. Therefore, while additional prospective evidence based on one (or both) of the existing theoretical models would be useful, the collective evidence now available must be viewed as sufficiently consistent and robust to support the very clear conclusion that OS is causally linked, either indirectly or directly, with CVD.

This being so, the next generation of research may well need to focus on interventions to reduce OS in the workplace (Nieuwenhuijsen et al. 2010), either through strategies targeted at individual workplace behaviors or on efforts to

modify the workplace itself to reduce those structural and organizational factors predisposing to OS. There is already emerging evidence that targeted interventions to reduce OS in the workplace have utility to achieve stress reduction (Werneburg et al. 2011) though nothing yet which bears on the extension of this finding to reductions in CVD risk. Speculation suggests that the overall result may be modest (Kivimaki et al. 2012). But to effectively demonstrate the role of OS reduction in reducing risk of CVD, future intervention-based research must of necessity involve longitudinal studies of large samples, diverse in regard to occupational status, age, and gender. That research must also apply theoretically driven strategies of psychological intervention based on the best available overall evidence demonstrating the therapeutic effectiveness of those strategies. And almost inevitably this work will need to address the legal and political realm of industrial relations. However, the provision of a fully safe workplace – now mandated in a growing number of countries – needs to encompass freedom from OS, and if this achieves an effective lowering of CVD risk in the working population, it is a freedom well worth seeking.

References

Albertsen, K., Borg, V., & Oldenburg, B. (2006). A systematic review of the impact of work environment on smoking cessation, relapse and amount smoked. *Preventive Medicine, 43*(4), 291–305.

Alfredsson, L., & Theorell, T. (1983). Job characteristics of occupations and myocardial infarction risk: Effect of possible confounding factors. *Social Science and Medicine, 17*(20), 1497–1503.

Alfredsson, L., Karasek, R., & Theorell, T. (1982). Myocardial infarction risk and psychosocial work environment: An analysis of the male Swedish working force. *Social Science and Medicine, 16*, 463–467.

Alfredsson, L., Hammar, N., Fransson, E., de Faire, U., Hallqvist, J., Knutsson, A., et al. (2002). Job strain and major risk factors for coronary heart disease among employed males and females in a Swedish study on work, lipids and fibrinogen. *Scandinavian Journal of Work, Environment and Health, 28*(4), 238–248.

Bishop, G. D., Enkelmann, H. C., Tong, E. M. W., Why, Y. P., Diong, S. M., Ang, J., et al. (2003). Job demands, decisional control, and cardiovascular responses. *Journal of Occupational Health Psychology, 8*(2), 146–156.

Bolm-Audorff, U., & Siegrist, J. (1983). Occupational morbidity data in myocardial infarction. *Journal of Occupational Medicine, 25*(5), 367–371.

Bongard, S., & al'Absi, M. (2005). Domain-specific anger expression and blood pressure in an occupational setting. *Journal of Psychosomatic Research, 58*(1), 43–49.

Bosma, H., Peter, R., Siegrist, J., & Marmot, M. (1998). Two alternative job stress models and the risk of coronary heart disease. *American Journal of Public Health, 88*(1), 68–74.

Byrne, D. G. (2000). The frustration of success: Type A behavior, occupational stress and cardiovascular disease. In D. T. Kenny, J. G. Carlson, F. J. McGuigan, & J. L. Sheppard (Eds.), *Stress and health. Research and clinical applications*. Amsterdam: Harwood Academic Publishers.

Byrne, D. G., & Mazanov, J. (2008). Personality, stress and the determination of smoking behaviour in adolescents. In G. Boyle, G. Matthews, & D. Saklofske (Eds.), *Handbook of personality theory and testing*. London: Sage.

Campbell, C. Y., Nasir, K., Sarwar, A., Meneghelo, R. S., Carvalho, J. A., Blumenthal, R. S., et al. (2007). Combined effect of high low-density lipoprotein cholesterol and metabolic

syndrome on subclinical coronary atherosclerosis in white men without clinical evidence of myocardial ischemia. *American Journal of Cardiology, 100*(5), 840–843.

Carlsson, R. H., Hansen, A. M., Kristiansen, J., Nielsen, M. L., Blond, M., & Netterstron, B. (2014). Workplace reorganization and changes in physiological stress markers. *Occupational Medicine and Health Affairs, 2*(1), 148. doi:10.4172/2329-6879.1000148.

Cesana, G., Sega, R., Ferrario, M., Chiodini, P., Corrao, G., & Mancia, G. (2003). Job strain and blood pressure in employed men and women: A pooled analysis of four northern Italian population samples. *Psychosomatic Medicine, 65*, 558–563.

Chandola, T., Brunner, E., & Marmot, M. (2006). Chronic stress at work and the metabolic syndrome: Prospective study. *British Medical Journal, 332*(7540), 521–525.

Clays, E., De Bacquer, D., Delanghe, J., Kittel, F., Van Renterghem, L., & De Backer, G. (2005). Associations between dimensions of job stress and biomarkers of inflammation and infection. *Journal of Occupational & Environmental Medicine, 47*(9), 878–883.

De Vogli, R., Ferrie, J. E., Chandola, T., Kivimaki, M., & Marmot, M. G. (2007). Unfairness and health: Evidence from the Whitehall II study. *Journal of Epidemiology and Community Health, 61*(6), 513–518.

Demiral, Y., Soysal, A., Can Bilgin, A., Kilic, B., Unal, B., Ucku, R., et al. (2006). The association of job strain with coronary heart disease and metabolic syndrome in municipal workers in Turkey. *Journal of Occupational Health, 48*(5), 332–338.

Din-Dzietham, R., Nembhard, W. N., Collins, R., & Davis, S. K. (2004). Perceived stress following race-based discrimination at work is associated with hypertension in African-Americans. The Metro Atlanta Heart Disease Study, 1999–2001. *Social Science and Medicine, 58*(3), 449–461.

Djindjic, N., Jovanovic, J., Djindjic, B., Jovanovic, M., & Jovanovic, J. J. (2012). Associations between the Occupational Stress Index and hypertension, type 2 diabetes mellitus, and lipid disorders in middle-aged men and women. *Annals of Occupational Hygiene, 56*(9), 1051–1062.

Dolezsar, C. M., McGrath, J. J., Herzig, J. J. M., & Miller, S. B. (2014). Perceived racial discrimination and hypertension: A comprehensive systematic review. *Health Psychology, 33*(1), 20–34.

Fan, L.-B., Blumenthal, J. A., Hinderliter, A. L., & Sherwood, A. (2013). The effect of job strain on nighttime blood pressure dipping among men and women with high blood pressure. *Scandinavian Journal of Work and Environmental Health, 39*(1), 112–119.

French, J. R. P., & Caplan, R. D. (1970). Psychosocial factors in coronary heart disease. *Industrial Medicine and Surgery, 39*(9), 31–45.

French, J. R. P., Caplan, R. D., & Harrison, R. V. (1982). *The mechanisms of job stress and strain*. London: Wiley.

Frost, P., Kolstad, H. A., & Bonde, J. P. (2009). Shift work and the risk of ischemic heart disease – A systematic review of the epidemiological evidence. *Scandinavian Journal of Work and Environmental Health, 35*(3), 163–179.

Greiner, B. A., Krause, N., Ragland, D., & Fisher, J. M. (2004). Occupational stressors and hypertension: A multi-method study using observer-based job analysis and self-reports in urban transit operators. *Social Science and Medicine, 59*(5), 1081–1094.

Guimont, C., Brisson, C., Dagenais, G. R., Milot, A., Vezina, M., Masse, B., et al. (2006). Effects of job strain on blood pressure: A prospective study of male and female white collar workers. *American Journal of Public Health, 96*(8), 1436–1443.

Hallqvist, J., Diderichsen, F., Theorell, T., Reuterwall, C., Ahlbom, A., & Sheep Study Group. (1998). Is the effect of job strain on myocardial infarction risk due to interaction between high psychological demands and low decision latitude? Results from Stockholm Heart Epidemiology Program (SHEEP). *Social Science and Medicine, 46*(11), 1405–1415.

Hausser, J. A., Mojzisch, A., Niesel, M., & Schulz-Hardt, S. (2010). Ten years on: A review of recent research on the Job Demand-Control (Support) model and psychological well-being. *Work and Stress, 24*(1), 1–35.

Haynes, S. G., Feinleib, M., Levine, S., Scotch, N., & Kannel, W. B. (1978). The relationship of psychosocial factors to coronary heart disease in the Framingham study. I. Methods and risk factors. *American Journal of Epidemiology, 107*(5), 362–381.

Heslop, P., Smith, G. D., Metcalfe, C., Macleod, J., & Hart, C. (2002). Change in job satisfaction, and its association with self-reported stress, cardiovascular risk factors and mortality. *Social Science and Medicine, 54*, 1589–1599.

Hildrum, B., Mykletun, A., Hole, T., Midthjell, K., & Dahl, A. A. (2007). Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: The Norwegian HUNT 2 study. *BMC Public Health, 7*(1), 220.

Hintsanen, M., Kivimaki, M., Elovainio, M., Pulkki-Raback, L., Keskivaara, P., Juonala, M., et al. (2005). Job strain and early atherosclerosis: The cardiovascular risk in young Finns study. *Psychosomatic Medicine, 67*, 740–747.

Hwang, W. J., & Lee, C. L. (2014). Effect of psychosocial factors on metabolic syndrome in male and female blue collar workers. *Japan Journal of Nursing Science, 11*, 23–34.

John, U., Riedel, J., Rumpf, H. J., Hapke, U., & Meyer, C. (2006). Associations of perceived work strain with nicotine dependence in a community sample. *Occupational & Environmental Medicine, 63*(3), 207–211.

Johnson, J. V., & Hall, E. M. (1988). Job strain, workplace social support and cardiovascular disease: A cross-sectional study of a random sample of the Swedish working population. *American Journal of Public Health, 78*(10), 1336–1342.

Jonsson, D., Johansson, S., Rosengren, A., Lappas, G., & Wilhelmsen, L. (2003). Self-perceived psychological stress in relation to psychosocial factors and work in a random population sample of women. *Stress and Health, 19*(3), 149–162.

Karasek, R., & Theorell, T. (1990). *Healthy work*. New York: Basic Books.

Kinnunen, M. L., Feldt, T., Kinnunen, U., Kaprio, J., & Pulkkinen, L. (2006). Association between long-term job strain and metabolic syndrome factor across sex and occupation. *Journal of Individual Differences, 27*(3), 151–161.

Kittel, F., Leynen, F., Stam, M., Dramaix, M., de Smet, P., Mak, R., et al. (2002). Job conditions and fibrinogen in 14 226 Belgian workers. The Belstress study. *European Heart Journal, 23*, 1841–1848.

Kivimaki, M., Leino-Arjas, P., Luukkonen, R., Riihimaki, H., Vahtera, J., & Kirjonen, J. (2002). Work stress and risk of cardiovascular mortality: Prospective cohort study of industrial employees. *British Medical Journal, 325*(7369), 857–861.

Kivimaki, M., Ferrie, J. E., Brunner, E., Head, J., Shipley, M. J., Vahtera, J., et al. (2005). Justice at work and reduced risk of coronary heart disease among employees: The Whitehall II Study. *Archives of Internal Medicine, 165*(19), 2245–2251.

Kivimaki, M., Head, J., Ferric, J. E., Brunner, E., Marmot, M. G., Vahtera, J., et al. (2006a). Why is evidence on job strain and coronary heart disease mixed? An illustration of measurement challenges in the Whitehall II study. *Psychosomatic Medicine, 68*, 398401.

Kivimaki, M., Nyberg, S. T., Batty, G. D., Fransson, E. I., Heikkila, K., Alfredsson, L., IDP-Work Consortium, et al. (2012). *The Lancet, 380*, 1491–1497.

Kobayashi, T., Suzuki, E., Takao, S., & Doi, H. (2012). Long working hours and metabolic syndrome among Japanese men: A cross-sectional study. *BMC Public Health, 12*, 395. doi:10.1186/1471-2458-12-395.

Kornitzer, M., Kittel, F., Debacker, G., & Dramaix, M. (1981). The Belgian heart disease prevention project: Type A behavior pattern and the prevalence of coronary heart disease. *Psychosomatic Medicine, 43*(2), 133–145.

Kouvonen, A., Kivimaki, M., Virtanen, M., Pentti, J., & Vahtera, J. (2005). Work stress, smoking status, and smoking intensity: An observational study of 46, 190 employees. *Journal of Epidemiology and Community Health, 59*(1), 63–69.

Kouvonen, A., Vahtera, J., Elovainio, M., Cox, S. J., Cox, T., Linna, A., et al. (2007). Organisational justice and smoking: The Finnish public sector study. *Journal of Epidemiology and Community Health, 61*(5), 427–433.

Kuper, H., & Marmot, M. (2003). Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study. *Journal of Epidemiology and Community Health, 57*, 147–153.

Kuper, H., Marmot, M., & Hemingway, H. (2002). Systemic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. *Seminars in Vascular Medicine, 2*(3), 267–314.

Landsbergis, P. A., Schnall, P. L., Pickering, T. G., Warren, K., & Schwartz, J. E. (2003). Lower socioeconomic status among men in relation to the association between job strain and blood pressure. *Scandinavian Journal of Work, Environment and Health, 29*(3), 206–215.

Lazarus, R. S. (1966). *Psychological stress and the coping process*. New York: McGraw Hill.

Lee, S., Colditz, G., Berkman, L., & Kawachi, L. (2002). A prospective study of job strain and coronary heart disease in US women. *International Journal of Epidemiology, 31*(6), 1147–1153.

Leone, A. (2007). Smoking, haemostatic factors, and cardiovascular risk. *Current Pharmaceutical Design, 13*(16), 1661–1667.

Levenstein, S., Smith, M. W., & Kaplan, G. A. (2001). Psychosocial predictors of hypertension in men and women. *Archives of Internal Medicine, 161*(10), 1341–1346.

Levi, L. (1972). *Stress and distress in response to psychosocial stimuli: Laboratory and real-life studies on sympatho-adrenomedullary and related reactions*. Oxford: Pergamon Press.

Liljefors, I., & Rahe, R. H. (1970). An identical twin study of psychosocial factors in coronary heart disease in Sweden. *Psychosomatic Medicine, 32*(5), 523–542.

Malinauskiene, V., Theorell, T., Grazuleviciene, R., Azaraviciene, A., Obelenis, V., & Azelis, V. (2005). Psychosocial factors at work and myocardial infarction among men in Kaunas, Lithuania. *Scandinavian Journal of Work, Environment and Health, 31*(3), 218–223.

Melamed, S., Shirom, A., Toker, S., Berliner, S., & Shapira, I. (2006). Burnout and risk of cardiovascular disease: Evidence, possible causal paths, and promising research directions. *Psychological Bulletin, 132*(3), 327–353.

Metcalfe, C., Smith, G. D., Wadsworth, E., Sterne, J. A. C., Heslop, P., Macleod, J., et al. (2003). A contemporary validation of the Reeder Stress Inventory. *British Journal of Health Psychology, 8*(1), 83–94.

Ming, E. E., Adler, G. K., Kessler, R. C., Fogg, L. F., Matthews, K. A., Herd, J. A., et al. (2004). Cardiovascular reactivity to work stress predicts subsequent onset of hypertension: The Air Traffic Controller Health Change Study. *Psychosomatic Medicine, 66*(4), 459–465.

Moller, J., Theorell, T., de Faire, U., Ahlbom, A., & Hallqvist, J. (2005). Work related stressful life events and the risk of myocardial infarction. Case-control and case-crossover analyses within the Stockholm heart epidemiology programme (SHEEP). *Journal of Epidemiology and Community Health, 59*, 23–30.

Ng, D. M., & Jeffery, R. W. (2003). Relationships between perceived stress and health behaviors in a sample of working adults. *Health Psychology, 22*(6), 638–642.

Nieuwenhuijsen, K., Bruinvels, D., & Frings-Dresen, M. (2010). Psychosocial work environment and stress-related disorders, a systematic review. *Occupational Medicine, 60*, 277–286.

O'Connor, D. B., O'Connor, R. C., White, B. L., & Bundred, P. E. (2001). Are occupational stress levels predictive of ambulatory blood pressure in British GP's? An exploratory study. *Family Practice, 18*(1), 92–94.

Ohlin, B., Berglund, G., Nilsson, P. M., & Melander, O. (2007). Job strain, decision latitude and alpha2B-adrenergic receptor polymorphism significantly interact, and associate with higher blood pressure in men. *Journal of Hypertension, 25*(8), 1613–1619.

Panagiotakos, D. B., Chrysohoou, C., Pitsavos, C., Antoniou, S., Vavouranakis, E., Stravopodis, P., et al. (2003). The association between occupational stress and the risk of developing acute coronary syndromes: The CARDI02000 Study. *Central European Journal of Public Health, 11*(1), 25–30.

Peter, R., & Siegrist, J. (1997). Chronic work stress, sickness absence, and hypertension in middle managers: General or specific sociological explanations? *Social Science and Medicine, 45*(7), 1111–1120.

Peter, R., Alfredsson, L., Hammar, N., Siegrist, J., Theorell, T., & Westerholm, P. (1998). High effort, low reward, and cardiovascular risk factors in employed Swedish men and women: Baseline results from WOLF study. *Journal of Epidemiology and Community Health, 52*, 540–547.

Peter, R., Alfredsson, L., Knutsson, A., Siegrist, J., & Westerholm, P. (1999). Does a stressful psychosocial work environment mediate the effects of shift work on cardiovascular risk factors? *Scandinavian Journal of Work, Environment and Health, 25*(4), 376–381.

Peter, R., Siegrist, J., Hallqvist, J., Reuterwall, C., & Theorell, T. (2002). Psychosocial work environment and myocardial infarction: Improving risk estimation by combining two complementary job stress models in the SHEEP study. *Journal of Epidemiology and Community Health, 56*, 294–300.

Peter, R., Hammarstrom, A., Hallqvist, J., Siegrist, J., & Theorell, T. (2006). Does occupational gender segregation influence the association of effort-reward imbalance with myocardial infarction in the SHEEP study? *International Journal of Behavioral Medicine, 13*(1), 34–43.

Preis, S. R., Hwang, S.-J., Coady, S., Pencina, M. J., D'Agostino, R. B., Savage, P. J., Levy, D., & Fox, C. S. (2009). Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation, 119*, 1728–1735.

Radi, S., Lang, T., Lauwers-Cances, V., Diene, E., Chatellier, G., Larabi, L., et al. (2005). Job constraints and arterial hypertension: Different effects in men and women: The IHPAF II case control study. *Occupational & Environmental Medicine, 62*(10), 711–717.

Rau, R., Georgiades, A., Fredrikson, M., Lemne, C., & de Faire, U. (2001). Psychosocial work characteristics and perceived control in relation to cardiovascular rewind at night. *Journal of Occupational Health Psychology, 6*(3), 171–181.

Riese, H., Van Doormen, I. L., Houtman, L. J., & De Geus, E. J. C. (2000). Job strain and risk indicators for cardiovascular disease in young female nurses. *Health Psychology, 19*(5), 429–440.

Rose, G., Kumlin, L., Dimberg, L., Bengtsson, C., Orth-Gomer, K., & Cai, X. (2006). Work-related life events, psychological well-being and cardiovascular risk factors in male Swedish automotive workers. *Occupational Medicine, 56*(6), 386–392.

Rosenman, R. H. (1990). Type A behavior pattern: A personal overview. *Journal of Social Behavior and Personality, 5*(1), 1–24.

Russek, H. L. (1965). Stress, tobacco, and coronary disease in North American professional groups; survey of 12,000 men in 14 occupational groups. *Journal of the American Medical Association, 192*, 89–94.

Sacker, A., Bartley, M. J., Frith, D., Fitzpatrick, R. M., & Marmot, M. G. (2001). The relationship between job strain and coronary heart disease: Evidence from an English sample of the working male population. *Psychological Medicine, 31*, 279–290.

Salsberry, P. J., Corwin, E., & Reagan, P. B. (2007). A complex web of risks for metabolic syndrome race/ethnicity, economics, and gender. *American Journal of Preventive Medicine, 33*(2), 114–120.

Siegrist, J. (2005). Social reciprocity and health: New scientific evidence and policy implications. *Psychoneuroendocrinology, 30*, 1033–1038.

Siegrist, J., & Klein, D. (1990). Occupational stress and cardiovascular reactivity in blue-collar workers. *Work and Stress, 4*(4), 295–304.

Siegrist, J., & Marmot, M. (2004). Health inequalities and the psychosocial environment – Two scientific challenges. *Social Science and Medicine, 58*, 1463–1473.

Siegrist, J., & Rodel, A. (2006). Work stress and health risk behavior. *Scandinavian Journal of Work, Environment and Health, 32*(6), 473–481.

Siegrist, J., Dittmann, K., Rittner, K., & Weber, L. (1982). The social context of active distress in patients with early myocardial infarction. *Social Science and Medicine, 16*, 443–453.

Siegrist, J., Matschinger, H., Cremer, P., & Seidel, D. (1988). Atherogenic risk in men suffering from occupational stress. *Atherosclerosis, 69*(2–3), 211–218.

Steptoe, A., Siegrist, J., Kirschbaum, C., & Marmot, M. (2004). Effort-reward imbalance, overcommitment, and measures of cortisol and blood pressure over the working day. *Psychosomatic Medicine, 66*, 323–329.

Su, C. T., Yang, H. J., Lin, C. F., Tsai, M. C., Shieh, Y. H., & Chiu, W. T. (2001). Arterial blood pressure and blood lipids as cardiovascular risk factors and occupational stress in Taiwan. *International Journal of Cardiology, 81*, 181–187.

Suwazono, Y., Dochi, M., Sakata, K., Okubo, Y., Oishi, M., Tanaka, K., Kobayashi, E., & Nogawa, K. (2008). Shift work is a risk factor for increased blood pressure in Japanese men: A 14-year historical cohort study. *Hypertension, 52*, 581–586.

Theorell, T. (2002). Job stress and fibrinogen. *European Heart Journal, 23*, 1799–1801.

Theorell, T. (2003). To be able to exert control over one's own situation: A necessary condition for coping with stressors. In J. C. Quick & L. E. Tetrick (Eds.), *Handbook of occupational health psychology* (pp. 201–219). Washington, DC: American Psychological Association.

Theorell, T., & Karasek, R. A. (1996). Current issues relating to psychosocial job strain and cardiovascular disease research. *Journal of Occupational Health Psychology, 1*(1), 9–26.

Theorell, T., de Faire, U., Johnson, J., & Hall, E. (1991). Job strain and ambulatory blood pressure profiles. *Scandinavian Journal of Work, Environment and Health, 17*(6), 380–385.

Theorell, T., Ahlberg-Hulten, G., Jodko, M., & Sigala, F. (1993). Influence of job strain and emotion on blood pressure in female hospital personnel during workhours. *Scandinavian Journal of Work, Environment and Health, 19*(5), 313–318.

Theorell, T., Alfredsson, L., Westerholm, P., & Falck, B. (2000). Coping with unfair treatment at work – What is the relationship between coping and hypertension in middle-aged men and women? *Psychotherapy and Psychosomatics, 69*(2), 86–94.

Toker, S., Shirom, A., Shapira, I., Berliner, S., & Melamed, S. (2005). The association between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women. *Journal of Occupational Health Psychology, 10*(4), 344362.

Toren, K., Schioler, L., Giang, W. K., Novak, M., & Soderberg, M. (2014). A longitudinal general population-based study of job strain and risk for coronary heart disease and stroke in Swedish men. *BMJ Open, 4*, e004355. doi:10.1136/bmjopen-2013-oo4355.

Tsutsumi, A., Tsutsumi, K., Kayaba, K., Theorell, T., Nago, N., Kario, K., et al. (1998). Job strain and biological coronary risk factors: A cross-sectional study of male and female workers in a Japanese rural district. *International Journal of Behavioral Medicine, 5*(4), 295–311.

Tsutsumi, A., Theorell, T., Hallqvist, J., Reuterwall, C., & de Faire, U. (1999). Association between job characteristics and plasma fibrinogen in a normal working population: A cross sectional analysis in referents of the SHEEP study. *Journal of Epidemiology and Community Health, 53*, 348–354.

Tsutsumi, A., Kayaba, K., Tsutsumi, K., Igarashi, M., & Jichi Medical School Cohort Study Group. (2001). Association between job strain and prevalence of hypertension: A cross-sectional analysis in a Japanese working population with a wide range of occupations: The Jichi Medical School cohort study. *Occupational & Environmental Medicine, 58*(6), 367–373.

Tsutsumi, A., Kayaba, K., Yoshimura, M., Sawada, M., Ishikawa, S., Sakai, K., et al. (2003). Association between job characteristics and health behaviors in Japanese rural workers. *International Journal of Behavioral Medicine, 10*(2), 125–142.

van Vegchel, N., de Jonge, J., Bosma, H., & Schaufeli, W. (2005). Reviewing the effort-reward imbalance model: Drawing up the balance of 45 empirical studies. *Social Science and Medicine, 60*, 1117–1131.

Wamala, S. P., Mittleman, M. A., Horsten, M., Schenck-Gustafsson, K., & Orth-Gomer, K. (2000). Job stress and the occupational gradient in coronary heart disease risk in women. The Stockholm Female Coronary Risk Study. *Social Science and Medicine, 51*, 481–489.

Wang, H. X., Leineweber, C., Kirkeeide, R., Svane, B., Schenck-Gustafsson, K., Theorell, T., et al. (2007). Psychosocial stress and atherosclerosis: Family and work stress accelerate progression of coronary disease in women. The Stockholm Female Coronary Angiography Study. *Journal of Internal Medicine, 261*(3), 245–254.

Werneburg, B. L., Herman, L. L., Preston, H. R., Rausch, S. M., Warren, B. A., Olsen, K. D., & Clark, M. M. (2011). Effectiveness of a multidisciplinary worksite stress reduction programme for women. *Stress and Health, 27*, 356–364.

Westerlund, H., Theorell, T., & Alfredsson, L. (2004). Organizational instability and cardiovascular risk factors in white-collar employees. *European Journal of Public Health, 14*, 37–42.

Weycker, D., Nichols, G. A., O'Keefe-Rosetti, M., Edelsberg, J., Khan, Z. M., Kaura, S., et al. (2007). Risk-factor clustering and cardiovascular disease risk in hypertensive patients. *American Journal of Hypertension, 20*(6), 599–607.

Wiernik, E., Pannier, B., Czernochow, S., Nabi, H., Hanon, O., Tabassome, S., Simon, T., Simon, J.-M., Thomas, F., Bean, K., Consoli, S. M., Danchin, N., & Lemogne, C. (2013). Occupational status moderates the association between current perceived stress and high blood pressure: Evidence from the IPC Cohort Study. *Hypertension, 61*, 571–577.

Woodward, M., Rumley, A., Welsh, P., MacMahon, S., & Lowe, G. (2007). A comparison of the associations between seven hemostatic or inflammatory variables and coronary heart disease. *Journal of Thrombosis and Haemostasis, 5*(9), 1795–1800.

Yang, H., Schnall, P. L., Jaurequi, M., Su, T. C., & Baker, D. (2006). Work hours and self-reported hypertension among working people in California. *Hypertension, 48*(4), 744–750.

Yarnell, J. (2008). Stress at work – An independent risk factor for coronary disease? *European Heart Journal, 29*, 579–580.

Disorders of Sleep and Cardiovascular Disease

Matthew T. Naughton

Contents

M.T. Naughton (✉)
Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Monash University, Melbourne, VIC, Australia
e-mail: m.naughton@alfred.org.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_20

Abstract

Despite decades of effort, one of the greatest mysteries in biology is to understand sleep. Sleep is more than simply rest. Depriving someone of sleep has powerful adverse effects on their mental, metabolic, and cardiovascular health. The timing of sleep also plays an important role in terms of the onset of cardiovascular events. Finally, the effects of sleep on ventilation and the downstream effects of sleep apnea in the pathogenesis of all cardiovascular conditions have come of age in the evidence-based medicine field.

Keywords

Sleep • Apnea • Mood • Cardiovascular disease

Introduction

Disorders of sleep, mood, and associated cardiovascular disorders are common and the interaction is quite complex. It is estimated that a disturbance of sleep is an extremely common symptom in relation to most cardiovascular illnesses and psychological and psychiatric conditions. This chapter will outline normal sleep, insomnia, hypersomnia, and obstructive sleep apnea (OSA). Thereafter, the chapter will focus on common cardiovascular conditions which interact with OSA, namely, systemic hypertension, atrial fibrillation, ischemic heart disease, and heart failure. Finally, the interaction between heart failure and central sleep apnea (also known as Cheyne–Stokes respiration) will also be discussed.

Normal Sleep

Sleep is a ubiquitous phenomenon in all animal species involving recurring, partial disengagement from the surrounding environment, reduced sensory input, and generally decreased energy expenditure. In mammals, existence occurs in three states, wakefulness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. Each of these states has its own distinct neuroanatomic, neurophysiologic, and neuropharmacologic mechanisms and behavioral features.

Many cardiopulmonary functions reduce during sleep (e.g., stroke volume, heart rate, minute volume of ventilation all fall by ~20 %) secondary to sympathetic withdrawal and parasympathetic dominance, as depicted by heart rate variability (see Table 1 (Trinder et al. 2001)) in addition to a 1 °C drop in temperature. In contrast, immune function (Majde and Krueger 2005), hormone release (growth

Table 1 Blood pressure, heart rate, and heart rate variability (mean (SD)) in healthy patients while awake, and stage 2, slow-wave, and rapid eye movement sleep (From Trinder et al. (2001))

	Wake	Stage 2	Slow-wave sleep	REM
SBP	108(13)	104(12)	109(13)	94(13)
DBP	56(8)	55(13)	57(7)	48(7)
Heart rate	64(13)	57(10)	58(10)	60(10)
High frequency	72(56)	186(161)	184(177)	126(112)
Low frequency	141(105)	122(86)	80(61)	209(177)

hormone and cortisol), and protein synthesis become activated. Memory is also highly reliant upon sleep (Stickgold 2005).

Considerable variation exists in the "normal" amount of sleep required. It has been estimated that prior to the widespread availability of electricity in the 1890s (and when physical labor was commonplace), 9–10 h sleep per night was the norm. Currently, 7–8 h appears to be considered "the norm" due to greater "electrical" and Internet connectivity. Combined with a more sedentary lifestyle, sleep quality and quantity have suffered.

The Glymphatic System

During wakefulness (especially prolonged wakefulness – i.e., sleep deprivation), neural metabolism results in several neurotoxins which build up in the brain's interstitial fluid. Examples of these toxins include β-amyloid, α-synuclein, and tau. Neurons are very sensitive to these toxins, and their products of degradation, which result in neural damage and conditions such as dementia. Therefore, it is crucial to have these toxic waste products of neural metabolism removed quickly and efficiently from the brain's interstitial space. However, in contrast to other bodily organs, the brain lacks a lymphatic system to clear toxins. Instead, it has a glymphatic system, which allows exchange between the CSF and interstitial fluid and thereby removes interstitial toxins. This exchange is controlled by astrocytic aquaporin-4 water channels. Deletion of these water channels impairs the clearance of toxins by 65 %. Wakefulness is associated with a much higher level of toxins compared with normal sleep. Recently, it has been shown that sleep activates these water channels, thereby increasing glymphatic clearance of toxins by up to 60 % (Xie et al. 2013).

Melatonin

The sleep/wake cycle is controlled predominantly in man by light. Sensed by the retina, light signal is relayed by the retinothalamic track to the suprachiasmatic nucleus (SCN) also known as the "biological clock" situated in the anterior hypothalamus. Neural pathways from the SCN lead to lateral hypothalamus (VLPO) and to the superior cervical ganglion (controller of sympathetic activity)

and then to the pineal gland which releases melatonin (Armstrong et al. 1986). Darkness results in the release of melatonin, whereas light suppresses melatonin release. This chain reaction with melatonin also controls three groups of neurons (thalamus–VLPO, hypothalamus, and pons) and their neurotransmitter release (Saper et al. 2005).

Flip-Flop Switch

Sleep is thought to be controlled by neurotransmitters released from the pons and hypothalamus which impact upon the thalamus and cerebral cortex. These neurons release γ-aminobutyric acid (GABA), orexin, monoamines (norepinephrine, histamine, serotonin, dopamine), and acetylcholine.

Wakefulness is characterized by orexin release from lateral hypothalamus which excites the locus coeruleus (noradrenaline), raphe (serotonin), and tuberomammillary nucleus (histamine) plus the reticular activating system (acetylcholine).

In contrast, non-REM sleep is characterized by heightened activity of the VLPO (release of GABA) which inhibits both lateral hypothalamus (orexin) and the locus coeruleus (noradrenaline), raphe (serotonin), and tuberomammillary nucleus (histamine).

REM sleep is characterized by activated cortex along with inhibition of muscle tone and arousals. Many of the central activating systems including the brainstem reticular formation are active during this state. Cholinergic neurons discharge at maximal rates during REM sleep. GABA release during REM is thought to inhibit the locus coeruleus and thereby inhibit motor activity during REM sleep.

The balance between wake and sleep and the interaction of neurotransmitters from the VLPO, pons, and hypothalamus have been described as a "flip-flop" switch (Saper et al. 2005). This has provided a framework upon which to assist understanding the complexities of neurotransmitters and sleep plus a basis to understand the mechanisms of alerting and sedating drugs.

Two-Process Model

Sleep is also regulated, theoretically, by a two-process model: namely, sleep pressure (process S) and a circadian process (process C) (Borbely 1982). Sleep deprivation is associated with an increased pressure for more sleep, but this pressure occurs when the circadian process allows (see Fig. 1). This helps to understand the adverse effects of accruing sleep debt over days.

Polysomnography

Sleep can be objectively measured by EEG, EMG, and EOG analysis from which REM and non-REM can be identified. REM sleep was identified and defined by

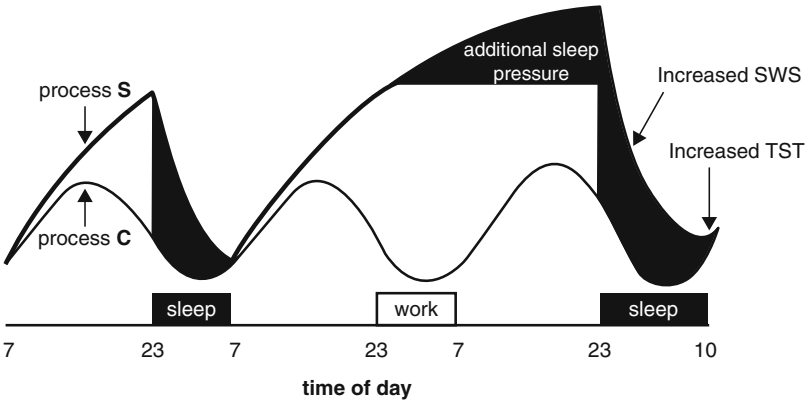


Fig. 1 Two-process model (Borbely 1982) to illustrate the natural circadian aspect of sleepiness (process C) with an additional accumulative sleep debt (process S) over three 24 h cycles. Note the accumulation of sleep debt and the impact upon increasing total sleep time (*TST*) and slow-wave sleep (*SWS*)

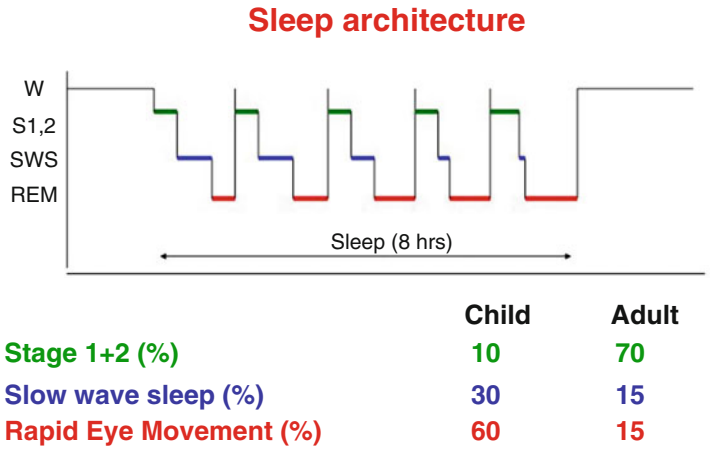


Fig. 2 Diagram of a typical sleep architecture. Note the cyclic nature of stages 1 and 2, slow-wave, and REM sleep, each cycle lasting about 1.5 h and four to five cycles per night. Note also the increased amount of REM in childhood compared with adults

Aserinsky and Kleitman in 1953 (Aserinsky and Kleitman 1953). Non-REM sleep can be further broken down to stage 1, stage 2, and stage 3 (slow-wave) sleep. REM sleep can be subdivided into phasic and tonic REM.

Under normal circumstances, there are four to five REM–non-REM cycles per night, usually 1.5 h each cycle. This cyclic REM–non-REM pattern is often described as the sleep architecture (Fig. 2). The amount of sleep per time of recording is the sleep efficiency.

Actigraphy

The timing of sleep within the 24 h cycle is called the circadian rhythm. In many developed countries, sleep is taken in one "dose" overnight, whereas in others it is taken in two parts: overnight and early afternoon (i.e., siesta). Indeed the latter siesta pattern is associated with a chronic low-grade overnight sleep deprivation, a common lifestyle pattern in developed world.

Measurement of circadian rhythm can be estimated from a sleep diary, usually over 7–14 days. Alternatively, measurement can be made objectively when a lightweight wrist actigraph is worn for 7–14 days. Actigraphy provides a reliable estimate of movement and light, from which circadian rhythm can be estimated (Fig. 3). For experimental situations, core temperature and serial plasma or salivary melatonin levels can also be used.

Disorders of Sleep

Introduction

Lack of sleep is extremely common. Reduced duration of sleep can result from choice (i.e., volitional), societal pressures (e.g., work or family commitments), or during times of illness (hospitalization in noisy environments). Fragmented or poor quality sleep can occur due to medical (e.g., arthritis, asthma, apnea), psychological (e.g., anxiety), or psychiatric disorders. Pharmaceutical drugs (antidepressants, beta blockers, narcotics, glucocorticoids), devices (pacemakers, dialysis), and interventions (e.g., ventilatory support in an intensive care unit) can result in marked derangement in sleep quality. Overall classification of sleep disorders can be summarized as follows:

1. Insomnia
2. Sleep-related breathing disorders
3. Hypersomnia
4. Circadian rhythm disorders
5. Parasomnias
6. Sleep-related movement disorders
7. Isolated sleep symptoms
8. Others

Sleep Deprivation

In rodents, experiments of sleep deprivation by Rechtschaffen and colleagues indicated that both REM and total sleep deprivation caused premature death 37 and 21 days, respectively (Rechtschaffen and Bergmann 2002; Rechtschaffen et al. 2002; Everson et al. 1989; Kushida et al. 1989). These short durations were preceded by elevations in epinephrine and norepinephrine, cortisol, and thyroxin,

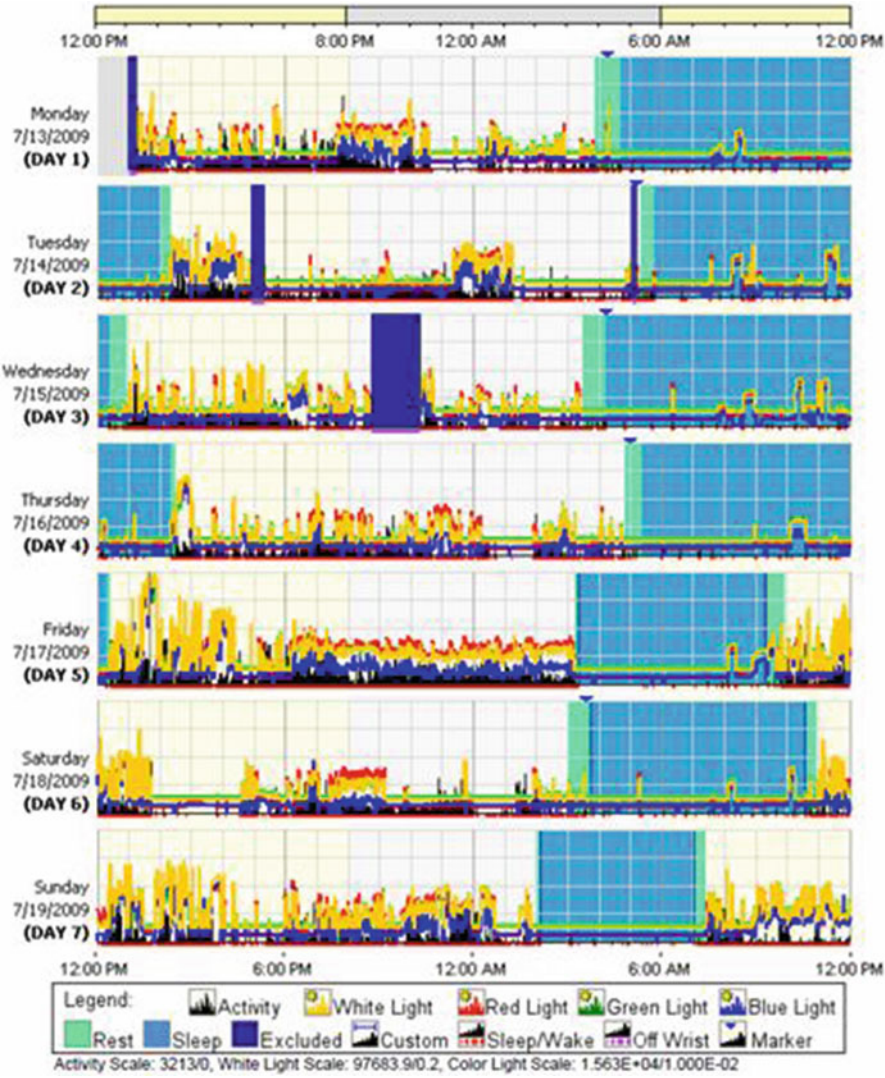


Fig. 3 Example of an actigraphy report. Note the movement (*black line*) and the light sensor (*white*, *green,* and *light-blue lines*) across seven consecutive 24 h periods. *Sky-blue* boxes represent periods of estimated sleep

while clinically the rats developed sepsis, cardiomegaly, fluid retention, and a catabolic state (increased appetite with weight loss). These pivotal studies lay the basis of human sleep deprivation studies thereafter.

In humans, a reduction in sleep quality or quantity can result in behavioral change (change in appetite (Spiegel et al. 2004)), neurocognitive impairment (e.g., memory loss (Stickgold 2005), personality change, judgment, physical agility

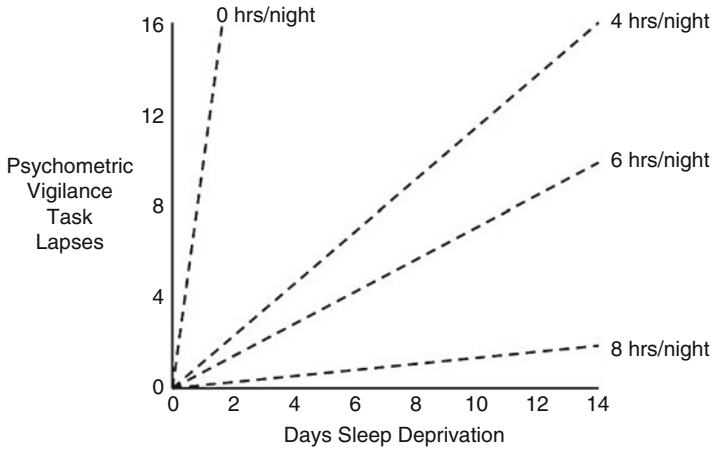


Fig. 4 Graph indicating the effects of varying degrees of sleep deprivation upon performance. Note four groups of otherwise healthy young adults who had 0, 4, 6, and 8 h sleep over 14 days upon performance as measured by lapses in the psychometric vigilance test. Note the 0 h sleep group was unable to complete more that 48 h of testing before withdrawing from the study (Graph is redrawn from data of Van Dongen et al. (2003))

(Dinges et al. 1997; Van Dongen et al. 2003) (Fig. 4)), hormonal change (insulin resistance and hyperglycemia) (Spiegel et al. 1999) which may lead to adverse health effects, prolonged reaction times (Van Dongen et al. 2003) and resultant accidents (work and/or motor vehicle (Taffinder et al. 1998; Landrigan et al. 2004; Lockley et al. 2004)), infections (Majde and Krueger 2005), impaired response to immunizations (Spiegel et al. 2002), obesity (Gangwisch et al. 2005), and diabetes mellitus (Spiegel et al. 1999). Sleep deprivation is also a powerful trigger of seizures. Epidemiological evidence from large cohorts in Japan (Tamakoshi and Ohno 2004) and the USA (Ayas et al. 2003) followed for 20 years indicates sleep deprivation may also contribute to cardiovascular disease and premature death. Importantly, sleep deprivation appears to more important cause of motor vehicle accidents than does OSA (Pack et al. 2006).

Insomnia

Insomnia is defined as >30 min inability to sleep when desiring to sleep plus impairment of cognition while awake (e.g., drowsiness). Short-term insomnia is common, experienced by most people at some stage of their lives. Chronic insomnia (>6 months) is less common and should be considered seriously. Insomnia has also been classified as difficulty *initiating* sleep or difficulty *maintaining* sleep.

Insomnia can result from poor sleep hygiene. Sleep hygiene is a term used to describe lifestyle choices which impact upon sleep. Good sleep hygiene includes choosing to sleep in a cool dark quite room; avoiding strenuous exercise within 2 h

of bedtime; enjoying a bedtime ritual (e.g., reading fiction); avoidance of excessive caffeine, alcohol, or nicotine; and minimizing food intake for 2 h before bed, particularly food high in fat or protein.

Insomnia can also result from an acute adjustment (i.e., an acute stressor), cognitive hypervigilance, mental health disorder, drugs or substance abuse, or medical conditions.

If insomnia persists beyond simple sleep hygiene measures and identification and treatment of underlying medical, psychological, or psychiatric conditions, then relaxation techniques, sleep restriction, and cognitive behavioral therapy should be considered. Only thereafter should medium- to long-term pharmacological therapy be considered.

Circadian Rhythm Disorders

Timing of sleep, i.e., disorders of circadian rhythm, has health important implications. Shift work, defined regular work outside the normal 8 am to 6 pm time slot, can be further subdivided into those with regular and irregular rotations. About 30 % of the working population are shift workers and in general sleep ~2 h less than the non-shift working population. Occupational areas which commonly employ shift workers include the healthcare arena, transport industry, and the computer industry. Given the huge numbers of aircraft, relatively inexpensive airfares, and the global structure of many businesses, a huge population of "white-collar" transmeridian travelers are emerging as another important class of shift workers. Adolescents commonly have a delayed sleep phase syndrome, such that they retire to be late and "sleep in" to late morning. Advanced sleep phase syndrome is characterized by early to bed early to rise: often seen in elderly. Both advanced and delayed patterns improve with light therapy and melatonin.

Several cardiovascular disorders (stroke, fatal arrhythmias, myocardial infarction) have a strong circadian pattern (Muller et al. 1989). Shift work as also been observed to contribute as a cardiovascular risk factor (Boggild and Knutsson 1999). Although precise mechanisms are not clear, it well regarded that shift workers are more likely to smoke, be overweight and of lower socioeconomic status, and have less access to healthcare.

Hypersomnia

Excessive daytime sleepiness may be due to narcolepsy, in the absence of sleep deprivation, mood disorder, sleep disordered breathing, and drugs. This rare disorder has an onset at 15–25 years of age and is characterized by cataplexy, sleep paralysis, hallucinations at sleep onset and offset (hypnogogic and hypnopompic), and excessive daytime sleepiness. Cataplexy is defined as a sudden loss of bilateral muscle tone provoked by strong emotions, lasting seconds to minutes, without loss of consciousness. It is thought to be caused by a failure to control REM, such that

REM occurs episodically throughout the day and night. There is a theory that low orexin (aka hypocretin) in the hypothalamic region is associated with the development of narcolepsy. Some believe narcolepsy to be post-viral or autoimmune. There is an association with a specific human leukocyte antigen subtype (HLA DQB1*0602). Narcolepsy is confirmed with a clear history of cataplexy and a positive MSLT (<10 min) sometimes with sleep onset REM. Idiopathic hypersomnia, aka atypical narcolepsy, occurs in the absence of cataplexy.

Strategies to overcome drowsiness due to the lack of quality, quantity, or timing (i.e., circadian) of sleep include social drugs (caffeine, alcohol, nicotine) and prescribed medication such as stimulants (e.g., dexamphetamines and modafinil), chronotropics (e.g., melatonin), or sedatives. Three classes of sedatives are commonly used: benzodiazepines (e.g., temazepam), cyclopyrrolones (e.g., zolpidem), and imidazopyridines (e.g., zopiclone). Novel ideas such as blue light therapy times to a specific phase in the circadian rhythm may also assist as does physical activity.

Mood and Sleep

Patients with depression and/or anxiety commonly complain of abnormal sleep. Excessive daytime sleepiness is commonly related to depression. Bixler et al. (2005) reported the commonest explanation of sleepiness, in descending order, to be depression, obesity, age, typical sleep duration, diabetes, smoking, and sleep apnea. Depression in general is associated with un-refreshing sleep with ongoing fatigue and sleepiness despite "normal" amounts of sleep. Delayed onset of REM is also seen on polysomnography. Anxiety however is often associated with insomnia. A confounding issue in relation to mood disorders and sleep is that antidepressants (a) commonly cause weight gain (diabetes, sleep apnea) which may interfere with sleep quality, (b) change the neurochemical milieu and cause drowsiness, and (c) directly cause periodic limb movements which fragment sleep.

Parasomnias

These are unpleasant or undesirable behavioral phenomena that occur predominantly or exclusively during sleep. These can occur predominantly during REM sleep, usually elderly males with vascular disease who act out their dreams. Non-REM parasomnias usually are conditions such as sleepwalking, talking, and night terrors, often in young children. This latter condition is benign and usually self-limiting (Mahowald and Schenck 2005).

Restless Legs Syndrome

This disorder is characterized by an unpleasant sensation in the limbs (usually legs) especially when inactive (seated or lying in bed), with an irresistible urge to

move, which has a partial relief of symptoms (Earley 2003). There is a strong circadian aspect, which can be used to measure severity: severe = onset before dinner, modest = after dinner, and mild = in bed. In addition, frequency of nights per week affected by RLS can guide severity. The etiology of RLS is unclear although some evidence suggests low neurotransmitter dopamine and/or low ferritin. In others, there is either antidepressant use (especially SSRIs) or a strong family history. Often periodic limb movements occur in such patients during non-REM sleep. Treatment of RLS usually involves iron therapy and dopamine agonists.

Sleep-Related Breathing Disorders

Sleep-related breathing disorders can be classified as relating to (a) the upper airway pathophysiology (e.g., benign snoring and obstructive apnea); (b) hypoventilation due to chest wall (e.g., kyphoscoliosis), neuromuscular disease (e.g., motor neuron disease), pulmonary disease (e.g., COPD), drugs (e.g., sedatives), or morbid obesity (obesity hypoventilation syndrome); and (c) hyperventilation disorders (e.g., heart failure and Cheyne–Stokes respiration).

Physiologically, sleep has a huge impact upon respiration. The first is that muscle tone drops with sleep onset: this includes skeletal muscles mainly of posture but also the upper airway. There are 13 pairs of muscles from the tip of the nose to the larynx (Earley 2003; Dempsey et al. 2010), which when relaxed increase inspiratory resistance and also result in a reduction in the diameter of the oropharynx. In contrast to the nose and trachea, the oropharynx has no bony or cartilaginous rigid support, allowing it to narrow during sleep.

The second event unique to sleep is that the lung volumes fall, by about 20 %. As ~50 % of the body's oxygen stores are kept within the lungs, a reduction in lung volume (oxygen store) will cause an amplification of hypoxemia for any given apnea length.

The third event is that the factors that control ventilation change from wakefulness to sleep (especially non-REM sleep). While awake, our cerebral cortex and brain stem "waking neural drive" operate in addition to a chemical drive (mainly arterial CO2 sensed at the carotid body). With the transition from wake to sleep, cerebral cortex and waking neural drive are lost and arterial CO2 is the main driver of ventilation. With each level of sleep "depth" (stage 1–2 to 3–4), the ventilation sensitivity to CO2 becomes more blunted. The importance of this is that during normal sleep, the prevailing CO2 level rises about 2 mmHg, to allow minute volume of ventilation to drop ~20 % and thereby allow the normal subject to sleep.

Sleep apnea can occur when there is a disturbance to either of these three physiological mechanisms.

At the most basic level, excessive narrowing of the oropharynx, while maintaining ventilation at ~80 %, will result in a reverberating noise. This is most prominent when there are gravitational factors interplaying (i.e., in the supine position) during slow-wave sleep (when arousability from sleep is impaired) –

characterized by several minutes of uninterrupted snoring. With increasing severity of snoring, it will occur while a subject is in any body position and for longer periods of time.

Obstructive hypopneas occur when there is a reduction in airflow, for >10 s, associated with either a fall in arterial oxyhemoglobin saturation measured by pulse oximetry (SpO2) of >2 % or an arousal from sleep. The arousal from sleep, often subconscious and not recognized by the subject, is also associated with a rise in ventilation (more sensitive to prevailing PaCO2 level) which restores SpO2 and allows the subject to return to sleep. Obstructive apneas are simply a more complete impairment to airflow, again >10 s, and however clinically are associated with witnessed apneas. Figure 5 illustrates polysomnograms of snoring, obstructive sleep apnea, and central sleep apnea with Cheyne–Stokes respiration.

The severity of obstructive apnea and hypopneas is measured by the frequency of combined events, divided by the sleep time (the apnea–hypopnea index [AHI]), although other markers assist, namely, markers of hypoxemia (commonly mean and minimum SpO2 and the total sleep time spent with SpO2 <90 %), sleep quality (sleep efficiency and % SWS and REM), and cardiac function (mean sleep heart rate and morning blood pressure). Of note the AHI explains 25 % of the variance of snoring noise as a % of the night (Marshall et al. 2008) and 44 % of snoring intensity (Maimon et al. 2010). Importantly both AHI and minimum SpO2 correlate with the peak negative intrathoracic pressure (Suzuki et al. 2005) which drops to about −120 mmHg. Normally AHI <5 and min SpO2 92–92 % during sleep. Mild OSA is defined by AHI 5–15 and min SpO2 88–92 %, moderate AHI 15–30 and min SpO2 80 = −88 %, and severe AHI >30 and min SpO2 <80 %. An AHI can reach as high as 160 events per hour and minimum SpO2 into the 30 % range.

Factors that predispose to OSAH include anatomic, lifestyle, and medical. Anatomic factors can be soft tissue (e.g., enlarged tonsils and adenoids), macroglossia, rhinitis (allergic and nonallergic), bony (maxillary restriction, retro-, or micrognathia). Lifestyle factors can be weight gain and social drugs (alcohol, cigarettes). Medical issues include endocrine (e.g., hypothyroid, amyloid), fluid-retaining (e.g., renal and heart failure) medications which suppress arousability (e.g., antiepilepsy, sedatives), retain fluid (e.g., steroids, NSAIDs), or alter respiratory drive (e.g., narcotics) (Fig. 6).

Accordingly the examination of a patient with snoring should include neck circumference (Flemons 2002), Mallampati (Friedman et al. 2002), and lateral pharyngeal wall (Tsai et al. 2003).

The physiological consequences of obstructive hypopneas and apneas are severalfold, intermittent hypoxemia and reoxygenation – this is associated with excessive oxygen radical formation, inflammation, and sympathetic excitation and vasoconstriction (Fig. 7). Second, large negative intrathoracic pressures are induced by forceful diaphragm activity, while upper airway is partially or completely occluded. The negative intrathoracic pressures elicit greater

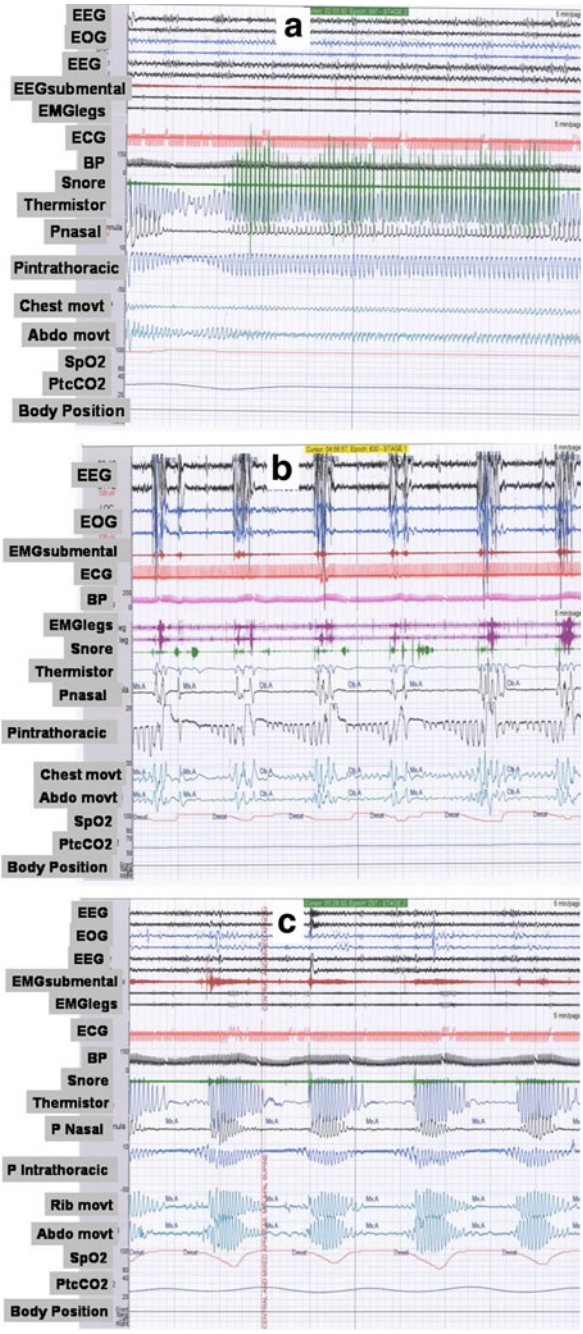


Fig. 5 Three polysomnograms, each of 5 min duration. (**a**) Represents snoring and please note the increase in intrathoracic pressure swings. (**b**) Represents obstructive sleep apnea with large negative intrathoracic pressures. (**c**) Represents central sleep apnea with a Cheyne–Stokes pattern of respiration. Legend: *EEG* electroencephalogram; *EOG* electrooculogram; *EMG* electromyogram of submentalis or anterior tibialis, thermistor marker of oronasal flow; *Pnasal* nasal pressure; *Pintrathoracic* intrathoracic pressure measured by esophageal manometer; *chest and abdominal movt* chest and abdominal movement sensed by inductance plethysmography; *SpO2* pulse oximetry; *PtcCO2* transcutaneous CO2; *body position* left, right, front, back

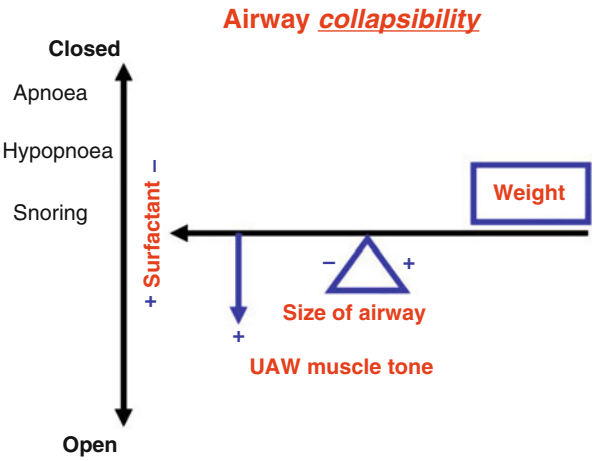


Fig. 6 Diagram to explain the factors involved in upper airway collapsibility due to competing forces, namely, (body) weight, size of the upper airway lumen, tone of the upper airway musculature, and the surfactant properties of the upper airway

Underlying Mechanisms →	Primary Events →	Physiological consequences →	Clinical Features
Upper airway collapse ↓Muscle tone ↓Airway size ↓Surface tension ↑Rostral fluid shift ↑Upstream resistance ↑Airway length ↑Load on lung volume ↑Muscle injury **Cyclic apnea-hyperpnea** ↑Chemosensitivity ↑Overshoot (Loop gain)	Sleep onset ↓ Apnoea ↓ ↓O_2↑CO_2↓pH ↓ Arousal ↓ Airflow ↓ Sleep	Intrathoracic pressure ↓ Cardiac afterload ↑ Autonomic disturbance Brady-tachycardia Pulmonary vasoconstriction Systemic vasoconstriction CO_2 retention Endothelial dysfunction Vascular oxidative stress Inflammation Pro-coagulopathy Metabolic dysregulation	Daytime sleepiness Obesity Insulin resistance & diabetes Systemic hypertension Pulmonary hypertension AV block Atrial fibrillation Ischaemic heart disease Diastolic heart failure Systolic heart failure Stroke Mortality

Fig. 7 Pathophysiology and downstream consequences of obstructive sleep apnea

transmural pressures across vascular structures, the heart and aortic arch baroreceptors, which can lead to reduced cardiac output and resetting of baroreceptors. In addition, it is thought the reverberation effects of snoring can cause fracture of coronary atheromatous plaques. Large intrathoracic pressures can also alter pulmonary vascular pressures to cause transient right to left shunts via open patent foramenovale (i.e., episodic profound falls in SpO2) (Shanoudy et al. 1998). Finally large intrathoracic pressures can induce an exaggerated vagal response (hypoxia without airflow). Third, arousals at the end of the apnea/hypopnea, which fragment sleep and reduced amounts of "quality REM and slow-wave sleep," cause further augmentation of sympathetic activity and vasoconstriction.

The clinical consequences of obstructive sleep apnea–hypopnea can be divided into (a) neurocognitive (excessive daytime sleepiness, impaired concentration, memory, delayed reaction times) and (b) cardiovascular (tachy–brady pattern in continuous heart rate monitoring, atrial and ventricular arrhythmias, systemic and pulmonary hypertension, increased coagulability, accelerated atherosclerosis with ischemic heart disease, and stroke). Populations of snorers and obstructive sleep apnea have greater costs in terms of lost employment and medical expenses as a result (Jennum and Kjellberg 2011).

In a general ambulant community male population, OSA defined by an AHI $>$15/h occurs in 10 % of 30–49-year-olds and 17 % in 50–70-year-olds. In women, the same age groups have 3 and 9 %. These numbers represent a 14–55 % increase in prevalence over two to three decades (Peppard et al. 2013). The prevalence of OSA in cardiovascular disorders, such as hypertension on $\geq$2 drugs, stroke, or heart failure, is in excess of 50 %.

Treatment of Snoring and Obstructive Sleep Apnea

Identification of trigger factors to treat OSA is important as many patients may be asymptomatic. They may have been brought to the attention of the healthcare provider by a bed partners disturbed by snoring. Others may present with daytime sleepiness, unstable cardiovascular function.

Five therapeutic pillars are available to treat the spectrum from benign snoring to obstructive sleep apnea. First is to identify and guide improvement in lifestyle factors such as alcohol, obesity, allergic rhinitis (nasal steroid), and/or smoking. Suggesting patients to avoid sleeping with a flexed neck and to sleep in their side or raise the head of the bed 5–10 cm H2O may assist.

Second is to surgically correct anatomic pathology (e.g., adeno-tonsillectomy, correcting a chronically deviated nasal septum, maxillomandibular advancement) can be helpful particularly in younger patients with fewer lifestyle risk factors. Excision of tongue base and refashioning the uvula may be helpful in a small select group of patients.

Third is to pneumatically splint open the upper airway with continuous positive airway pressure (CPAP), delivered by a nasal or oronasal mask. Adherence to treatment can be easily measured with meters within the flow generator (i.e., CPAP device) and range between 30 % and 80 % (as with pharmaceutical treatments in general). Added humidifiers, pressure settings, alternative masks, and patient education have been crucial in improving adherence.

Fourth are dental devices to either advance the jaw or widen the maxilla. These are mainly successful in patients with mild OSAH plus good dentition and nasal flow. Excessive salivation and teeth movement can occur over years.

A fifth pillar includes devices which show promise but are yet to be established mainline treatment options. This includes upper airway muscle pacemakers, expiratory nasal valves, and negative-pressure oral devices.

Table 2 Summary of cross-sectional prevalence and prospective incidence epidemiological trials which show an independent link between severe OSA and cardiovascular risk, adjusted for all known confounding factors and OSA treatment randomized controlled trials (interventional) (Hamilton n.d.)

	Cross-sectional prevalence	Prospective incidence	Interventional
Hypertension	Yes	Yes (not elderly)	Yes
Ischemic heart disease	Yes	Yes	Not available
Atrial fibrillation	Yes	Not available	Not available
Heart failure	Yes	Yes	Yes
Stroke	Yes	Yes	Not available
Mortality	Yes	Yes (uncertain in elderly)	Not available

Cardiovascular Complications of Snoring and Obstructive Sleep Apnea

Background

Robust short-term physiological experiments in animals and humans have supported the OSAH CV link. Large cross-sectional epidemiological studies also provide strong circumstantial data, and emerging prospective "incident" data is appearing positive (Table 2 (Hamilton and Naughton 2013)). Many outcome-based interventional trials have also been positive, while larger and longer-term studies are currently underway

Systemic Hypertension

Systemic hypertension and OSAH commonly coexist – the prevalence of OSAH in systemic hypertension populations is reported to vary from 30 % to 83 % (Logan et al. 2001). Several large epidemiological cross-sectional studies of community dwellers indicate that the presence of untreated OSA is associated with a greater prevalence of hypertension, when controlled for known confounding factors (Shahar et al. 2001) although the association is weaker in prospective incidence studies (O'Connor et al. 2009). Although prospective incidence studies in middle-aged adults are positive, showing that untreated OSA is associated with a two- to threefold risk of developing hypertension, over a 4–8-year period (Peppard et al. 2000) not in all studies are positive (O'Connor et al. 2009). In addition, the relationship between OSA and hypertension has not been confirmed in subjects aged >65 years (Bixler et al. 2000), probably because of additional accumulating risk factors.

Treatment of OSA with CPAP has been shown to lead to a reduction in mean systemic blood pressure measured over 24 h, although these falls are small (~2–3 mmHg), with the greatest benefit seen in those with more severe OSA (Bazzano et al. 2007). A greater fall is seen in subjects with drug-resistant hypertension (Martinez-Garcia et al. 2013). There is also evidence that treatment with mandibular advancement splints leads to an improvement in hypertension (Gotsopoulos et al. 2004), suggesting the benefit of OSA treatment with respect to blood pressure is independent of the treatment modality.

Despite this, pharmacological antihypertensive therapy (e.g., valsartan) is more effective (~9 mmHg fall in mean 24 h blood pressure) than CPAP (~2 mmHg fall) over 8 weeks according to one randomized controlled study of 23 patients with hypertension and obstructive sleep apnea (Pepin et al. 2010).

An important consideration is the breath by breath variability in systemic blood pressure when measured continuously (Davies et al. 1994). Large swings in blood pressure (i.e., large standard deviation) are thought to be more detrimental in terms of stroke risk than is the mean blood pressure (Rothwell et al. 2010). Obstructive sleep apnea is characterized by huge swings in systemic blood pressure in addition to an increased mean blood pressure. The treatment of sleep apnea with CPAP will reduce the swing in blood pressure considerably; however the mean may fall only 2–3 mmHg (when measured by ambulatory blood pressure monitoring). In contrast, antihypertensive drugs may drop the mean blood pressure, but will have very little impact upon OSA, and thereby the large swings in blood pressure due to the ongoing OSA may persist. A combination of CPAP and antihypertensive drugs is sometimes required (see Fig. 8).

Four important messages need consideration regarding OSA and hypertension. First, clinicians should assess for OSA symptoms and consider a sleep study in patients with resistant hypertension (Levy and McNicholas 2013). Second, OSA treatment in hypertensive OSA patients may improve blood pressure control but without large reductions, while snoring and quality of life should improve. Third, CPAP is not a substitute for pharmacological treatments. Finally, obesity is a unifying factor and accordingly assistance with weight loss is a good objective for clinicians.

Cardiac Arrhythmias

Benign cardiac arrhythmias are commonly present in OSA. Examples include cyclic tachycardia–bradycardia, atrial and ventricular ectopics, bigeminy, heart block, and atrial fibrillation (Stevenson et al. 2008). In one large study, subjects with severe OSA (AHI >30) were more likely to have atrial fibrillation (fourfold risk), non-sustained ventricular tachycardia (4.4-fold risk), and quadrigeminy (two-fold risk) compared with subjects without OSA (Mehra et al. 2006). The clinical significance of this is unknown. Similar data was provided in Australians with moderate OSA (AHI >15), with an odds ratio of 3 for having atrial fibrillation (Stevenson et al. 2008).

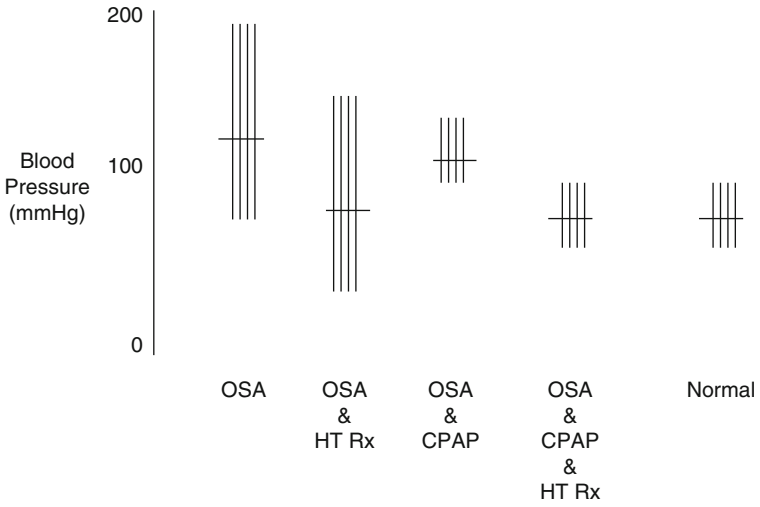


Fig. 8 Illustration of swings in systemic blood pressure with untreated OSA, CPAP-treated OSA, drug-treated hypertension, and both drug- and CPAP-treated hypertension. Note that OSA causes wide BP swings which are attenuated by CPAP, although mean may fall only 2–3 mmHg. Also note that antihypertensive medications may drop the mean BP but unless OSA is treated the wide swings in blood pressure will remain

Some data suggest all arrhythmias improve with CPAP treatment (Ryan et al. 2005), whereas other data are not as supportive (Craig et al. 2009). One study suggested the 12-month recurrence of atrial fibrillation post-cardioversion was significantly lower if coexistent OSA was treated with CPAP compared with untreated OSA (Kanagala et al. 2003).

Although the risk of fatal arrhythmias from OSA is unknown, an increased risk is suggested from data showing that subjects with OSA who die of sudden death are more likely to do so at night compared to those without OSA (Gami et al. 2005).

Although randomized controlled trials of OSA treatment upon cardiac arrhythmia frequency and severity are lacking, it does appear prudent to question for OSA symptoms in patients with difficult to control arrhythmias, such as tachy–brady syndrome or atrial fibrillation, especially when they occur during sleep.

Ischemic Heart Disease

The prevalence of OSA is high in patients with ischemic heart disease (IHD), estimated to be between 30 % and 58 % (Peker et al. 2002). In the general community, cross-sectional epidemiological evidence supports a link between OSA and IHD. OSA is associated with a greater risk for acute myocardial infarction than with smoking or hypertension (Hung et al. 1990). Furthermore, the presence of OSA in patients with established IHD is associated with greater 7-year mortality

compared with those without OSA (Peker et al. 2002). Whether underlying OSA is contributory to the well-described circadian distribution of myocardial infarction (peak incidence ~8 am) (Muller et al. 1989) remains to be determined. Randomized controlled trials of OSA treatment upon the development or outcomes of IHD are presently lacking.

Congestive Heart Failure

Both diastolic and systolic heart failures (HFs) are common in OSA populations (Kee and Naughton 2009). In addition to OSA's proposed effect upon CVD, large swings in negative intrathoracic and positive intravascular pressures which result from OSA are thought to contribute to the development of cardiomyopathy (Dempsey et al. 2010). Epidemiological data indicates an ~threefold greater prevalence of diastolic and systolic HF in community dwellers with severe OSA (AHI >30) compared with no OSA (Chami et al. 2008). Furthermore, the risk of developing incident HF due to untreated OSA is estimated to be 1.6 times greater, based upon 4,422 community dwellers (controlled age, gender, race, diabetes, and hypertension) followed for a mean of 8.7 years (Gottlieb et al. 2010).

OSA and central sleep apnea are also commonly seen within HF populations. One study has demonstrated that 55–85 % of HF patients have sleep apnea (either obstructive or central) when patients were tested several times over a 12-month period (Pinna et al. 2010). In general, central sleep apnea is seen in more advanced severe spectrum of HF and can be explained by additional pathophysiology to that seen in pure OSA. This high prevalence of either apnea type does not appear to have been affected by the introduction of beta blockers or spironolactone (Yumino et al. 2009).

Evidence suggests that coexistent OSA worsens heart failure and is improved by CPAP therapy. Two randomized controlled studies show that the treatment of patients with OSA (AHI >15/h) and systolic HF with fixed pressure CPAP over 1–3 months is associated with improvements in systolic function, quality of life, exercise capacity, and autonomic control (Mansfield et al. 2004). Nevertheless, the data is not universally positive. Neither study was large enough to assess mortality; however an observational study suggests an improvement in survival with long-term CPAP treatment, compared to untreated OSA (Wang et al. 2007).

Stroke

Patients with untreated OSA have an elevated risk of developing stroke, and the data are more consistently positive than for cardiac disease (Loke et al. 2012), including in the elderly (Munoz et al. 2006). Mechanisms include large swings in systemic blood pressure, local vibrational damage to the carotid artery bifurcation (Lee et al. 2008), increased coagulopathy, surreptitious development of atrial fibrillation during sleep with thrombus formation, and paradoxical emboli through

asymptomatic patent foramenovale opening during transient sleep-related hypoxemia with pulmonary hypertension.

Prospective observational studies show increasing risk for ischemic stroke with increasing OSA severity (Redline et al. 2010). A large US epidemiological study showed the risk for stroke in men was increased almost three times once the AHI was >19/h, but the risk in women was much smaller and did not become significant until AHI was >25/h (Redline et al. 2010).

CPAP treatment may reduce stroke risk; however large randomized controlled trials are lacking. Observational studies have shown that the treatment of OSA reduces stroke risk. The only randomized controlled trial assessing the effect of CPAP on risk of mortality and subsequent stroke did not show a benefit, but had only small numbers and was not adequately powered to address the issue (Parra et al. 2011).

Mortality

Several large, longitudinal epidemiological studies have consistently indicated that severe untreated OSA (AHI >30/h) in middle-aged populations is associated with greater mortality compared with treated OSA, mild–moderate OSA, or no-OSA groups (Punjabi et al. 2009). This data suggests that severe OSA confers a mortality risk, which is prevented by CPAP treatment. Nevertheless, these studies were not randomized controlled trials, and given that unrecognized bias may confound the results, whether OSA is a reversible risk factor for mortality remains inconclusive.

The mortality effects of untreated OSA are less certain in the elderly. In a large cohort of 14,589 Israeli subjects, severe OSA led to increased mortality only for those aged <50 years (Lavie et al. 2005). Similarly, a large US study also failed to show increased mortality in those aged >70 years (Punjabi et al. 2009). However, a recent Spanish observational trial reported that elderly patients (>65 years old) with severe untreated OSA (AHI >30) had 2.25 times increased mortality – due largely to stroke and heart failure, but not ischemic heart disease (Lavie et al. 2005). No excess mortality was seen in CPAP treated severe OSA or in less severe OSA.

Central Sleep Apnea Related to Established Heart Failure

Patients with heart failure of all causes commonly exhibit hyperventilation, which drives the PaCO2 level low. During non-REM sleep, when the drive to breathe is exquisitely controlled by the CO2 level, oscillatory breathing patters occur. Typically these are ~1 min cycles of crescendo then decrescendo ventilation followed by a central apnea (i.e., no respiratory effort). Initially thought to be deleterious because of associated hypoxemia and fragmented sleep which may occur, it has now been thought to be simply a marker of severe heart failure.

Given many such patients can live for many years with CSA and that certain physiological benefits are associated with CSA, it has been thought by some that

CSA in the setting of heart failure may be compensatory (Naughton 2012). The physiological benefits of CSA include (a) transient rest in a high work of breathing environment, (b) maintaining an alkalotic pH to avert patients from deleterious acidosis in times of HF instability, (c) transient increase in end-expiratory lung volume and thereby oxygen stores, and (d) low cyclic intrathoracic pressure swings that assist forward cardiac output.

These theoretical benefits of CSA in heart failure should not preclude optimization of heart function. It has been shown that CSA in heart failure resolves with improved cardiac function following medical therapy, valve replacement, pacemaker insertion, LVAD, and cardiac transplantation.

In the event ongoing CSA occurs despite optimization of therapies directed toward the failing heart; continuous positive airway pressure may be beneficial as it is for OSAH and acute cardiogenic pulmonary edema. These CPAP mechanisms of action, beyond pneumatically maintaining a patent oropharynx during sleep, include increasing lung volume and oxygenation and reducing cardiac wall tension and chamber size and thereby reducing bother the work of breathing and of the heart.

Conclusions

Sleep has emerged as an intriguing physiological state that has huge influences upon how one feels, performs, and reacts to external factors. Importantly, sleep also places the cardiovascular system under stress, as does an exercise test. The most powerful components of sleep, namely, sleep deprivation and obstructive sleep apnea, place enormous strain upon the cardiovascular system.

References

Armstrong, S. M., Cassone, V. M., Chesworth, M. J., Redman, J. R., & Short, R. V. (1986). Synchronization of mammalian circadian rhythms by melatonin. *Journal of Neural Transmission, 21*, 375–394.

Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science (New York, NY), 118*(3062), 273–274.

Ayas, N. T., White, D. P., Manson, J. E., Stampfer, M. J., Speizer, F. E., Malhotra, A., et al. (2003). A prospective study of sleep duration and coronary heart disease in women. *Archives of Internal Medicine, 163*(2), 205–209.

Bazzano, L. A., Khan, Z., Reynolds, K., & He, J. (2007). Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension, 50*(2), 417–423.

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Ten Have, T., Leiby, B. E., Vela-Bueno, A., et al. (2000). Association of hypertension and sleep-disordered breathing. *Archives of Internal Medicine, 160*(15), 2289–2295. Aug 14–28.

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Calhoun, S. L., Vela-Bueno, A., & Kales, A. (2005). Excessive daytime sleepiness in a general population sample: The role of sleep apnea, age, obesity, diabetes, and depression. *The Journal of Clinical Endocrinology and Metabolism, 90*(8), 4510–4515.

Boggild, H., & Knutsson, A. (1999). Shift work, risk factors and cardiovascular disease. *Scandinavian Journal of Work, Environment & Health, 25*(2), 85–99.

Borbely, A. A. (1982). A two process model of sleep regulation. *Human Neurobiology, 1*(3), 195–204.

Chami, H. A., Devereux, R. B., Gottdiener, J. S., Mehra, R., Roman, M. J., Benjamin, E. J., et al. (2008). Left ventricular morphology and systolic function in sleep-disordered breathing: The Sleep Heart Health Study. *Circulation, 117*(20), 2599–2607.

Craig, S., Pepperell, J. C., Kohler, M., Crosthwaite, N., Davies, R. J., & Stradling, J. R. (2009). Continuous positive airway pressure treatment for obstructive sleep apnoea reduces resting heart rate but does not affect dysrhythmias: A randomised controlled trial. *Journal of Sleep Research, 18*(3), 329–336.

Davies, R. J., Crosby, J., Vardi-Visy, K., Clarke, M., & Stradling, J. R. (1994). Non-invasive beat to beat arterial blood pressure during non-REM sleep in obstructive sleep apnoea and snoring. *Thorax, 49*(4), 335–339.

Dempsey, J. A., Veasey, S. C., Morgan, B. J., & O'Donnell, C. P. (2010). *Pathophysiology of sleep apnea. Physiological Reviews, 90*(1):47–112. Jan.

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., et al. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep, 20*(4), 267–277.

Earley, C. J. (2003). Clinical practice. Restless legs syndrome. *The New England Journal of Medicine, 348*(21), 2103–2109.

Everson, C. A., Bergmann, B. M., & Rechtschaffen, A. (1989). Sleep deprivation in the rat: III. Total sleep deprivation. *Sleep, 12*(1), 13–21.

Flemons, W. W. (2002). Clinical practice. Obstructive sleep apnea. *The New England Journal of Medicine, 347*(7), 498–504.

Friedman, M., Ibrahim, H., & Bass, L. (2002). Clinical staging for sleep-disordered breathing. *Otolaryngology and Head and Neck Surgery, 127*(1), 13–21.

Gami, A. S., Howard, D. E., Olson, E. J., & Somers, V. K. (2005). Day-night pattern of sudden death in obstructive sleep apnea. *The New England Journal of Medicine, 352*(12), 1206–1214.

Gangwisch, J. E., Malaspina, D., Boden-Albala, B., & Heymsfield, S. B. (2005). Inadequate sleep as a risk factor for obesity: Analyses of the NHANES I. *Sleep, 28*(10), 1289–1296.

Gotsopoulos, H., Kelly, J. J., & Cistulli, P. A. (2004). Oral appliance therapy reduces blood pressure in obstructive sleep apnea: A randomized, controlled trial. *Sleep, 27*(5), 934–941.

Gottlieb, D. J., Yenokyan, G., Newman, A. B., O'Connor, G. T., Punjabi, N. M., Quan, S. F., et al. (2010). Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The sleep heart health study. *Circulation, 122*(4):352–360.

Hamilton, G. S., & Naughton, M. T. (2013). Impact of obstructive sleep apnoea on diabetes and cardiovascular disease. *The Medical Journal of Australia, 199*(8):S27–S30.

Hung, J., Whitford, E. G., Parsons, R. W., & Hillman, D. R. (1990). Association of sleep apnoea with myocardial infarction in men. *Lancet, 336*(8710), 261–264.

Jennum, P., & Kjellberg, J. (2011). Health, social and economical consequences of sleep-disordered breathing: A controlled national study. *Thorax, 66*(7):560–566.

Kanagala, R., Murali, N. S., Friedman, P. A., Ammash, N. M., Gersh, B. J., Ballman, K. V., et al. (2003). Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation, 107*(20), 2589–2594.

Kee, K., & Naughton, M. T. (2009). Heart failure and sleep-disordered breathing: Mechanisms, consequences and treatment. *Current Opinion in Pulmonary Medicine, 15*(6), 565–570.

Kushida, C. A., Bergmann, B. M., & Rechtschaffen, A. (1989). Sleep deprivation in the rat: IV. Paradoxical sleep deprivation. *Sleep, 12*(1), 22–30.

Landrigan, C. P., Rothschild, J. M., Cronin, J. W., Kaushal, R., Burdick, E., Katz, J. T., et al. (2004). Effect of reducing interns' work hours on serious medical errors in intensive care units. *The New England Journal of Medicine, 351*(18), 1838–1848.

Lavie, P., Lavie, L., & Herer, P. (2005). All-cause mortality in males with sleep apnoea syndrome: Declining mortality rates with age. *The European Respiratory Journal, 25*(3), 514–520.

Lee, S. A., Amis, T. C., Byth, K., Larcos, G., Kairaitis, K., Robinson, T. D., et al. (2008). Heavy snoring as a cause of carotid artery atherosclerosis. *Sleep, 31*(9), 1207–1213.

Levy, P., & McNicholas, W. T. (2013). Sleep apnoea and hypertension: Time for recommendations. *The European Respiratory Journal, 41*(3):505–506.

Lockley, S. W., Cronin, J. W., Evans, E. E., Cade, B. E., Lee, C. J., Landrigan, C. P., et al. (2004). Effect of reducing interns' weekly work hours on sleep and attentional failures. *The New England Journal of Medicine, 351*(18), 1829–1837.

Logan, A. G., Perlikowski, S. M., Mente, A., Tisler, A., Tkacova, R., Niroumand, M., et al. (2001). High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *Journal of Hypertension, 19*(12), 2271–2277.

Loke, Y. K., Brown, J. W., Kwok, C. S., Niruban, A., & Myint, P. K. (2012). Association of obstructive sleep apnea with risk of serious cardiovascular events: A systematic review and meta-analysis. *Circular Cardiovascular Quality Outcomes, 5*(5):720–728. 1 Sep.

Mahowald, M. W., & Schenck, C. H. (2005). Insights from studying human sleep disorders. *Nature, 437*(7063), 1279–1285.

Maimon, N., & Hanly, P. J. (2010). Does snoring intensity correlate with the severity of obstructive sleep apnea? *J Clin Sleep Med, 6*(5):475–478.

Majde, J. A., & Krueger, J. M. (2005). Links between the innate immune system and sleep. *The Journal of Allergy and Clinical Immunology, 116*(6), 1188–1198.

Mansfield, D. R., Gollogly, N. C., Kaye, D. M., Richardson, M., Bergin, P., & Naughton, M. T. (2004). Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. *American Journal of Respiratory and Critical Care Medicine, 169*(3), 361–366.

Marshall, N. S., Wong, K. K., Cullen, S. R., Knuiman, M. W., & Grunstein, R. R. (2008). Snoring is not associated with all-cause mortality, incident cardiovascular disease, or stroke in the Busselton Health Study. *Sleep, 35*(9):1235–1240.

Martinez-Garcia, M. A., Capote, F., Campos-Rodriguez, F., Lloberes, P., Diaz de Atauri, M. J., Somoza, M., et al. (2013). Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: The HIPARCO randomized clinical trial. *JAMA, 310*(22):2407–2415. 11 Dec.

Mehra, R., Benjamin, E. J., Shahar, E., Gottlieb, D. J., Nawabit, R., Kirchner, H. L., et al. (2006). Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. *American Journal of Respiratory and Critical Care Medicine, 173*(8), 910–916.

Muller, J. E., Tofler, G. H., & Stone, P. H. (1989). Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation, 79*(4), 733–743.

Munoz, R., Duran-Cantolla, J., Martinez-Vila, E., Gallego, J., Rubio, R., Aizpuru, F., et al. (2006). Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke; a Journal of Cerebral Circulation, 37*(9), 2317–2321.

Naughton, M. T. (2012). Cheyne-stokes respiration: Friend or foe? *Thorax, 67*(4):357–360. Apr.

O'Connor, G. T., Caffo, B., Newman, A. B., Quan, S. F., Rapoport, D. M., Redline, S., et al. (2009). Prospective study of sleep-disordered breathing and hypertension: The Sleep Heart Health Study. *American Journal of Respiratory and Critical Care Medicine, 179*(12), 1159–1164.

Pack, A. I., Maislin, G., Staley, B., Pack, F. M., Rogers, W. C., George, C. F., et al. (2006). Impaired performance in commercial drivers: Role of sleep apnea and short sleep duration. *American Journal of Respiratory and Critical Care Medicine, 174*(4), 446–454.

Parra, O., Sanchez-Armengol, A., Bonnin, M., Arboix, A., Campos-Rodriguez, F., Perez-Ronchel, J., et al. (2011). Early treatment of obstructive apnoea and stroke outcome: A randomised controlled trial. *The European Respiratory Journal, 37*(5):1128–1136. May.

Peker, Y., Hedner, J., Norum, J., Kraiczi, H., & Carlson, J. (2002). Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: A 7-year follow-up. *American Journal of Respiratory and Critical Care Medicine, 166*(2), 159–165.

Pepin, J. L., Tamisier, R., Barone-Rochette, G., Launois, S. H., Levy, P., & Baguet, J. P. (2010). Comparison of continuous positive airway pressure and valsartan in hypertensive patients with sleep apnea. *American Journal of Respiratory and Critical Care Medicine, 182*(7):954–960.

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W., & Hla, K. M. (2013). Increased prevalence of sleep-disordered breathing in adults. *American Journal of Epidemiology, 177* (9):1006–1014.

Peppard, P. E., Young, T., Palta, M., & Skatrud, J. (2000). Prospective study of the association between sleep-disordered breathing and hypertension. *New England Journal of Medicine, 342* (19), 1378–1384.

Pinna, G. D., Maestri, R., Mortara, A., Johnson, P., Andrews, D., Ponikowski, P., et al. (2010). Long-term time-course of nocturnal breathing disorders in heart failure patients. *The European Respiratory Journal, 35*(2):361–367.

Punjabi, N. M., Caffo, B. S., Goodwin, J. L., Gottlieb, D. J., Newman, A. B., O'Connor, G. T., et al. (2009). Sleep-disordered breathing and mortality: A prospective cohort study. *PLoS Medicine, 6*(8), e1000132.

Rechtschaffen, A., & Bergmann, B. M. (2002). Sleep deprivation in the rat: An update of the 1989 paper. *Sleep, 25*(1), 18–24.

Rechtschaffen, A., Bergmann, B. M., Everson, C. A., Kushida, C. A., & Gilliland, M. A. (2002). Sleep deprivation in the rat: X. Integration and discussion of the findings. 1989. *Sleep, 25*(1), 68–87.

Redline, S., Yenokyan, G., Gottlieb, D. J., Shahar, E., O'Connor, G. T., Resnick, H. E., et al. (2010). Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. *American Journal of Respiratory and Critical Care Medicine, 182*(2):269–277.

Rothwell, P. M., Howard, S. C., Dolan, E., O'Brien, E., Dobson, J. E., Dahlof, B., et al. (2010). Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurology, 9*(5):469–480.

Ryan, C. M., Usui, K., Floras, J. S., & Bradley, T. D. (2005). Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. *Thorax, 60*(9), 781–785.

Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature, 437*(7063), 1257–1263.

Shahar, E., Whitney, C. W., Redline, S., Lee, E. T., Newman, A. B., Nieto, F. J., et al. (2001). Sleep-disordered breathing and cardiovascular disease: Cross-sectional results of the Sleep Heart Health Study. *American Journal of Respiratory and Critical Care Medicine, 163*(1), 19–25.

Shanoudy, H., Soliman, A., Raggi, P., Liu, J. W., Russell, D. C., & Jarmukli, N. F. (1998). Prevalence of patent foramen ovale and its contribution to hypoxemia in patients with obstructive sleep apnea. *Chest, 113*(1), 91–96.

Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet, 354*(9188), 1435–1439.

Spiegel, K., Sheridan, J. F., & Van Cauter, E. (2002). Effect of sleep deprivation on response to immunization. *JAMA, 288*(12), 1471–1472.

Spiegel, K., Tasali, E., Penev, P., & Van Cauter, E. (2004). Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Annals of Internal Medicine, 141*(11), 846–850.

Stevenson, I. H., Teichtahl, H., Cunnington, D., Ciavarella, S., Gordon, I., & Kalman, J. M. (2008). Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. *European Heart Journal, 29*(13), 1662–1669.

Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature, 437*(7063), 1272–1278.

Suzuki, M., Ogawa, H., Okabe, S., Horiuchi, A., Okubo, M., Ikeda, K., et al. (2005). Digital recording and analysis of esophageal pressure for patients with obstructive sleep apnea-hypopnea syndrome. *Sleep & Breathing = Schlaf & Atmung, 9*(2), 64–72.

Taffinder, N. J., McManus, I. C., Gul, Y., Russell, R. C., & Darzi, A. (1998). Effect of sleep deprivation on surgeons' dexterity on laparoscopy simulator. *Lancet, 352*(9135), 1191.

Tamakoshi, A., & Ohno, Y. (2004). Self-reported sleep duration as a predictor of all-cause mortality: Results from the JACC study, Japan. *Sleep, 27*(1), 51–54.

Trinder, J., Kleiman, J., Carrington, M., Smith, S., Breen, S., Tan, N., et al. (2001). Autonomic activity during human sleep as a function of time and sleep stage. *Journal of Sleep Research, 10*(4), 253–264.

Tsai, W. H., Remmers, J. E., Brant, R., Flemons, W. W., Davies, J., & Macarthur, C. (2003). A decision rule for diagnostic testing in obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine, 167*(10), 1427–1432.

Van Dongen, H. P., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep, 26*(2), 117–126.

Wang, H., Parker, J. D., Newton, G. E., Floras, J. S., Mak, S., Chiu, K. L., et al. (2007). Influence of obstructive sleep apnea on mortality in patients with heart failure. *Journal of the American College of Cardiology, 49*(15), 1625–1631.

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., et al. (2013). Sleep drives metabolite clearance from the adult brain. *Science (New York, NY), 342*(6156):373–377.

Yumino, D., Wang, H., Floras, J. S., Newton, G. E., Mak, S., Ruttanaumpawan, P., et al. (2009). Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. *Journal of Cardiac Failure, 15*(4), 279–285.

Psychogenic Hypertension

Murray Esler

Contents

Abstract

In searching for biological evidence that essential hypertension is caused by chronic mental stress, a disputed proposition, parallels are noted with panic disorder, which provides an explicit clinical model of recurring stress responses: (i) There is clinical comorbidity; panic disorder prevalence is increased threefold

M. Esler (✉)
Human Neurotransmitters Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia
e-mail: murray.esler@bakeridi.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_42

in essential hypertension. (ii) Plasma cortisol is elevated in both. (iii) In panic disorder and essential hypertension, but not in health, single sympathetic nerve fibers commonly fire repeatedly within an individual cardiac cycle (these salvoes of nerve firing constituting a stress "signature"). (iv) For both, adrenaline cotransmission is present in sympathetic nerves, as is seen in experimental models of stress. (v) There is induction of the adrenaline synthesizing enzyme, PNMT, in sympathetic nerves, an explicit indicator of mental stress exposure. Patients with essential hypertension exhibit a further manifestation of mental stress: there is activation of noradrenergic brainstem neurons, most likely of the Al and AS nuclei, projecting rostrally to the hypothalamus and amygdala. Activation of the renal sympathetic outflow is pivotal in hypertension development. In the presence of high dietary sodium intake, endemic in contemporary life, this activation of the renal sympathetic nerves provides concurrent "neural," "renal," and "sodium" mechanisms of hypertension development. Relaxation and stress reduction measures lower blood pressure, but less than anticipated, and not sufficient for BP control in severe grades of hypertension. A modern and commonly successful development in the therapeutics of severe and resistant hypertension is the targeting of the final common pathway in the hypertension pathogenesis, with ablation of the renal sympathetic nerves by radiofrequency energy delivered as a one-off procedure, using a specially engineered catheter sited in the renal arteries, the procedure of endovascular renal denervation.

Keywords

Hypertension • Brain norepinephrine turnover • Epinephrine • Plasma cortisol • Stress biomarkers • Sympathetic nerve cotransmitter • Sympathetic nervous system • Neurogenic hypertension • Phenylethanolamine-*N*-methyltransferase (PNMT) • Stress-induced hypertension

Introduction

The idea that essential hypertension may arise through psychosomatic mechanisms is an old one, invoked before the standard methods of indirect blood pressure measurement were used clinically. Concerning his male patients with hypertension (systolic pressure having been measured with a finger plethysmograph), Geisbock wrote: "one finds an unusual frequency of those who as directors of big enterprises had a great deal of responsibility and demanding jobs, and who, after a long period of mental overwork, became nervous" (Geisbock et al. 1976). Although providing proof that essential hypertension is a psychosomatic disorder has been difficult, the supporting evidence which has accumulated slowly over the succeeding century is now very persuasive (Folkow 2004).

This support comes from three evidence streams, from experimental models of stress-induced hypertension, from epidemiological and clinical studies testing for a nexus between mental stress and hypertension, and from pathophysiological studies documenting the presence of stress-related biology in essential hypertension patients.

Experimental Models of Stress-Induced Hypertension

Because of the logistic and ethical difficulties which exist in exploring the relation of chronic mental stress to the development of human hypertension, animal models have been developed. An acceptable animal model of presumed psychogenic hypertension should meet the following criteria:

(i) The blood pressure elevation should be permanent, persisting after removal of the stimulus.
(ii) Cardiovascular complications of hypertension, such as strokes, atherosclerosis, left ventricular hypertrophy, and myocardial infarction, should develop.
(iii) The model should be plausible and have points in common with human circumstances and behavior.

A model of psychosocial hypertension developed in mice (Henry et al. 1975) fulfilled these prerequisites. In Henry's mice experiments, colonies of animals were established from "asocial males," raised in isolation, and normally socialized females. Crowding was avoided. The male mice fought intensely over territories, failing to establish a stable social hierarchy. Blood pressure rose promptly and progressively in the males, associated with features of sympathetic nervous system overactivity and increased secretion of renin. At first, the elevation in blood pressure was reversible when the mice were returned from the colony to isolation. But, after interacting in the colony for 6 months or more, the pressure rise was irreversible and accompanied by cardiovascular complications.

Epidemiological and Clinical Evidence

While the studies with experimental stress in animals are interesting and important, in demonstrating that psychological stressors can cause permanent hypertension, and in identifying the crucial role of neural mechanisms in the development of the hypertension, it is another matter to demonstrate that essential hypertension is due to chronic mental stress.

Clinical Studies

Research pivotal to the stress/hypertension proposition came from observations on the hemodynamics of essential hypertension during its developmental phases (Brod 1960). Crucial here was the delineation of the differences between the hemodynamics of early, mild hypertension, and long-established, more severe hypertension. Research by Brod in young men with minimally elevated blood pressure was pivotal. The hemodynamic increases he observed in cardiac output and blood pressure suggested to him that the "defense reaction," evoked by

laboratory mental stress in healthy humans, was actually persistently engaged in patients with mild hypertension. Others confirmed that an elevated cardiac output was a common characteristic of early, borderline human hypertension (Julius and Conway 1968). In now historic longitudinal studies, reversal over decades of this hemodynamic pattern was documented, to the normal cardiac output, high peripheral vascular resistance form which is typical of more severe and long-standing essential hypertension (Lund-Johansen 1994). Blood pressure-dependent arteriolar hypertrophy as is central to this slow but progressive vascular remodeling (Folkow 1982; Korner 2007). In long-standing hypertension, the hemodynamic origins have been obliterated, and cardiac output is normal or reduced.

Epidemiological Studies

Epidemiological and clinical studies provide increasingly strong support for the notion that behavioral and psychological factors, in particular suppressed hostility, are of importance in the pathogenesis of human hypertension (Harburg et al. 1973; Esler et al. 1977; Perini et al. 1986; Henry and Grim 1990). Importantly, the increased prevalence of hypertension in Afro-Americans has been linked to high levels of psychosocial stress, associated with an underlying genetic propensity to sodium retention by the kidneys, perhaps attributable to the survival benefit this might have provided at times of severe dietary sodium shortage on slave ship voyages (Harburg et al. 1973; Henry and Grim 1990).

Long-term follow-up studies of human populations, such as the celebrated study of cloistered nuns in Umbria (Timio et al. 1988), who live in a secluded and unchanging environment, and in whom blood pressure does not show the expected rise with age, have been influential. Also important are studies linking hypertension development to chronic mental stress in the workplace (Steptoe and Willemsen 2004; Chandola et al. 2006). Additional key observations have been made on human populations who demonstrate blood pressure elevation soon after migration (Poulter et al. 1990), this rise in pressure being attributed primarily to mental stress, although changes in physical activity and diet are also operative. Pertinent also is the observation that panic disorder and essential hypertension are commonly comorbid conditions (Davies et al. 1999). Patients with panic disorder have recurring and often severe stress responses accompanied by sympathetic nervous system activation and acute blood pressure elevation (Alvarenga et al. 2006). The inference here is that the recurring stress responses in panic disorder can initiate the development of persistently elevated pressure.

In short, although the concept that in some patients essential hypertension may be psychogenic in origin is not definitively proven, there is a wealth of supporting experimental and clinical evidence. As discussed below, long-term neural effects of stress on renal function are most likely the principal blood pressure elevating mechanism (Light and Obrist 1980; Koepke et al. 1988; DiBona 2005).

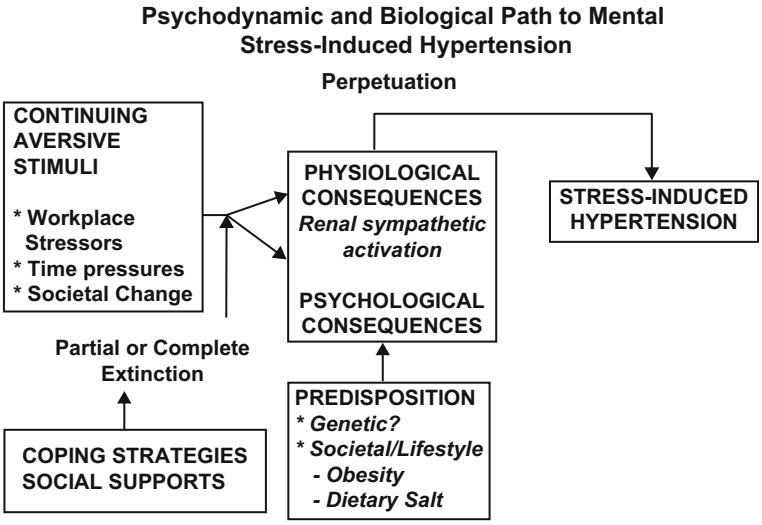


Fig. 1 What might be the mechanism by which chronic mental stress leads to essential hypertension? The figure presents a general scheme for the path to stress-induced illnesses, including high blood pressure. An ongoing aversive stimulus, which can be modified, extinguished or perpetuated, in particular circumstances can lead to illness. As indicated in this formulation, the existence of strong social supports in a person's life or their possession of good coping strategies can dampen the stressor impact, minimizing its transfiguration into pathophysiology or psychopathology. For hypertension there are two well-documented aversive patterns of work environment demonstrated to be causal for high blood pressure (Karasek et al. 1981; Siegrist 1996; Steptoe and Willemsen 2004; Chandola et al. 2006). The first is the "high job strain" workplace, characterized by lack of control over the pace of work and its targets and deadlines. The second is the "effort-reward imbalanced" workplace, typified by demanding work which causes little personal gratification. Additionally, inescapable time pressure constitutes a unique stressor of the present day (Klein 2007), this being intensified by the immediacy demands of the electronic age. The mediating pathophysiology involves ongoing activation of the sympathetic nervous system, specifically of the renal sympathetic outflow, interacting adversely with excess dietary intake of sodium (Koepke et al. 1988; DiBona 2005; DiBona and Esler 2010)

A Psychodynamic and Biological Formulation of Stress-Induced Hypertension

What might be the mechanism by which chronic mental stress leads to essential hypertension? Figure 1 presents a scheme for the path to stress-induced high blood pressure. Ongoing aversive stimuli, described below, which can be modified, extinguished or perpetuated in particular circumstances can potentially lead to hypertension. As indicated in this formulation, the existence of strong social supports in a person's life or their possession of good coping strategies can dampen the stressor impact, minimizing its transfiguration into pathophysiology or psychopathology. Also impacting on this is the presence or absence of genetic and lifestyle

predisposition. In the unfavorable circumstances of poor coping strategies, absent social supports and the presence of genetic or lifestyle predisposition, the effects of the aversive stimulus can be perpetuated, with the development of hypertension. For essential hypertension, specific information is available on both the aversive stimuli and the mediating pathophysiology but not the genetically predisposing factors.

Aversive Stressors for Hypertension

Two well-documented patterns of adverse work environment are demonstrated to be causal for high blood pressure (and also coronary heart disease) (Karasek et al. 1981; Siegrist 1996): first, the "high job strain" workplace, characterized by lack of control over the pace of work and its targets and deadlines, and, second, the "effort-reward imbalanced" workplace, typified by demanding work which causes little personal gratification because of lack of appreciation and unjustified criticism by workplace superiors. The scientific case for causality here is very strong indeed.

The cliched response of skeptics often takes the form: "surely life was more stressful for hunter-gatherer societies in paleolithic times than in the present." Not necessarily so, inescapable time pressures constitute the unique stress of the present day (Klein 2007), this being intensified by the immediacy demands of the electronic age. Time pressures, coupled with difficulties in adjusting to the societal changes which are relentless in contemporary living, are claimed to be pivotal. The probable mediating mechanisms are discussed below but do seem to involve ongoing activation of the sympathetic nervous system.

Stress Biological Markers (Stress "Finger Prints") in Essential Hypertension

The theme to be developed in this section is that in essential hypertension chronic mental stress is the primary driver and that this leaves identifiable stress "finger prints." To test the causal importance of chronic mental stress, which does remain a disputed proposition, rather than using the conventional epidemiological approach (typified by "measuring blood pressure in air traffic controllers") in recent studies we have searched for stress biomarkers in patients with hypertension (Table 1).

Table 1 Biological markers of mental stress in essential hypertension

1. Increased turnover of noradrenaline in subcortical brain areas
2. Increased sympathetic nervous system activity
3. Multiple firing of sympathetic nerve fibers in a cardiac cycle, in salvos
4. Elevated plasma cortisol concentration
5. Adrenaline co-transmission in sympathetic nerves
6. Presence of phenylethanolamine-N-methyltransferase (PNMT) in sympathetic nerves

As detailed below, findings such as the activation of suprabulbar projections of noradrenergic brain stem neurons in patients with essential hypertension, the presence of persistent sympathetic nervous stimulation, and the release of epinephrine as a cotransmitter in their sympathetic nerves are all presumptive biological markers of stress.

Documenting the presence of these stress biomarkers in patients with essential hypertension (Esler et al. 2008a, b) supplements the evidence drawn from other sources in affirming the importance of chronic mental stress in pathogenesis.

Increased Brain Norepinephrine Turnover in Essential Hypertension

The hypothalamus and amygdala receive projections from brain stem noradrenergic neurons. These projections have been shown in experimental animals to be important in stimulating sympathetic nervous system outflow. Using internal jugular venous sampling, we have developed methods to measure brain norepinephrine turnover (synthesis rate) differentially in subcortical and cortical brain areas, to test whether this mechanism applies in human hypertension (Ferrier et al. 1992). By measuring the overflow of norepinephrine and its lipophilic metabolites into the internal jugular veins, the turnover of norepinephrine in suprabulbar subcortical brain regions can be measured. The internal jugular vein which predominantly drains subcortical brain regions (usually the left vein) is identified using a cerebral venous sinus scan (Ferrier et al. 1992). This sampling excludes the brain stem, which drains primarily into the spinal veins.

We have documented that norepinephrine turnover in the brain is increased in patients with essential hypertension but in subcortical areas only. The findings suggest an importance of increased firing in noradrenergic A1 and A5 brain stem neurons which project rostrally to the hypothalamus and amygdala, and underlying mental stress in hypertension pathogenesis, mediated by sympathetic nervous activation. Our results find a parallel in the primary importance of the medial amygdala in the blood pressure elevation of the BPH/2J genetically hypertensive mouse (Jackson et al. 2014), and in the linking of activation of the amygdala, demonstrated with MRI, to the magnitude of stress-induced blood pressure elevation in humans (Gianaros et al. 2008).

Sympathetic Nervous System Activation

Activation of the sympathetic nervous system is a pathophysiological hallmark of essential hypertension (Esler et al. 1988, 2010; Grassi et al. 1998, 2005; Greenwood et al. 1999; Rumantir et al. 1999; Lambert et al. 2007; DiBona and Esler 2010). As described below, stimulation of the renal sympathetic outflow is thought to be pivotal in hypertension pathogenesis. It is possible to record the firing of individual human sympathetic fibers, in postganglionic sympathetic fibers directed to the skeletal muscle vasculature. In essential hypertension salvos of single-fiber firings

(multiple firings within a cardiac cycle) are commonly detected (Lambert et al. 2007; Esler et al. 2008a). Nerve salvos have a disproportionately strong influence on the cardiovascular system. Salvos of single-fiber firings appear to be a "signature" of stress exposure. This contrasts with the sympathetic nervous system activation in contexts not specifically linked to mental stress, such as in obesity, where there is an increase in multiunit burst firing frequency (Lambert et al. 2007), due to recruitment of previously silent fibers, but without the occurrence of sympathetic single-fiber firing salvos.

Plasma Cortisol Concentration

Mid-morning plasma cortisol was measured (arterial sampling) in untreated patients with essential hypertension and from matching healthy subjects (Esler et al. 2008a). In patients with essential hypertension, plasma cortisol concentration was 74 (7) ng/ml (mean, SEM) compared with 47 (7) ng/ml in the matched healthy volunteers ($P = 0.03$). These findings provide presumptive evidence of higher stress levels in essential hypertension than in healthy people.

Epinephrine as a Sympathetic Nerve Cotransmitter

An additional line of evidence supporting the importance of mental stress in the sympathetic activation of essential hypertension comes from the observation that the stress hormone, epinephrine, is a cotransmitter in the sympathetic nerves of hypertensive patients (Table 1) (Rumantir et al. 2000). My colleagues and I demonstrated this with isotope dilution methodology, involving the intravenous infusion of tritiated epinephrine and the sampling of blood from the coronary sinus of the heart. Our results indicate that epinephrine constitutes approximately 10 % of the catecholamine released by the sympathetic nerves of the heart in essential hypertension. Epinephrine co-release in sympathetic nerves is not seen in healthy people but occurs in experimental models of mental stress.

The co-released epinephrine seems to originate from in situ synthesis, involving phenylethanolamine-N-methyltransferase (PNMT) in sympathetic nerves of patients with essential hypertension (Esler et al. 2008a). Biopsy of small forearm or hand veins to access sympathetic nerve tissue (these veins have dense sympathetic innervation) allowed us to analyze sympathetic nerve proteins in patients with essential hypertension. Our principal interest was in PNMT. This enzyme does not occur in sympathetic nerves in health, being confined in its distribution to the adrenal medulla and adrenaline synthesizing neurons of the brain stem. PNMT is induced in sympathetic nerves of experimental animals during chronic stress exposure (Micutkova et al. 2004). Immunoblot staining methods were developed for demonstrating PNMT in sympathetic nerve proteins extracted from the vein biopsies in the hypertensive patients. The blot was probed with a polyclonal antibody for PNMT, the positive control being homogenized human adrenal gland lysate. With Western blot analysis, we

documented the presence of PNMT in four of five patients with essential hypertension but in none of six healthy people (Esler et al. 2008a, b).

Illustrative parallels can be drawn between hypertension, and ***panic disorder,*** which provides an explicit clinical model of recurring stress responses (Davies et al. 1999; Esler et al. 2008a, b). The findings reinforce the biological case for essential hypertension being caused by chronic mental stress, in that there were many instances of parallel neural biological disturbance:

(i) There is clinical comorbidity; panic disorder prevalence is increased threefold in essential hypertension.
(ii) In panic disorder and essential hypertension, but not in health, single sympathetic nerve fibers commonly fire repeatedly, in salvos, within an individual cardiac cycle.
(iii) For both, epinephrine co-transmission is present in sympathetic nerves.
(iv) There is induction of the epinephrine-synthesizing enzyme, PNMT, in sympathetic nerves in essential hypertension and panic disorder.

Pathophysiological Mechanisms of the Hypertension

The weight of evidence supports the importance of neural mechanisms involving the sympathetic nervous system in the pathogenesis of essential hypertension (Esler et al. 1988, 2010; Grassi et al. 1998, 2005; Greenwood et al. 1999; Rumantir et al. 1999; Lambert et al. 2007; DiBona and Esler 2010) and doubly so in hypertension attributable to chronic mental stress (Esler et al. 2008a). Surprisingly, cortisol is not the prime mover here, unlike in some other medical settings.

The Sympathetic Nervous System

Application of sympathetic nerve recording and norepinephrine spillover methodology (measurement of the release of norepinephrine from sympathetic nerves to plasma) has demonstrated activation of sympathetic nervous outflows to the kidneys, heart, and skeletal muscle vasculature, typically a doubling or trebling overall, in patients with essential hypertension (Esler et al. 1988, 2010; Grassi et al. 1998, 2005; Greenwood et al. 1999; Rumantir et al. 1999; Lambert et al. 2007; DiBona and Esler 2010). The syndrome of neurogenic essential hypertension appears to account for no less than 50 % of all cases of high blood pressure. This estimate is based on both the proportion of patients with essential hypertension who have demonstrable sympathetic excitation and the number in whom substantial blood pressure lowering is achieved with antiadrenergic drugs or devices (Krum et al. 2009; Symplicity Investigators 2010). Single-fiber sympathetic recording demonstrates increased firing frequencies (Greenwood et al. 1999; Lambert et al. 2007) and multiple firings within a cardiac cycle (firing salvos), not seen in health (Lambert et al. 2007; Esler et al. 2008).

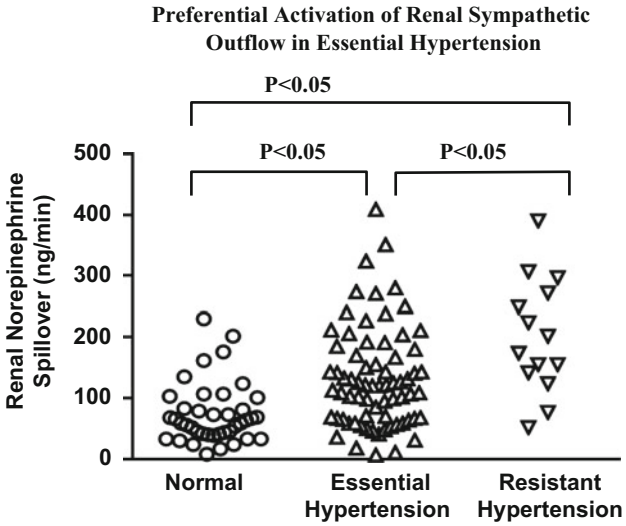


Fig. 2 Sympathetic activity in the kidneys, assessed using isotope dilution measurements of renal norepinephrine spillover to plasma, in healthy volunteers and patients with arterial hypertension, in whom renal sympathetic activation was evident in many. In untreated patients with mild-moderately severe essential hypertension (middle column), renal norepinephrine spillover was increased overall and elevated in approximately 50 %. In drug-resistant hypertension, with patients administered on average five antihypertensive drug classes, renal norepinephrine spillover was higher again, attributable to their hypertension, and also perhaps its treatment; vasodilators, dihydropyridine calcium channel blockers, and diuretics stimulate the sympathetic nervous system. From unpublished results of the author, Markus Schlaich, Gavin Lambert, and Dagmara Hering

Does this Sympathetic Activation Cause the Blood Pressure Elevation?

There is strong evidence, both historical and contemporary, that the answer to this question is "yes." In earlier times, prior to the availability of antihypertensive drugs, extensive surgical sympathectomy was effectively used as a treatment of severe hypertension (Smithwick et al. 1956). Of the antihypertensive drugs subsequently developed in the mid-twentieth century, most were antiadrenergic.

Activation of the sympathetic nervous outflow to the kidneys (Fig. 2) is pivotal in hypertension pathogenesis (Dibona and Esler 2010). Once it was thought that the sympathetic nervous system exerts minute by minute circulatory control only and was not of importance in causing hypertension. The regulatory effects of the renal sympathetic nerves on renal tubular reabsorption of sodium, renin release, renal blood flow and glomerular filtration rate are, however, now seen to provide hypertension-producing mechanisms. The renal sympathetic nerves are stimulated in patients with hypertension at all phases of the disease, in mild, developing hypertension through to severe grades, of drug-resistant hypertension (Fig. 2).

Neurogenic Hypertension: A Final Common Pathway for "Lifestyle Hypertension?"

Hypertension commonly arises from societal ills, from the obesity epidemic, from sedentary lifestyle, and as emphasized here from chronic mental stress both in the workplace (Steptoe and Willemsen 2004; Chandola et al. 2006) and in the life of nations (Poulter et al. 1990). There is compelling evidence that each elevates blood pressure primarily through neural mechanisms and, in particular, through activation of the renal sympathetic outflow (Esler et al. 1988, 2010; Rumantir et al. 1999; DiBona and Esler 2010).

No doubt it would be best to catch this pathophysiological fault of chronic renal sympathetic activation at its roots, through applying non-pharmacological treatment measures. The application of relaxation and stress reduction therapies has a helpful antihypertensive effect, but less than anticipated, given the importance of stress in pathogenesis, and surprisingly this effect is outstripped by weight loss from calorie restriction and by aerobic exercise training (Table 2). For minimal elevations of blood pressure, these non-pharmacological preventive and treatment modalities may be powerful enough. In more severe hypertension, although chronic mental stress may be an important causal factor, rather than changing the world, my colleagues and I have used a new device-based antihypertensive treatment, inhibiting what is the common final pathway, the renal sympathetic nerves, by ablating them using an intravascular radiofrequency catheter. In patients with resistant hypertension, although the final place of this technique in treating hypertension remains uncertain (Esler 2014a, b), the strategy has produced encouraging results (Krum et al. 2009; Symplicity Investigators 2010).

Table 2 Non-pharmacological blood pressure reduction: *the hierarchy*

1. Weight loss/calorie restriction
2. Repetitive aerobic exercise
3. Dietary sodium restriction
4. Restriction of alcohol consumption
5. Stress reduction/relaxation training
6. Vegetarian diet
7. Biofeedback

This is a rank ordering of the efficacy of non-drug methods of blood pressure lowering. Antihypertensive devices are excluded. Exercise training and weight loss are top of the list. Stress reduction and relaxation techniques are helpful, but lower blood pressure less than might be expected from the strength of the evidence supporting the "psychogenic hypertension" proposition. Perhaps this is attributable to the difficulty in sustaining these treatment interventions. Both weight loss and aerobic exercise training reduce sympathetic activity and preferentially the renal sympathetic outflow

Conclusion

The Renal Sympathetic Nerves Provide a Universal Common Pathway of Hypertension Pathogenesis

How can it be that renal sympathetic denervation is often effectively antihypertensive? I suggest it is because renal nerve ablation cuts the legendary Gordian knot, at the intersecting influence in hypertension pathogenesis of stress, the sympathetic nervous system, the kidneys, and dietary salt. Too often each of these factors is thought of as a unitary progenitor of hypertension, but they act in concert (Koepke et al. 1988; DiBona and Esler 2010).

Renal sympathetic activation in human hypertension has multiple origins, obesity (Rumantir et al. 1999), sedentary life (Meredith et al. 1991), and chronic mental stress (Tidgren and Hjemdahl 1989) being three, which explains its high prevalence. In the presence of high dietary sodium intake, all too common in developed societies, this activation of the renal sympathetic outflow provides concurrent "neural," "renal," and "sodium" mechanisms of hypertension development, primarily through the endpoint of excessive renal tubular reabsorption of sodium (Esler 2014a, b). Endovascular renal denervation can break the nexus between stress, salt, and the nervous system in hypertension pathogenesis.

References

Alvarenga, M. E., Richards, J. C., Lambert, G., & Esler, M. D. (2006). Psychophysiological mechanisms in panic disorder: A correlative analysis of noradrenaline spillover, neuronal noradrenaline reuptake, power spectral analysis of heart rate variability and psychological variables. *Psychosomatic Medicine, 68*, 8–16.

Brod, J. (1960). Essential hypertension: Haemodynamic observations with a bearing on its pathogenesis. *Lancet, ii*, 773–778.

Chandola, T., Brunner, E., & Marmot, M. (2006). Chronic stress at work and the metabolic syndrome. *British Medical Journal, 332*, 521–524.

Davies, S. J., Ghahramani, P., Jackson, P. R., Noble, T. W., Hardy, P. G., Hippislet-Cox, J., et al. (1999). Association of panic disorder and panic attacks with hypertension. *American Journal of Medicine, 107*, 310–316.

DiBona, G. F. (2005). Physiology in perspective: The wisdom of the body. Neural control of the kidney. *American Journal of Physiology Regulatory Integrative and Comparative Physiology, 289*, R633–R641.

DiBona, G. F., & Esler, M. (2010). Translational medicine: The antihypertensive effect of renal denervation. *American Journal of Physiology Regulatory Integrative and Comparative Physiology, 298*, R245–R253.

Esler, M. (2014a). Illusions of truths in the symplicity HTN-3 trial: Generic design strengths but neuroscience failings. *Journal of the American Society of Hypertension* doi: 10.1016/jash.2014.06.001.

Esler, M. (2014b). The John T Shepherd Lecture. Renal denervation for hypertension: Observations and predictions of a founder. *European Heart Journal*. doi:10.1093/eurheartj/ehu091.

Esler, M., Jennings, G., Korner, P., Willett, I., Dudley, F., Hasking, G., Anderson, W., & Lambert, G. (1988). The assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension, 11*, 3–20.

Esler, M., Julius, S., Zweifler, A., Randall, O., Harburg, E., Gardiner, H., et al. (1977). Mild high-renin essential hypertension: A neurogenic human hypertension? *New England Journal of Medicine, 296*, 405–411.

Esler, M., Eikelis, N., Schlaich, M., Lambert, G., Alvarenga, M., Dawood, T., et al. (2008a). Chronic mental stress is a cause of essential hypertension: Presence of biological markers of stress. *Clinical and Experimental Pharmacology and Physiology, 35*, 498–502.

Esler, M., Eikelis, N., Schlaich, M., Lambert, G., Alvarenga, M., Kaye, D., et al. (2008b). Human sympathetic nerve biology; Parallel influences of stress and epigenetics in essential hypertension and panic disorder. *Annals of New York Academy of Science, 1148*, 338–348.

Esler, M., Lambert, E., & Schlaich, M. (2010). Point counterpoint: Chronic activation of the sympathetic nervous system is the dominant contributor to systemic hypertension. *Journal of Applied Physiology, 109*, 1996–1998.

Ferrier, C., Esler, M., Eisenhofer, G., Wallin, G., Horne, M., Cox, H., et al. (1992). Increased norepinephrine spillover into the cerebrovascular circulation in essential hypertension: Evidence of high central nervous system norepinephrine turnover? *Hypertension, 19*, 62–69.

Folkow, B. (1982). Physiological aspects of primary hypertension. *Physiological Reviews, 62*, 348–504.

Folkow, B. (2004). Considering the "mind" as a primary cause. In J. I. S. Robertson & A. Zanchetti (Eds.), *Handbook of hypertension* (Hypertension in the Twentieth Century: Concepts and Achievements, Vol. 22, pp. 59–79). Amsterdam: Elsevier.

Geisbock, F., Cited in Julius, S., & Esler, M., (Eds.) (1976). *The nervous system in arterial hypertension*. Springfield: Charles C Thomas; page xii.

Gianaros, P., Sheu, L., Matthews, K., Jennings, J., Manuck, S., & Hariri, A. (2008). Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *Journal of Neuroscience, 28*, 990–999.

Grassi, G., Colombo, M., Seravalle, G., Spaziani, D., & Mancia, G. (1998). Dissociation between muscle and skin sympathetic nerve activity in essential hypertension, obesity, and congestive heart failure. *Hypertension, 31*, 64–67.

Grassi, G., Dell'Oro, R., Quarti-Trevano, F., Scopelliti, F., Seravalle, G., Paleari, F., et al. (2005). Neuroadrenergic and reflex abnormalities in patients with the metabolic syndrome. *Diabetologia, 48*, 1359–1365.

Greenwood, J. P., Stoker, J. B., & Mary, D. A. S. G. (1999). Single-unit sympathetic discharge. Quantitative assessment in human hypertensive disease. *Circulation, 100*, 1305–1310.

Harburg, E., Erfurt, J. C., & Hauenstein, L. S. (1973). Socio-ecological stress, suppressed hostility, skin colour, and black-white male blood pressure: Detroit. *Psychosomatic Medicine, 1973*(35), 276–296.

Henry, J. P., & Grim, C. E. (1990). Psychosocial mechanisms of primary hypertension. *Journal of Hypertension, 8*, 783–793.

Henry, J. P., Stephens, P. M., & Santisteban, G. A. (1975). A model of psychosocial hypertension showing reversibility and progression of cardiovascular complications. *Circulation Research, 36*, 156–164.

Jackson, K., Palma-Rigo, K., Nguyen-Huu, T., Davern, P., & Head, G. (2014). Major contribution of the medial amygdala to hypertension in BPH/2J genetically hypertensive mice. *Hypertension, 63*, 811–818.

Julius, S., & Conway, J. (1968). Hemodynamic studies in patients with borderline blood pressure elevation. *Circulation, 38*, 282–288.

Karasek, R., Baker, D., & Marxer, F. (1981). Job decision latitude, job demands, and cardiovascular disease: A prospective study of Swedish men. *American Journal of Public Health, 71*, 694–705.

Klein, S. (2007). The secret pulse of time. S. *Fischer Verlag, Berlin,* 2006 (Translation, Avalon Publishing Group, USA).

Koepke, J. P., Jones, S., & DiBona, G. F. (1988). Stress increases renal nerve activity and decreases sodium excretion in Dahl rats. *Hypertension, 11*, 334–338.

Korner, P. I. (2007). *Essential hypertension and its causes. Neural and non-neural mechanisms*. Oxford: Oxford University Press.

Krum, H., Schlaich, M. P., Whitbourn, R., Sobotka, P., Sadowski, J., Bartus, K., Kapelak, B., et al. (2009). Catheter-based renal sympathetic denervation for resistant hypertension: A multicentre safety and proof-of-principle cohort study. *The Lancet, 373*, 1275–1281.

Lambert, E., Straznicky, N., Schlaich, M. P., Dawood, T., Hotchkin, E., Esler, M. D., et al. (2007). Differing patterns of sympathoexcitation in normal weight and obesity-related hypertension. *Hypertension, 50*, 862–868.

Light, K. C., & Obrist, P. A. (1980). Cardiovascular reactivity to behavioral stress in young males with and without marginally elevated casual systolic pressures: Comparison of clinic, home, and laboratory measures. *Hypertension, 2*, 802–808.

Lund-Johansen, P. (1994). Haemodynamics of essential hypertension. In J. D. Swales (Ed.), *Textbook of hypertension* (pp. 61–76). Oxford: Blackwell Sci Publ.

Meredith, I. T., Friberg, P., Jennings, G. L., Dewar, E. M., Fazio, V. A., Lambert, G. W., et al. (1991). Regular exercise lowers renal but not cardiac sympathetic activity in man. *Hypertension, 18*, 575–582.

Micutkova, L., Krepsova, K., Sabban, E., Krizanova, O., & Kvetnansky, R. (2004). Modulation of catecholamine-synthesizing enzymes in the rat heart by repeated immobilization stress. *Annals of the New York Academy of Sciences, 1018*, 424–429.

Perini, C., Muller, F. B., Rauchfleisch, U., Battegay, R., Hobbi, V., & Buhler, F. R. (1986). Hyperadrenergic borderline hypertension is characterized by suppressed aggression. *Journal of Cardiovascular Pharmacology, 8*(Suppl 5), 53–56.

Poulter, N. R., Khaw, K. T., Hopwood, B. E. C., Mugambi, W., Peart, W. S., Rose, G., et al. (1990). The Kenyan Luo migration study: Observations on the initiation of the rise in blood pressure. *BMJ, 300*, 967–972.

Rumantir, M. S., Vaz, M., Jennings, G. L., Collier, G., Kaye, D. M., Seals, D. R., et al. (1999). Neural mechanisms in human obesity-related hypertension. *Journal of Hypertension, 17*, 1125–1133.

Rumantir, M. S., Jennings, G. L., Lambert, G. W., Kaye, D. M., Seals, D. R., & Esler, M. D. (2000). The "adrenaline hypothesis" of hypertension revisited: Evidence for adrenaline release from the heart of patients with essential hypertension. *Journal of Hypertension, 18*, 717–723.

Siegrist, J. (1996). Adverse health effects of high-effort/low-reward conditions. *Journal of Occupational Health Psychology, 71*, 694–705.

Smithwick, R. H., Bush, R. D., Kinsey, D., & Whitelaw, G. P. (1956). Hypertension and associated cardiovascular disease; Comparison of male and female mortality rates and their influence on selection of therapy. *Journal of the American Medical Association, 160*, 1023–1026.

Steptoe, A., & Willemsen, G. (2004). The influence of job control on ambulatory blood pressure and perceived stress over the working day in men and women from the Whitehall II cohort. *Journal of Hypertension, 22*, 915–920.

Symplicity HTN-2 Investigators. (2010). Renal sympathetic denervation in patients with treatment-resistant hypertension (the symplicity HTN-2 trial): A randomized controlled trial. *Lancet, 376*, 1903–1909.

Tidgren, B., & Hjemdahl, P. (1989). Renal responses to mental stress and epinephrine in man. *American Journal of Physiology, 257*, F682–F689.

Timio, M., Verdechioa, P., Rononi, M., Gentili, S., Francucci, B., Bichisao, E., et al. (1988). Age and blood pressure changes: A 20 year follow-up study of nuns of a secluded order. *Hypertension, 12*, 457–461.

Stress Cardiomyopathy

Ilan S. Wittstein

Contents

Keywords

Stress cardiomyopathy • Takotsubo cardiomyopathy • Apical ballooning • Catecholamines • Sympathetic nervous system

Introduction

Considerable evidence has emerged during the past few decades to support a strong association between acute psychological stress and cardiovascular morbidity and mortality. Well-designed case-crossover studies have demonstrated that acute emotional stressors such as anger and sadness more than double the risk of myocardial

I.S. Wittstein (✉)
Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: iwittste@jhmi.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_44

infarction (Mittleman et al. 1995; Steptoe et al. 2006). Large population-based studies have demonstrated that emotionally traumatic events such as earthquakes (Leor et al. 1996) and acts of war (Meisel et al. 1991) are associated with an increased incidence of myocardial infarction and sudden death. The pathophysiologic mechanisms implicated in acute stress-related cardiac morbidity and mortality include coronary vasoconstriction (Kop et al. 2001), acute plaque rupture (Burke et al. 1999), and lethal ventricular arrhythmias (Steinberg et al. 2004), but until fairly recently there has been very little known about the effects of acute psychological stress on cardiac contractile function.

During the past 10 years, a novel syndrome of acute heart failure precipitated by emotional or physical stress has been described. Patients with *stress cardiomyopathy* (SCM) typically present with chest pain, electrocardiographic abnormalities, cardiac enzyme elevation, and focal left ventricular wall motion abnormalities, and it is therefore not surprising that for many years this syndrome was mistaken for an acute coronary syndrome. As familiarity with SCM has increased, however, it has become evident that the clinical features and pathophysiology of this unique syndrome are distinct from those of an acute myocardial infarction. SCM appears to involve sympathetically mediated myocardial stunning that is independent of plaque rupture and coronary thrombosis, though the precise mechanism remains incompletely understood.

This chapter will review the prevalence, clinical features, prognosis, and treatment of stress cardiomyopathy. The proposed pathophysiologic mechanisms of the syndrome will be discussed in detail, and risk factors that may increase individual susceptibility to SCM will be reviewed. In particular, there is increasing evidence that individuals with mood disorders and anxiety may be particularly at risk for SCM, and the available data supporting this emerging relationship will be presented.

Nomenclature

During the past 20 years, SCM has been referred to by a variety of names in the medical literature. In the early 1990s, Japanese authors introduced the syndrome as *takotsubo cardiomyopathy*, which at the time they believed was a syndrome of acute myocardial dysfunction due to multivessel coronary artery spasm (Dote et al. 1991). The name takotsubo referred to an octopus-trapping pot with a wide base and narrow neck whose appearance resembled the unusual left ventricular shape of patients with this condition. Reports of takotsubo cardiomyopathy appeared almost exclusively in Japanese medical literature throughout the 1990s. When Japanese authors finally published a large series of these patients in an American medical journal in 2001, they introduced the condition as *transient left ventricular apical ballooning syndrome* (Tsuchihashi et al. 2001), a descriptive term that they likely felt would be more acceptable to a Western audience. The

syndrome remained relatively obscure in the medical literature until 2005 when two separate series from the United States were published in the same week (Sharkey et al. 2005; Wittstein et al. 2005). The names *stress cardiomyopathy* and *broken heart syndrome* were formally introduced (Wittstein et al. 2005) and were quickly popularized by the media, helping to bring worldwide attention to this previously underappreciated medical condition. In 2006, SCM was formally classified as an acquired primary cardiomyopathy in an American Heart Association scientific statement (Maron et al. 2006). Over the past 10 years, the medical literature regarding SCM has increased dramatically, and all four names have continued to be used interchangeably. The syndrome will be referred to as *stress cardiomyopathy* throughout this chapter, but the reader should be aware that at the present time a clear consensus regarding the optimal name for the syndrome has still not been established.

Incidence

While SCM was once felt to be a rare medical condition, it is clear from the rapidly expanding medical literature that the syndrome is far more prevalent than what was originally believed. A large number of retrospective series have demonstrated that approximately 1–2 % of patients admitted to the hospital with suspected acute coronary syndromes (ACS) are ultimately diagnosed with SCM (Akashi et al. 2005; Bellandi et al. 2012; Bybee et al. 2004; Eshtehardi et al. 2009; Haghi et al. 2006; Parodi et al. 2007; Previtali et al. 2009; Showkathali et al. 2014; Wedekind et al. 2006). In women presenting with suspected ACS, the incidence of SCM is even higher with rates ranging from 5 % to 7.5 % (Elian et al. 2006; Parodi et al. 2007; Previtali et al. 2009; Sy et al. 2013; Wedekind et al. 2006). Deshmukh and colleagues used the Nationwide Inpatient Sample database (a 20 % sample of US community hospitals) to estimate the prevalence of SCM in the United States in 2008. Using the ICD-9 discharge diagnosis code 429.83, they identified 6,837 cases of SCM, a cohort that accounted for approximately 0.02 % of all hospitalizations in the United States that year (Deshmukh et al. 2012). All of these studies likely underestimate the true incidence of SCM since they include only those patients presenting with suspected ACS who undergo coronary angiography, and they exclude the majority of cases that occur on inpatient wards and in medical, surgical, and neurologic intensive care units where the syndrome is prevalent but often under recognized. This is supported by the study from Park and colleagues that showed that 28 % of patients admitted to a medical intensive care unit with a noncardiac illness had echocardiographic evidence of left ventricular apical ballooning (Park et al. 2005). More widespread recognition of this syndrome by physicians in diverse subspecialties and larger prospective studies will be necessary before the true incidence of SCM can be fully appreciated.

Patient Demographics

Though originally described in Japan, it is now clear that SCM occurs in populations with diverse ethnic and racial backgrounds, and large series have been reported worldwide (Citro et al. 2012; Eitel et al. 2011; Elian et al. 2006; Eshtehardi et al. 2009; Isogai et al. 2014; Kwon et al. 2013; Looi et al. 2012; Murakami et al. 2014; Nunez Gil et al. 2015; Parodi et al. 2011; Redfors et al. 2015; Schultz et al. 2012; Sharkey et al. 2010; Song et al. 2012; Weihs et al. 2013). A common observation in all of these series is that SCM affects primarily women (Table 1), and several systematic reviews have demonstrated that women account for approximately 90 % of reported cases in the medical literature (Gianni et al. 2006; Pelliccia et al. 2015; Pilgrim and Wyss 2008). While SCM can affect individuals of any age and can even occur in children, the vast majority of cases have been reported in older postmenopausal women with mean ages ranging from 55 to 77 (Gianni et al. 2006; Pelliccia et al. 2015; Pilgrim and Wyss 2008). In fact, women older than 55 years have a 4.8-fold risk of developing SCM compared to women younger than 55 years (Deshmukh et al. 2012). In the United States, SCM affects primarily Caucasian women and occurs far less frequently in African American, Hispanic, and Asian populations (Deshmukh et al. 2012). Patients with SCM also appear to have higher incomes and live in wealthier zip codes than patients admitted to the hospital with other diagnoses (El-Sayed et al. 2012).

Traditional coronary risk factors are common in patients with SCM (Table 1). In a large systematic review of 1,109 patients with SCM, hypertension was reported in 54 % of the cases, hyperlipidemia in 32 %, diabetes mellitus in 17 %, and tobacco use in 22 % (Pelliccia et al. 2015). The prevalence of these risk factors in SCM, however, is still lower than in patients with acute myocardial infarction (El-Sayed et al. 2012; Falola et al. 2013). Other frequently observed comorbidities include chronic obstructive lung disease, cerebrovascular disease, thyroid disease, sepsis, and malignancy (Burgdorf et al. 2008a; El-Sayed et al. 2012; Falola et al. 2013; Pelliccia et al. 2015; Regnante et al. 2009). In addition, several series and systematic reviews have demonstrated a high prevalence of psychological disorders in patients with SCM, with these patients being two to three times more likely to have depression or anxiety compared to patients with acute coronary syndromes (El-Sayed et al. 2012). These observations suggest that chronic mood disorders and anxiety may be potent risk factors for the development of SCM. Possible explanations for this relationship will be discussed in more detail later in the chapter.

Clinical Symptoms and Presentation

Patients with SCM can present with symptoms that are indistinguishable from an acute myocardial infarction. The most common symptoms are chest pain and shortness of breath (Table 1), but other symptoms can include diaphoresis, nausea, weakness, and even syncope. The majority of patients are hemodynamically stable

Table 1 Clinical characteristics of stress cardiomyopathy from large case series

Reference	Number patients	Trigger identified (%)	Mean age (Yrs)	Female (%)	HTN (%)	HLD (%)	DM (%)	TOB (%)	CP (%)	SOB (%)	CHF (%)	Shock (%)	VT/VF (%)	Inpatient death (%)
Tsuchihashi et al. (2001)	88	73	67	86	48	24	12	NR	67	7	37	20	9	1
Elesber et al. (2007)	100	56	66	95	52	33	5	38	77	8	44	7	2	2
Regnante et al. (2009)	70	67	67	95	66	49	14	47	77	40	NR	9	4	1.4
Singh et al. (2010)	114	83	71 (A) 64 (NA)	93	66	33	8	47	69	18	10	7	1	1
Sharkey et al. (2010)	136	89	68	96	43	NR	NR	NR	63	18	NR	NR	NR	2
Previtali et al. (2011)	128	59	67	98	59	45	7	23	69	23	10[b]	10[b]	2	0.8
Eitel et al. (2011)	256	71	69	89	73	26	19	20	88[a]	88[a]	NR	NR	0	1.6
Parodi et al. (2011)	116	69	73	91	54	30	9	24	72	NR	17	5	1	2
Madhavan et al. (2011)	118	76	70	97	62	NR	13	NR	63	52	45	21	NR	3
Looi et al. (2012)	100	69	65	95	35	29	11	16	78	41	14	4	5	1
Citro et al. (2012)	190	72	66	92	48	34	6	18	80	11	16	6	4.5	2.8
Schultz et al. (2012)	115	100	64	86	31	NR	7	14	NR	NR	38	14	6	6
Song et al. (2012)	137	80	59	74	34	NR	18	6	52	56	42	35	13	9
Kwon et al. (2013)	208	89	66	73	51	16	26	19	37	42	26	11	4	8.7
Weihs et al. (2013)	179	57	69	94	77	24	20	18	82	32	4.5	3.4	1.7	0.6
Nunez Gil et al. (2015)	202	73	70	90	67	41	15	15	80	45	34	8	5	2.4
Redfors et al. (2015)	302	NR	66	84	41	21	10	18	NR	NR	NR	5	3	NR

A apical ballooning variant, *CHF* congestive heart failure during admission, *CP* chest pain on admission, *DM* history of diabetes mellitus, *HLD* history of hyperlipidemia, *HTN* history of hypertension, *NA* non-apical ballooning variant, *NR* not reported, *SOB* shortness of breath on admission, *TOB* current or prior tobacco use, *VF* ventricular fibrillation, *VT* ventricular tachycardia, *Yrs* years

[a]88 % had CP and/or dyspnea

[b]10 % had heart failure or shock

at the time of presentation, but up to a third can have serious complications that include decompensated heart failure, cardiogenic shock, and malignant ventricular arrhythmias. Some centers have reported the incidence of heart failure in SCM to be as high as 45 % (Table 1), and risk factors for the development of acute heart failure include age >70 years, the presence of a physical stressor, and an ejection fraction (EF) <40 % (Madhavan et al. 2011). Cardiogenic shock necessitating vasopressor support or intra-aortic balloon counterpulsation (IABP) occurs in up to 20 % of cases, while life-threatening arrhythmias have been reported in fewer than 10 % of patients in most series (Table 1). Other complications of SCM include left ventricular outflow tract obstruction (De Backer et al. 2014), acute mitral regurgitation (Izumo et al. 2011), apical thrombus formation and cardio-embolic stroke (de Gregorio et al. 2008), pericarditis, and rarely cardiac rupture (Kumar et al. 2011).

Several reports have suggested that SCM may have a temporal pattern of occurrence. In contrast to acute myocardial infarction that peaks during winter months, a number of groups have demonstrated that the incidence of SCM is highest during the summer (Aryal et al. 2014; Citro et al. 2009; Deshmukh et al. 2012; Song et al. 2013). Some reports also suggest that SCM occurs most commonly during morning hours (Citro et al. 2009; Song et al. 2013), though Sharkey and colleagues found the incidence to be highest between noon and 4 PM (Sharkey et al. 2012). More studies will be necessary to better understand whether these observations are the result of a circadian pattern of sympathetic nervous system activity in patients with SCM or simply reflect the time of day when these individuals are most often subjected to surgeries, procedures, and other daily stressors.

Diagnosis and Clinical Features

Despite the fact that SCM was first described almost 25 years ago, uniformly accepted diagnostic criteria are still lacking. The first and most widely cited criteria were proposed by Mayo Clinic investigators in 2004 and then modified in 2008 (Prasad et al. 2008). Since that time, other groups that have suggested diagnostic criteria include the Japanese Takotsubo Cardiomyopathy Study Group (Kawai et al. 2007), the Takotsubo Italian Network (Parodi et al. 2014), the Gothenburg group (Redfors et al. 2014b), and the Johns Hopkins group (Wittstein 2012). All of these proposed criteria have subtle differences and limitations that have recently been reviewed (Redfors et al. 2014b). The Johns Hopkins diagnostic criteria are comprised of both mandatory and nonmandatory criteria and are shown in Table 2. The following six criteria can be used to reliably make the diagnosis of SCM and distinguish it from acute myocardial infarction:

Presence of an acute trigger: While not required to make the diagnosis of SCM, an acute emotional or physical stressor can be identified in the majority of patients presenting with this syndrome. It is precisely this observation that inspired the

Table 2 Proposed Johns Hopkins diagnostic criteria for stress cardiomyopathy

Helpful, but not mandatory, criteria:
An acute identifiable trigger (either emotional or physical)
Characteristic electrocardiographic changes that may include some or all of the following:
ST-segment elevation at time of admission (often <2 mm in magnitude and usually not associated with reciprocal ST-segment depression)
Diffuse deep T-wave inversion (may be present on admission or may evolve during the first several hospital days)
QT interval prolongation (usually maximal by 24–48 h)
Mildly elevated cardiac troponin (often appears disproportionately low given the degree of wall motion abnormality)
Mandatory criteria (all three criteria must be met):
Absence of coronary thrombosis or angiographic evidence of acute plaque rupture
Regional ventricular wall motion abnormalities that extend beyond a single epicardial vascular distribution (ventricular "ballooning")
Complete recovery of regional wall motion abnormalities (recovery is usually within days to weeks)

name *stress cardiomyopathy* (Wittstein et al. 2005), and it is one of the many reasons why enhanced sympathetic stimulation is believed to be central to the syndrome's pathogenesis. Early reports highlighted primarily the emotional triggers of SCM, but increased recognition of the syndrome has made it clear that SCM can also be precipitated by a wide variety of physical stressors (Sharkey et al. 2010). The most frequently seen emotional trigger at Johns Hopkins is grief due to the loss of a loved one, while commonly observed physical triggers include neurologic disorders (e.g., stroke, seizure, subarachnoid hemorrhage), respiratory problems (e.g., pneumonia, asthma exacerbation), and surgical procedures (Table 3). While identification of an acute stressor is common and should raise suspicion for SCM, not all patients present with an obvious precipitant. About 5 % of patients admitted with SCM at Johns Hopkins have no identifiable trigger, and this number is considerably higher in other reported series (Table 1). In a systematic review of 1,109 patients with SCM, 74 % presented with an acute emotional or physical trigger while 26 % had no identifiable precipitant (Pelliccia et al. 2015).

Characteristic electrocardiographic features: Patients with SCM can have a wide variety of electrocardiographic (ECG) findings. At the time of the acute presentation, the ECG may be normal, may have nonspecific ST-segment and T-wave abnormalities, or may even demonstrate frank ST-segment elevation (Fig. 1). It is important to emphasize that no ECG findings have been identified that are absolutely diagnostic of SCM or that can reliably distinguish the syndrome from acute myocardial infarction, and therefore patients presenting with ST-segment elevation are typically referred for urgent coronary angiography. Some investigators have found that compared to acute infarction, patients with SCM typically have a smaller magnitude of ST elevation in precordial leads (Sharkey et al. 2008) and are less likely to have reciprocal inferior ST-segment depression

Table 3 Examples of acute triggers precipitating stress cardiomyopathy at Johns Hopkins Hospital

Emotional triggers	
Grief	Death of a loved one; death of a pet; house burned down
Fear	Motor vehicle accident; severe claustrophobia; victim of robbery
Anger	Domestic argument; anger in court
Anxiety	Panic attack; anxiety over public speaking; anxiety about surgery; anxiety about illness of a family member; marital stress
Surprise	Surprise birthday party; unexpected reunion with family member
Physical triggers	
Neurologic injury	Subarachnoid hemorrhage; seizure; stroke; subdural hematoma; intracranial hemorrhage; gunshot wound to the head; brain mass; migraine headache
Surgery/procedure	Orthopedic surgery; exploratory laparotomy; abdominal aortic aneurysm repair; adrenalectomy; cervical spine surgery; decortications of empyema; thyroidectomy
Respiratory	Pneumonia; asthma exacerbation; pulmonary embolism; pneumothorax
Drug related	Epinephrine administration; dobutamine administration; cocaine use; Ativan withdrawal; clonidine withdrawal; 5-fluorouracil infusion; antidepressant withdrawal
Syncope	Includes syncope, near syncope, and severe vertigo
Strenuous activity	Moving heavy furniture; triathlon; vigorous housework; sexual intercourse
Gastrointestinal	Nausea and vomiting; gastrointestinal bleeding; small bowel obstruction; acute pancreatitis
Metabolic	Diabetic ketoacidosis; acute hypoglycemia; acute hyponatremia
Severe pain	Kidney stones; severe muscle spasms; bone fracture
Cardiac arrest	Ventricular tachycardia; ventricular fibrillation
Allergic reaction	Transfusion reactions; medicine allergy; bee sting
Sepsis	

(Ogura et al. 2003). Patients with SCM can also present with Q waves in precordial leads. In contrast to acute myocardial infarction, these Q waves are typically transient and are thought to be secondary to myocardial edema and not tissue necrosis. Within 24–48 h of the initial presentation, many patients with SCM develop distinctive ECG findings that include deep symmetric T-wave inversion and QT interval prolongation that frequently involve both precordial and limb leads (Fig. 1) (Wittstein et al. 2005). While the QT interval prolongation typically improves within a few days, the T-wave inversions may take days, weeks, or even months to normalize (Mitsuma et al. 2007).

Characteristic cardiac biomarker profile: The majority of patients with SCM have an elevation in cardiac enzymes at the time of presentation. The levels of these enzymes are typically low and disproportionate to the extensive amount of left ventricular dysfunction typically seen in these patients, suggesting a minimal amount of myocardial necrosis in SCM. In contrast, brain natriuretic peptide (BNP) levels in patients with SCM are usually markedly elevated at the time of

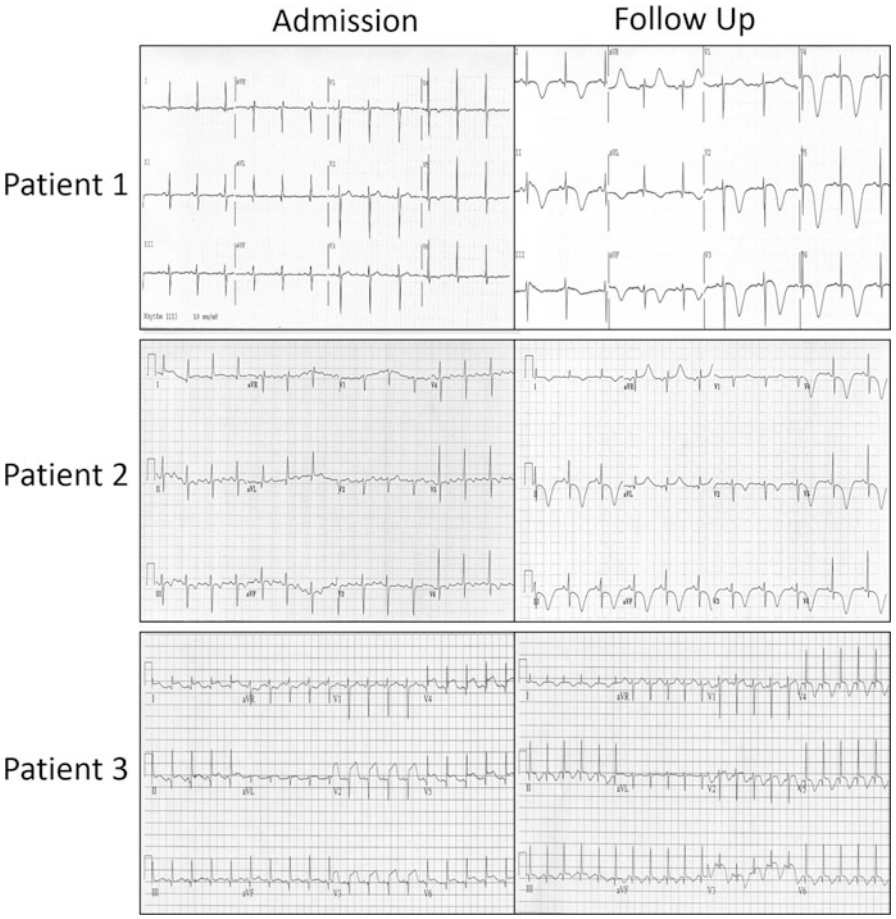


Fig. 1 Electrocardiographic findings of three patients with stress cardiomyopathy at the time of admission and at follow-up (within 48 h of admission). The ECG of patient 1 shows mild nonspecific T-wave changes at the time of admission, while patient 2 has more diffuse ST–T-wave abnormalities on admission. Patient 3 has marked ST-segment elevation diffusely with anteroseptal Q waves at the time of initial presentation. Despite the very different appearing electrocardiograms initially, all three patients develop characteristic ECG findings within 48 h of admission that include deep diffuse T-wave inversion and a markedly prolonged QT interval. Note also that the anterior Q waves seen at the time of admission in patient 3 are already resolving on the follow-up electrocardiogram

admission (Wittstein et al. 2005) and tend to be much higher than the levels seen in patients with acute myocardial infarction (Doyen et al. 2014). While the diagnosis of SCM cannot be definitively made from cardiac biomarkers alone, several authors have shown that an elevated BNP/troponin ratio at the time of presentation can help distinguish SCM from acute infarction with reasonable sensitivity and specificity (Doyen et al. 2014; Frohlich et al. 2012).

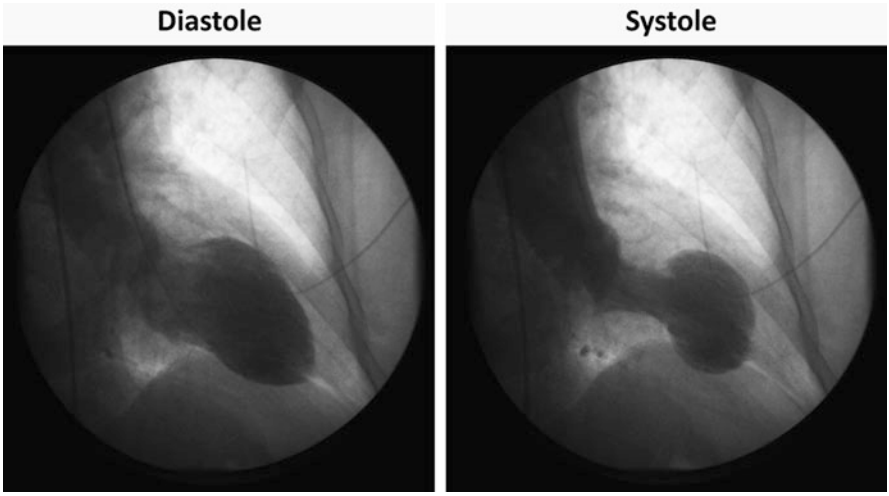


Fig. 2 Left ventriculography of a patient with stress cardiomyopathy during diastole (*left*) and systole (*right*). Note the typical pattern of apical ballooning which is characterized by akinesis of the apical and mid-ventricular walls with normal contractility of the basal segments

Absence of acute plaque rupture and coronary thrombosis: Most patients with SCM have normal coronary arteries at the time of angiography (Gianni et al. 2006; Pilgrim and Wyss 2008), but nonobstructive coronary atherosclerosis has been frequently reported in these patients (Hoyt et al. 2010; Winchester et al. 2008). Because patients with SCM present with chest pain, dynamic ECG changes, elevated cardiac enzymes, and focal left ventricular wall motion abnormalities, coronary angiography is recommended in most cases to rule out acute plaque rupture and coronary thrombosis, findings that would be diagnostic of an acute coronary syndrome and that would exclude the diagnosis of SCM. Interestingly, despite the absence of obstructive epicardial disease, patients with SCM often have abnormal coronary flow, suggesting that acute microcirculatory impairment may be central to the pathogenesis of this syndrome.

Ventricular "*ballooning*": Perhaps the most defining clinical feature of SCM is the unusual appearance of the left ventricle that is seen with ventriculography or echocardiography at the time of presentation. Unlike patients presenting with acute infarction, patients with SCM have left ventricular contractile abnormalities that extend beyond a single vascular territory. The majority of patients have akinesis or dense hypokinesis of the apical and mid-ventricular segments with sparing of the base of the ventricle, a contractile pattern that has been referred to as "left ventricular apical ballooning" (Fig. 2). Variants of the syndrome have been described, however, in which the mid- and basal portions of the heart are dysfunctional and the base is spared (Hurst et al. 2006; Reuss et al. 2007). These "mid-ventricular" and "basal" ballooning patterns account for approximately 20 % of SCM cases and are more commonly seen in men and in younger patients

(Nishida et al. 2014; Song et al. 2011). While SCM is characterized primarily by left ventricular contractile dysfunction, approximately one third of patients will have concurrent right ventricular dysfunction (A. A. Elesber et al. 2006). Patients with biventricular involvement are more likely to have heart failure and hemodynamic instability during the acute presentation.

Recovery of left ventricular function: SCM is characterized by complete and rapid recovery of ventricular systolic function. While the rate of recovery is variable, most patients demonstrate significant improvement in systolic function within a week of the initial presentation, with complete recovery occurring by the end of the third week. Cases of very slow left ventricular recovery taking up to a full year have been reported (Sharkey et al. 2010), but these cases are atypical. In general, if left ventricular contractile function has not completely normalized within 12 weeks of the initial presentation, alternative diagnoses should be considered.

Other Helpful Diagnostic Tools

Several imaging modalities have been used to help make the diagnosis of SCM and to distinguish the syndrome from acute infarction. Cardiac magnetic resonance imaging (MRI) provides analysis of regional wall motion abnormalities in both ventricles and can effectively identify the various ballooning patterns. Several studies have shown that the cardiac MRI of patients with SCM is characterized by myocardial edema and the absence of late gadolinium enhancement (LGE). These findings are indicative of myocardial viability and the absence of necrosis and help to distinguish SCM from other acute processes such as myocardial infarction and acute myocarditis (Eitel et al. 2011; Haghi et al. 2007; Sharkey et al. 2005; Wittstein et al. 2005).

Positron emission tomography (PET) has also been used to study myocardial metabolic activity in patients with SCM. Studies using F-18 fluorodeoxyglucose (FDG) PET have demonstrated marked metabolic impairment in regions of ventricular akinesis despite normal or only mildly impaired myocardial perfusion (Feola et al. 2006; Yoshida et al. 2007). The mechanism of this unique metabolic derangement is unknown but may result either from sympathetically mediated microcirculatory dysfunction or direct catecholamine-mediated impairment of myocyte glucose utilization.

Treatment of SCM

The treatment of SCM during the acute presentation is primarily supportive. Hemodynamically stable patients are frequently treated with diuretics, angiotensin-converting enzyme (ACE) inhibitors, and beta-blockers, though there are few data to support the benefit of these agents in this population. One study demonstrated that preexisting treatment with ACE inhibitors was protective

against shock, ventricular arrhythmias, and death in patients who subsequently developed SCM (Regnante et al. 2009), but a similarly protective effect was not observed with antecedent beta-blockade (Palla et al. 2012; Regnante et al. 2009). Patients with the apical ballooning variant of SCM are at particular risk for thrombus formation with subsequent cardio-embolic complications (de Gregorio et al. 2008), and short-term anticoagulation is therefore recommended unless there is a clear contraindication. For patients who are hemodynamically unstable at the time of presentation, reported treatments have included inotrope and vasopressor support, intra-aortic balloon counterpulsation (IABP), extracorporeal membrane oxygenation (Bonacchi et al. 2015), and even temporary left ventricular mechanical support (Zeballos et al. 2012). Catecholamine administration has been associated with left ventricular outflow tract obstruction (Sharkey et al. 2005) and increased mortality (Lee et al. 2010) in patients with SCM, and it has become standard practice at Johns Hopkins to use IABP to support hemodynamically unstable patients and to avoid exogenous catecholamines whenever possible. Fortunately, aggressive hemodynamic support is rarely required for more than a few days since even the most tenuous patients with SCM typically demonstrate rapid clinical improvement.

There is no consensus regarding the long-term treatment of SCM. While it seems reasonable to treat with ACE inhibitors and beta-blockers during the acute phase of this syndrome, the benefit of these agents once left ventricular systolic function has normalized is completely unknown. Chronic treatment with ACE inhibitors or angiotensin receptor blockers (ARBs) appeared to reduce the risk of SCM recurrence in a systematic review of 1664 patients (Singh et al. 2014), though ACE inhibitors, beta-blockers, aspirin, and statins had no effect on recurrence rate in a separate meta-analysis of 511 patients (Santoro et al. 2014). There have been no prospectively designed clinical trials examining the effect of standard pharmacologic therapy on outcomes in patients with SCM, and it is a routine practice at Johns Hopkins to discontinue ACE inhibitors and beta-blockers once left ventricular systolic function has fully recovered. A subset of patients with SCM may continue to have episodic chest discomfort for weeks to months after the initial presentation, and nitrates are frequently effective in relieving symptoms in these individuals.

There is a high prevalence of depression and anxiety in patients with SCM, but the impact of antidepressant use on morbidity and mortality in this population has not been studied prospectively. Dias and colleagues reported that antidepressant use in patients with SCM was associated with an increase in both in-hospital and long-term mortality (Dias et al. 2014). While antidepressant use may simply identify a group of patients with more severe psychiatric disease, it is also plausible that drugs such as selective norepinephrine reuptake inhibitors (SNRIs) may promote cardiotoxicity in patients with SCM by increasing local myocardial catecholamine concentrations. It seems reasonable that until more data are available, the routine use of antidepressants in patients with SCM should be avoided.

Prognosis and Recurrence

Most of the literature to date suggests that SCM has a favorable short- and long-term prognosis and relatively low risk of recurrence. In-hospital mortality from reported series has ranged from <1 % to as high as 9 % (Table 1), and the vast majority of deaths that occur in the hospital are from noncardiac causes. In a large meta-analysis of 2120 patients with SCM from 11 different countries, the in-hospital mortality rate was 4.5 % and was threefold higher in men than in women (Singh et al. 2014). Brinjikji and colleagues looked at 24,701 patients diagnosed with SCM in the National Inpatient Sample 2008–2009 and found a similar inpatient death rate of 4.2 % (Brinjikji et al. 2012). The vast majority of the patients who died had an underlying critical illness, and this is consistent with a previous observation that acute mortality in patients with SCM is associated with more severe systemic illness as determined by a higher Acute Physiology and Chronic Health (APACHE) II score (Joe et al. 2012). With respect to long-term prognosis, Redfors reported a 30-day mortality rate of 4.1 %, while Cacciotti found a death rate of 2.6 % at 2 years (Cacciotti et al. 2012; Redfors et al. 2015). In a large single-center retrospective experience from the Mayo Clinic, the 4-year mortality was 17 % which was similar to that observed in an age- and gender-matched population (Elesber et al. 2007). Sharkey and colleagues reported a 15 % 5-year mortality rate in a large series of patients with SCM. These patients had reduced survival compared to an age- and sex-matched population, but most of the deaths occurred within the first year and were due to noncardiac causes (Sharkey et al. 2010). Song reported an even higher mortality of 23 % at a median follow-up of 42 months, but once again only two of these patients died from cardiac causes (Song et al. 2010). When compared to patients with acute myocardial infarction, patients with SCM in one series were far more likely to develop malignancies at a median follow-up of 2.8 years. While the overall mortality did not differ significantly between the two groups, cardiac causes of death were relatively rare in patients with SCM (Burgdorf et al. 2008a). It is reasonable to conclude from these reports that cardiovascular mortality is quite low in patients with SCM, but overall prognosis is dependent on the presence and severity of underlying systemic disease.

The majority of patients with SCM will not experience a second episode, though recurrences have certainly been reported. In the series from Song et al., there were no recurrences during a median follow-up of 42 months (Song et al. 2010). This is in contrast to the Mayo Clinic series that reported a 4-year recurrence rate of 11.4 % (Elesber et al. 2007) and to the series from Sharkey and colleagues that reported a 5-year recurrence of 5 % (Sharkey et al. 2010). In a meta-analysis of 1664 patients with SCM, the annual rate of recurrence was 1.5 % with a cumulative incidence of recurrence of ~5 % at 6 years (Singh et al. 2014). It is interesting to note that recurrent episodes of SCM can occur many years apart and that each event may be characterized by a different ventricular ballooning pattern (Gach et al. 2012).

Pathophysiology of SCM

There is considerable evidence supporting the central role of enhanced sympathetic stimulation in the pathogenesis of SCM. An emotional or physical stressor precipitates the syndrome in the majority of cases, and SCM has been frequently associated with conditions of catecholamine excess such as pheochromocytoma (Takizawa et al. 2007) and central neurologic injury (Finsterer and Wahbi 2014). In addition, the clinical features of SCM and the various ventricular ballooning patterns can all be precipitated by the intravenous administration of catecholamines and beta-agonists (Abraham et al. 2009). Some patients with SCM due to emotional stress have markedly elevated plasma catecholamine levels compared to patients with Killip III myocardial infarction (Wittstein et al. 2005), though this observation has not been universal (Madhavan et al. 2009). Elevated coronary sinus norepinephrine levels have also been found in patients with SCM, suggesting an increase in local myocardial catecholamine release (Kume et al. 2008). Analysis of heart rate variability has demonstrated sympathetic predominance and a marked depression of cardiac parasympathetic activity in patients with SCM (Ortak et al. 2009), and an increase in muscle sympathetic nerve activity (MSNA) has been shown using microneurography (Vaccaro et al. 2014). Enhanced sympathetic tone in patients with SCM has also been demonstrated with myocardial scintigraphy using the norepinephrine analogue ^{123}I-metaiodobenzylguanidine (MIBG). These studies have shown a decreased heart/mediastinum (H/M) ratio and an increased washout rate suggesting abnormalities in presynaptic norepinephrine uptake and an increase in presynaptic catecholamine release (Burgdorf et al. 2008b). Interestingly, myocardial sympathetic function can remain abnormal for several months even after ventricular systolic function has recovered (Verberne et al. 2009). Endomyocardial biopsy and autopsy findings in patients with SCM frequently reveal an interstitial mononuclear inflammatory response and contraction band necrosis, histologic findings that are known to be associated with myocardial catecholamine exposure (Wittstein et al. 2005). Finally, several animal models have supported the central role of adrenergic stimulation in the pathogenesis of SCM. Immobilization stress precipitated left ventricular apical ballooning in rats, and this effect was attenuated with alpha- and beta-blockade (Ueyama et al. 2002). More recently, Redfors and colleagues demonstrated that different catecholamines could induce variable ventricular ballooning patterns in rats in what appeared to be an afterload-dependent mechanism (Redfors et al. 2014a).

Several pathophysiologic mechanisms have been proposed to explain how exaggerated sympathetic stimulation may precipitate the transient left ventricular dysfunction of SCM (Fig. 3):

Plaque rupture: Catecholamine-mediated plaque rupture has been proposed as a possible mechanism of SCM. Some authors have suggested that plaque rupture and rapid lysis of a developing thrombus might explain why these patients frequently have no obstructive coronary disease at the time of angiography. It has also been proposed that plaque rupture and transient coronary thrombosis

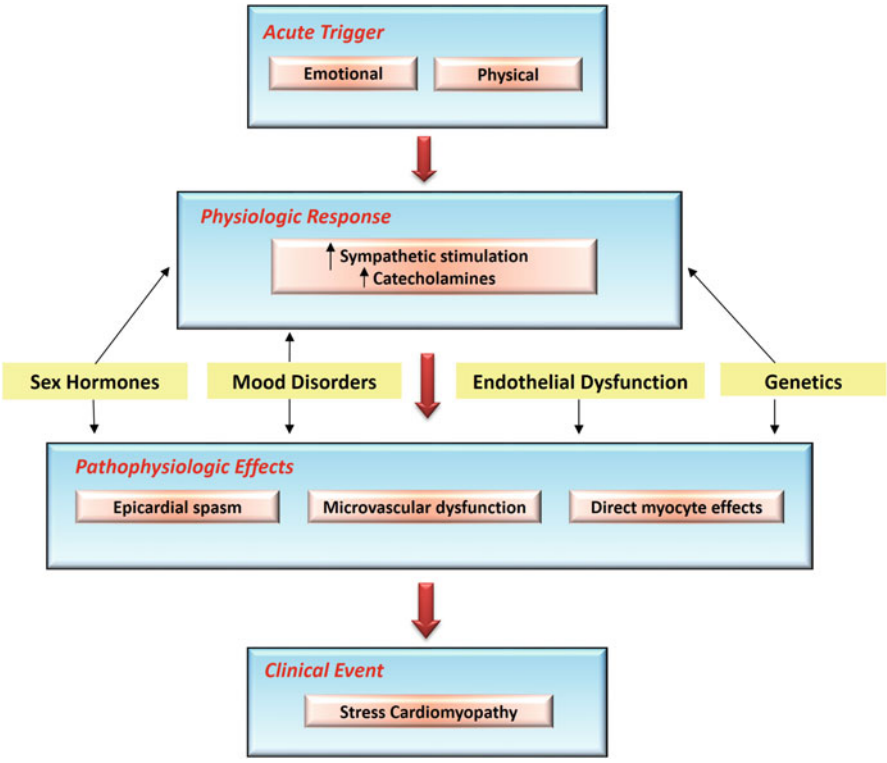


Fig. 3 A proposed paradigm illustrating the link between acute stress and the syndrome of stress cardiomyopathy. Increased sympathetic stimulation may mediate myocardial stunning through a variety of mechanisms that include coronary vasospasm, microvascular dysfunction, and myocyte calcium overload. Risk factors that may increase individual susceptibility to sympathetic stimulation are also shown (Modified from Prog Cardiovasc Dis 49(5), Bhattacharyya MR, Steptoe A. Emotional triggers of acute coronary syndromes: strength of evidence, biological processes, and clinical implications. Page 354, Fig. 1, copyright © 2007, with permission from Elsevier (Bhattacharyya and Steptoe 2007))

must occur in a long wraparound left anterior descending (LAD) coronary artery to explain the apical ballooning pattern. Eccentric atherosclerotic plaque in the midportion of the LAD has been reported in a small number of patients with SCM, but intravascular ultrasound has failed to identify plaque in most studies (Delgado et al. 2011; Haghi et al. 2010). It has also been clearly shown by several investigators that apical ballooning can occur even in the absence of a wraparound LAD and that this coronary anatomy is no more prevalent in SCM than in a control population (Hoyt et al. 2010). Further, ischemia in a wraparound LAD would not explain the non-apical variants that also characterize this syndrome. These data all support the conclusion that catecholamine-mediated plaque rupture with aborted myocardial infarction is not the primary pathophysiologic mechanism responsible for SCM.

Epicardial spasm: It has been proposed that SCM results from transient myocardial ischemia due to sympathetically mediated coronary artery spasm. While epicardial spasm has been reported in a small number of patients with SCM (Fiol et al. 2012), the vast majority of patients do not have spasm at the time of angiography. In the series from Tsuchihashi (Tsuchihashi et al. 2001) and Sato (Sato et al. 2008), coronary spasm could only be provoked with acetylcholine in 21 % and 23 % of the patients, respectively, and some investigators have been completely unable to provoke spasm with agents such as ergonovine (Martinez-Selles et al. 2010). Further, it is difficult to explain the unusual contractile patterns observed in this syndrome from coronary spasm alone since none of the ballooning variants correspond with an epicardial vascular distribution. These data would suggest that while abnormal coronary vasomotion may occur in some patients with SCM, sympathetically mediated epicardial spasm is unlikely the primary pathophysiologic mechanism underlying the syndrome.

Microvascular dysfunction: There is considerable evidence that catecholamine-mediated microvascular dysfunction may be central to the pathogenesis of SCM. Decreased coronary flow reserve (CFR) has been demonstrated noninvasively during the acute presentation with positron emission tomography/computed tomography (PET/CT) (Ghadri et al. 2014) and with echocardiography following the infusion of adenosine (Meimoun et al. 2008) and dipyridamole (Rigo et al. 2009). Invasive techniques demonstrating microcirculatory dysfunction in patients with SCM have included the use of Doppler flow wires showing decreased CFR (Kume et al. 2005) and intracoronary pressure/temperature guide wires that have demonstrated an increase in the index of microcirculatory resistance (IMR) (Daniels and Fearon 2011). Patients with SCM who undergo angiography also have elevated thrombolysis in myocardial infarction (TIMI) frame counts (Bybee et al. 2004) and abnormal TIMI myocardial perfusion grades (A. Elesber et al. 2006), both well-validated indexes of coronary blood flow. In most of these patients, TIMI frame counts are increased in multiple vessels, and perfusion abnormalities involve multiple coronary territories, suggesting a diffuse microcirculatory abnormality. Catecholamine-mediated endothelial dysfunction is further supported by an endomyocardial biopsy study from Uchida and colleagues who found that patients with SCM have elevated catecholamine levels and histologic evidence of microvascular endothelial cell apoptosis (Uchida et al. 2010). Further evidence suggests that sympathetically mediated endothelial dysfunction in SCM is a systemic process that involves more than just the coronary microcirculation. At the time of presentation, patients with SCM have marked impairment in brachial artery flow-mediated dilation compared to patients with myocardial infarction and to healthy controls, and this abnormality gradually improves over several weeks (Vasilieva et al. 2011).

Direct myocyte effects: The transient left ventricular dysfunction that characterizes SCM could alternatively result from the direct effects of catecholamines on cardiac myocytes. Catecholamines can decrease myocyte viability through cyclic adenosine monophosphate-mediated calcium overload (Mann

et al. 1992), and there is evidence that patients with SCM may have abnormal cardiomyocyte calcium regulation at the time of presentation. Looking at myocytes from left ventricular endomyocardial biopsy samples, Nef and colleagues demonstrated significant downregulation of sarcoplasmic Ca^{2+} ATPase (SERCA2a) gene expression, increased ventricular expression of sarcolipin, and dephosphorylation of phospholamban (PLN) (Nef et al. 2009). They hypothesized that the increased PLN/SERCA2a ratio could potentially result in myocardial contractile dysfunction through decreased calcium affinity, and repeat biopsies performed after left ventricular function had recovered demonstrated normalization of these intracellular proteins. An abnormality of calcium handling has also been demonstrated in a rat model of SCM where acute beta-adrenergic stimulation resulted in left ventricular dysfunction and myocyte injury due to calcium leakage from hyperphosphorylation of the ryanodine receptor 2 (RyR2) (Ellison et al. 2007). More recently, Paur and colleagues used a rat model to demonstrate that high circulating levels of epinephrine had a negative inotropic effect on the cardiac myocyte by causing a switch from G_s to G_i protein signaling via the β_2-adrenergic receptor (Paur et al. 2012). This effect was most pronounced at the apex of the ventricle where β_2-adrenergic receptor density was highest, and blocking G_i protein signaling resulted in increased mortality. The authors proposed, therefore, that reduced left ventricular apical contractility due to a switch from G_s to G_i protein signaling was cardioprotective during periods of hyperadrenergic stimulation. While this hypothesis is intriguing, it does not readily explain the mechanism underlying the non-apical variants of SCM or why some patients with recurrent episodes present with variable ballooning patterns.

Factors that May Increase Susceptibility to Stress Cardiomyopathy

Despite the fact that psychological and physical stressors are ubiquitous and a normal part of everyday human life, only a relatively small number of individuals develop the clinical syndrome of SCM. This suggests that there are risk factors that make certain individuals particularly susceptible to this condition, likely by either augmenting the sympathetic stress response or by increasing cardiomyocyte and microcirculatory susceptibility to the effects of catecholamines (Fig. 3). It is likely that many such risk factors exist, but only those most supported by clinical observations and research will be discussed here.

Psychological disorders: Many investigators have reported a high incidence of mood disorders and anxiety in patients with SCM (Table 4). In a retrospective case-control study, Summers demonstrated that 68 % of patients with SCM had either anxiety or depression, and the prevalence of these disorders was higher than in patients with myocardial infarction or in healthy controls (Summers et al. 2010). El-Sayed looked retrospectively at over 24,000 patients with SCM and similarly found that psychological disorders occurred more frequently in patients with SCM

Table 4 Prevalence of psychological disorders in stress cardiomyopathy

Study	Study type	# SCM patients	Prevalence of psychological disorders	Observations
Regnante et al. (2009)	Retrospective	70	37 % depression or anxiety	Psychological disorders common in SCM
Summers et al. (2010)	Retrospective case-control	25	48 % depression, 56 % anxiety; 68 % anxiety or depression	Frequency of anxiety and depression significantly higher in SCM than in STEMI and healthy controls; social isolation and divorce more prevalent in SCM
Del Pace et al. (2011)	Prospective case-control	50	60 % high-anxiety trait	High-anxiety trait common in SCM, but no higher than in STEMI; anxiety was not a predictor of SCM nor was it associated with a worse clinical outcome
Citro et al. (2012)	Partially prospective	190	19.4 % psychiatric disorders	Prevalence highest in patients over 65 years
El-Sayed et al. (2012)	Retrospective	24,701	15 % mood disorder, 8.9 % anxiety	Prevalence of psychological disorders in SCM higher than in MI and orthopedic patients
Deshmukh et al. (2012)	Retrospective	6837	NR	Anxiety associated with increased risk of developing SCM
Weihs et al. (2013)	Retrospective	179	15 % depression; 21 % on antidepressant	Antidepressant use common in SCM
Delmas et al. (2013)	Prospective	45	78 % anxiety or depression; 44 % with chronic psychological stress	Depression and anxiety common in SCM and more common than in patients with ACS
Isogai et al. (2014)	Retrospective	3719	5.9 % "psychiatric disease"	Relatively low incidence of "psychiatric disease," compared to other series; type of psychiatric disease not specified
Lacey et al. (2014)	Partially prospective case-control	58	57 % depression, 40 % anxiety	Prevalence of mood disorders and anxiety similar to healthy controls; increased neuroticism in SCM
Kastaun et al. (2014)	Retrospective	19	11 % depression; 5 % phobic anxiety	Prevalence of depression and anxiety in SCM no higher than controls; high incidence of stressful life events in SCM

(*continued*)

Table 4 (continued)

Study	Study type	# SCM patients	Prevalence of psychological disorders	Observations
Dias et al. (2014)	Retrospective	78	21 % depression; 30 % anxiety; 19 % taking SSRI	SSRI use associated with increased hospital death and decreased long-term survival
Pelliccia et al. (2015)	Systematic review	1109	9 % mood disorders, 13 % anxiety	Psychological disorders common in SCM

ACS acute coronary syndrome, *MI* myocardial infarction, *NR* not reported, *SCM* stress cardiomyopathy, *SSRI* selective serotonin reuptake inhibitor, *STEMI* ST-segment elevation myocardial infarction

than they did in patients with myocardial infarction or in noncardiac controls (El-Sayed et al. 2012). In one of the few prospective trials examining psychological disorders in patients with SCM, Delmas found the incidence of depression and anxiety to be as high as 78 %, significantly higher than what was seen in patients with acute coronary syndromes (Delmas et al. 2013). Patients with SCM also appear to have a high prevalence of type D personality which is characterized by negative affectivity and social inhibition and has been previously associated with increased cardiovascular risk (Compare et al. 2013). Psychological disorders may have pathogenic importance in SCM. Depressed patients have an exaggerated norepinephrine response to emotional stress (Mausbach et al. 2005), and a subset of patients with major depressive disorders have increased spillover and decreased reuptake of norepinephrine (Barton et al. 2007). Patients with panic disorder and anxiety may also have impairment of the norepinephrine transporter resulting in decreased catecholamine reuptake (Marlies E. Alvarenga et al. 2006). In addition, the increased use of antidepressants such as selective norepinephrine reuptake inhibitors in this population may facilitate myocardial stunning by increasing local catecholamine levels. The increased sympathetic response to acute stress combined with greater cardiac sympathetic sensitivity may place patients with chronic stress, mood disorders, and anxiety at particularly high risk for developing SCM.

Hormonal factors: There is a striking preponderance of postmenopausal females in all series of SCM to date. This suggests a pathogenic hormonal influence, and declining estrogen levels may make women increasingly susceptible to SCM as they age. It is relatively uncommon for young women to present with SCM, and as mentioned earlier, women older than 55 years have an almost fivefold risk of developing SCM compared to women younger than 55 years (Deshmukh et al. 2012). Female hormones exert important influences on the sympathetic neurohormonal axis, and there is significant decrease in cardiac vagal tone and baroreflex sensitivity as women age (Lavi et al. 2007). Estrogen has an important influence on vasomotor tone through the upregulation of endothelial nitric oxide synthase activity (Sader and Celermajer 2002), and there is

clinical evidence that estrogen can attenuate catecholamine-mediated vasoconstriction (Sung et al. 1999) and decrease the sympathetic response to mental stress in perimenopausal women (Komesaroff et al. 1999). Sugimoto illustrated the protective effect of female hormones on cardiac systolic function by showing that low estradiol levels in postmenopausal women increased the risk of focal left ventricular wall motion abnormalities following subarachnoid hemorrhage (Sugimoto et al. 2012). In an animal model of SCM, estrogen supplementation in ovariectomized rats attenuated the negative effect of immobilization stress on left ventricular systolic function (Ueyama et al. 2007). All of these data support the idea that a decline in estrogen during menopause may represent an acquired risk factor for SCM by increasing myocyte and endothelial vulnerability to enhanced sympathetic stimulation.

Inherent endothelial dysfunction: There are data to support that patients with SCM may be individuals with inherent endothelial dysfunction who have chronic dysregulation of vasomotor tone. Indeed, SCM has been associated with other conditions of abnormal vasomotor function such as migraine headache and Raynaud's phenomenon (Scantlebury et al. 2013). Several investigators have examined endothelial function and vasoreactivity in individuals who have fully recovered from their episode of SCM. Barletta performed cold pressor testing (CPT) in women who were 1–3 years out from their acute episode of SCM. In contrast to an age-, sex-, and risk factor-matched control group that demonstrated increased coronary flow with CPT, CPT in subjects with a history of SCM resulted in significant catecholamine elevation, transient apical and mid left ventricular wall motion abnormalities, and no detectable increase in coronary blood flow (Barletta et al. 2009). Martin and colleagues used peripheral arterial tonometry (PAT) to assess endothelial function in subjects with a history of SCM being subjected to mental stress testing (Martin et al. 2010). Subjects with prior SCM demonstrated increased catecholamine production, impaired vascular vasodilation, and increased vasoconstriction, findings that were not observed in a control group of postmenopausal women. Patel performed coronary vasomotor function testing in ten subjects at a median of 5 months following an acute presentation with SCM (Patel et al. 2013). Using an intracoronary Doppler flow wire, he demonstrated that the majority of women with SCM had evidence of severe microvascular dysfunction with the infusion of intracoronary acetylcholine. Further, the greatest amount of microcirculatory impairment was observed in subjects who had experienced recurrent episodes of SCM. All of these studies suggest that individuals who develop SCM may have inherent endothelial and microvascular dysfunction that make them particularly susceptible to myocardial stunning during periods of exaggerated sympathetic stimulation.

Genetic factors: SCM has been reported in siblings (Pison et al. 2004) and in mothers and daughters (Sharkey et al. 2013), suggesting that the syndrome may have genetic determinants. Investigators have looked for evidence of abnormal adrenergic signaling in patients with SCM, and genetic analyses have yielded conflicting findings. Zaroff reported an increased frequency of specific alpha- and beta-receptor polymorphisms in patients with neurogenic stunned myocardium

following subarachnoid hemorrhage, a condition believed to be catecholamine mediated that likely shares an overlapping pathophysiology with SCM (Zaroff et al. 2006). Similarly, Vriz demonstrated an increased genotype frequency of a beta-1 adrenergic receptor (β1AR) polymorphism (amino acid position 389) in patients with SCM compared to controls (Vriz et al. 2011), but Sharkey was unable to identify an increase in genotype frequency for either the β1AR polymorphism (amino acid positions 389 and 49) or alpha-2c receptor (α2cR) polymorphism (deletions 322–325) in patients with SCM (Sharkey et al. 2009). Several groups have examined the frequency of the L41Q polymorphism of the G-protein-coupled receptor kinase 5 (GRK5). The L41 variant of GRK5 enhances β-adrenergic receptor desensitization and attenuates the receptor's response to catecholamine stimulation. An increased frequency of this polymorphism was observed in patients with SCM compared to controls in two small studies (Novo et al. 2014; Spinelli et al. 2010), but no increase in frequency of GRK5, β1AR, or β2AR polymorphisms was observed in a larger cohort of SCM patients (Figtree et al. 2013). While larger genetic studies are clearly needed, these initial reports suggest the intriguing possibility that SCM susceptibility may at least in part be influenced by genetically determined alterations in adrenergic cell signaling.

Early reports of SCM suggested that severe emotional or physiologic stress was required to precipitate the clinical syndrome. With increasing recognition of SCM, it has become clear that some patients present with fairly mild triggers, and up to 30–40 % of patients in several large series have no identifiable trigger at all (Table 1). An explanation for this is illustrated in Fig. 4 which proposes that the intensity of the trigger required to precipitate SCM may be inversely related to the number of risk factors an individual has that increase catecholamine release and/or enhance myocyte and microvascular susceptibility to sympathetic stimulation. In this paradigm, a young man who has no clinical risk factors may require massive catecholamine release, such as that seen with neurologic injury or intravenous epinephrine, in order to develop the clinical syndrome of SCM. A moderate amount of sympathetic stimulation (e.g., intense emotional stress) may be required to induce SCM in a middle-aged woman whose only risk factor is being perimenopausal. As the number of risk factors in a given individual increases, however, the threshold for developing SCM is lowered to a point where even relatively mild sympathetic stimulation is sufficient to precipitate the clinical syndrome. This model offers an explanation as to why there is such individual variability in the intensity of the triggers needed to provoke SCM, and it is certain that additional inherent and acquired risk factors will be identified in the future as experience with the syndrome continues to grow.

Conclusion

In just a few short years, SCM has evolved from an obscure and relatively unheard of condition to a widely accepted clinical syndrome. Better recognition of the unique clinical features of SCM has made it possible to readily distinguish the

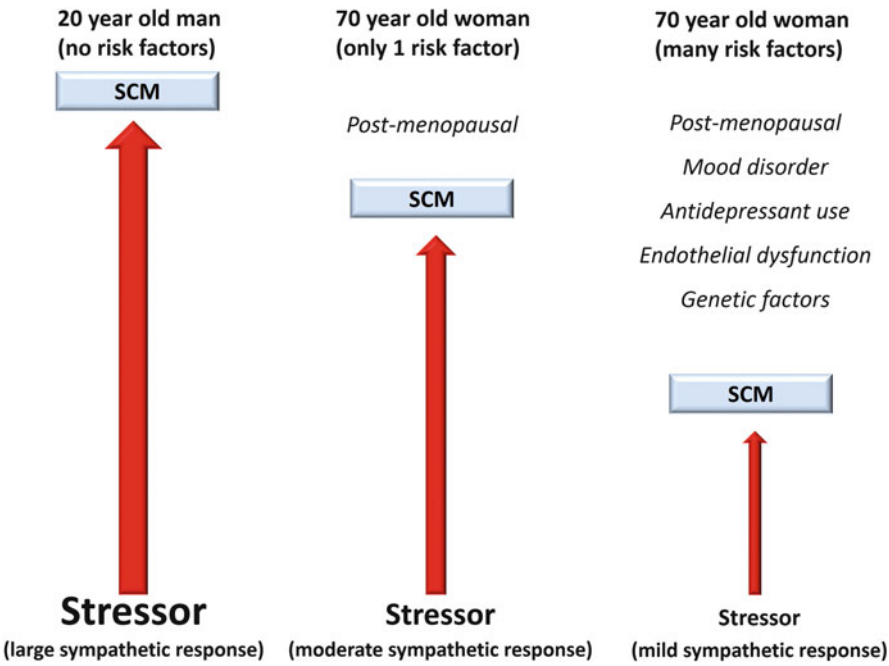


Fig. 4 A proposed model to explain how stress cardiomyopathy can be precipitated by triggers of variable intensity. The amount of stress needed to precipitate the clinical syndrome is dependent on individual risk factors that likely influence catecholamine production and/or myocyte and microvascular sensitivity to sympathetic stimulation (see text). *SCM* stress cardiomyopathy (Reproduced with kind permission from Springer: Cell Mol Neurobiol, Stress Cardiomyopathy: A Syndrome of Catecholamine Mediated Myocardial Stunning, 2012, page 855, Wittstein, IS, Fig. 3 (Wittstein 2012))

syndrome from acute myocardial infarction, and it is now clear that a broad spectrum of emotional and physiologic stressors can indeed acutely precipitate cardiac contractile dysfunction and heart failure. The preponderance of evidence suggests that SCM results from sympathetically mediated microcirculatory dysfunction, though the precise mechanism of catecholamine-mediated myocardial stunning remains incompletely understood. A number of risk factors have been identified that appear to increase individual susceptibility to SCM, possibly by either enhancing catecholamine production or by increasing myocyte and microcirculatory sensitivity to catecholamines. In particular, there is increasing evidence that mood disorders, anxiety, and chronic psychological stress may increase the risk of acute stress-related myocardial dysfunction, but it is unknown whether treatment of these psychological conditions will result in improved cardiovascular outcomes. Behavioral and psychological interventions have never been studied in patients with SCM, and commonly used antidepressants could potentially have deleterious effects by increasing local myocardial catecholamine levels. It seems clear that future research examining the psychological constructs of SCM will be vital to not only better understand the

precise mechanisms of acute stress-induced myocardial stunning but also to establish effective treatment strategies for this syndrome.

References

Abraham, J., Mudd, J. O., Kapur, N. K., Klein, K., Champion, H. C., & Wittstein, I. S. (2009). Stress cardiomyopathy after intravenous administration of catecholamines and beta-receptor agonists. *Journal of the American College of Cardiology, 53*(15), 1320–1325. doi:10.1016/j.jacc.2009.02.020.

Akashi, Y., Musha, H., Kida, K., Itoh, K., Inoue, K., Kawasaki, K., . . . Miyake, F. (2005). Reversible ventricular dysfunction takotsubo cardiomyopathy. *Europe Journal Heart Fail, 7*(7), 1171–1176. doi:10.1016/j.ejheart.2005.03.011.

Alvarenga, M. E., Richards, J. C., Lambert, G., & Esler, M. D. (2006). Psychophysiological mechanisms in panic disorder: A correlative analysis of noradrenaline spillover, neuronal noradrenaline reuptake, power spectral analysis of heart rate variability, and psychological variables. *Psychosomatic Medicine, 68*(1), 8–16. doi:10.1097/01.psy.0000195872.00987.db.

Aryal, M. R., Pathak, R., Karmacharya, P., & Donato, A. A. (2014). Seasonal and regional variation in takotsubo cardiomyopathy. *American Journal of Cardiology, 113*(9), 1592. doi:10.1016/j.amjcard.2014.03.002.

Barletta, G., Del Pace, S., Boddi, M., Del Bene, R., Salvadori, C., Bellandi, B., . . . Gensini, G. F. (2009). Abnormal coronary reserve and left ventricular wall motion during cold pressor test in patients with previous left ventricular ballooning syndrome. *Europe Heart Journal, 30*(24), 3007–3014. doi:10.1093/eurheartj/ehp325.

Barton, D. A., Dawood, T., Lambert, E. A., Esler, M. D., Haikerwal, D., Brenchley, C., . . . Lambert, G. W. (2007). Sympathetic activity in major depressive disorder: Identifying those at increased cardiac risk? *Journal Hypertension, 25*(10), 2117–2124. doi:10.1097/HJH.0b013e32829baae7.

Bellandi, B., Salvadori, C., Parodi, G., Ebert, A. G., Petix, N., Del Pace, S., . . . Bovenzi, F. (2012). Epidemiology of Tako-tsubo cardiomyopathy: The tuscany registry for Tako-tsubo cardiomyopathy. *Giornale Italiano di Cardiologia (Rome), 13*(1), 59–66. doi:10.1714/1015.11057.

Bhattacharyya, M. R., & Steptoe, A. (2007). Emotional triggers of acute coronary syndromes: strength of evidence, biological processes, and clinical implications. *Progress in Cardiovascular Diseases, 49*(5), 353–365. doi:10.1016/j.pcad.2006.11.002.

Bonacchi, M., Vannini, A., Harmelin, G., Batacchi, S., Bugetti, M., Sani, G., & Peris, A. (2015). Inverted-Takotsubo cardiomyopathy: Severe refractory heart failure in poly-trauma patients saved by emergency extracorporeal life support. *Interactive Cardiovascular and Thoracic Surgery, 20*(3), 365–371. doi:10.1093/icvts/ivu421.

Brinjikji, W., El-Sayed, A. M., & Salka, S. (2012). In-hospital mortality among patients with takotsubo cardiomyopathy: A study of the National Inpatient Sample 2008 to 2009. *American Heart Journal, 164*(2), 215–221. doi:10.1016/j.ahj.2012.04.010.

Burgdorf, C., Kurowski, V., Bonnemeier, H., Schunkert, H., & Radke, P. W. (2008a). Long-term prognosis of the transient left ventricular dysfunction syndrome (Tako-Tsubo cardiomyopathy): Focus on malignancies. *European Journal of Heart Failure, 10*(10), 1015–1019. doi:10.1016/j.ejheart.2008.07.008.

Burgdorf, C., von Hof, K., Schunkert, H., & Kurowski, V. (2008b). Regional alterations in myocardial sympathetic innervation in patients with transient left-ventricular apical ballooning (Tako-Tsubo cardiomyopathy). *Journal of Nuclear Cardiology, 15*(1), 65–72. doi:10.1016/j.nuclcard.2007.08.005.

Burke, A. P., Farb, A., Malcom, G. T., Liang, Y., Smialek, J. E., & Virmani, R. (1999). Plaque rupture and sudden death related to exertion in men with coronary artery disease. *JAMA, 281*(10), 921–926.

Bybee, K. A., Prasad, A., Barsness, G. W., Lerman, A., Jaffe, A. S., Murphy, J. G., . . . Rihal, C. S. (2004). Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. *American Journal Cardiology, 94*(3), 343–346. doi:10.1016/j.amjcard.2004.04.030.

Cacciotti, L., Passaseo, I., Marazzi, G., Camastra, G., Campolongo, G., Beni, S., . . . Ansalone, G. (2012). Observational study on Takotsubo-like cardiomyopathy: Clinical features, diagnosis, prognosis and follow-up. *BMJ Open, 2*(5). doi:10.1136/bmjopen-2012-001165.

Citro, R., Previtali, M., Bovelli, D., Vriz, O., Astarita, C., Patella, M. M., . . . Manfredini, R. (2009). Chronobiological patterns of onset of Tako-Tsubo cardiomyopathy: A multicenter Italian study. *Journal American College Cardiology, 54*(2), 180–181. doi:10.1016/j.jacc.2009.03.048.

Citro, R., Rigo, F., Previtali, M., Ciampi, Q., Canterin, F. A., Provenza, G., . . . Bossone, E. (2012). Differences in clinical features and in-hospital outcomes of older adults with tako-tsubo cardiomyopathy. *Journal American Geriatrics Society, 60*(1), 93–98. doi:10.1111/j.1532-5415.2011.03730.x.

Compare, A., Bigi, R., Orrego, P. S., Proietti, R., Grossi, E., & Steptoe, A. (2013). Type D personality is associated with the development of stress cardiomyopathy following emotional triggers. *Annals of Behavioral Medicine, 45*(3), 299–307. doi:10.1007/s12160-013-9474-x.

Daniels, D. V., & Fearon, W. F. (2011). The index of microcirculatory resistance (IMR) in takotsubo cardiomyopathy. *Catheterization and Cardiovascular Interventions, 77*(1), 128–131. doi:10.1002/ccd.22599.

De Backer, O., Debonnaire, P., Gevaert, S., Missault, L., Gheeraert, P., & Muyldermans, L. (2014). Prevalence, associated factors and management implications of left ventricular outflow tract obstruction in takotsubo cardiomyopathy: A two-year, two-center experience. *BMC Cardiovascular Disorders, 14*, 147. doi:10.1186/1471-2261-14-147.

de Gregorio, C., Grimaldi, P., & Lentini, C. (2008). Left ventricular thrombus formation and cardioembolic complications in patients with Takotsubo-like syndrome: A systematic review. *International Journal of Cardiology, 131*(1), 18–24. doi:10.1016/j.ijcard.2008.05.060.

Del Pace, S., Parodi, G., Bellandi, B., Zampini, L., Venditti, F., Ardito, M., . . . Tuscany Registry of Tako-tsubo, C. (2011). Anxiety trait in patients with stress-induced cardiomyopathy: A case-control study. *Clinical Research Cardiology, 100*(6), 523–529. doi:10.1007/s00392-010-0276-x.

Delgado, G. A., Truesdell, A. G., Kirchner, R. M., Zuzek, R. W., Pomerantsev, E. V., Gordon, P. C., & Regnante, R. A. (2011). An angiographic and intravascular ultrasound study of the left anterior descending coronary artery in takotsubo cardiomyopathy. *American Journal of Cardiology, 108*(6), 888–891. doi:10.1016/j.amjcard.2011.05.012.

Delmas, C., Lairez, O., Mulin, E., Delmas, T., Boudou, N., Dumonteil, N., . . . Carrie, D. (2013). Anxiodepressive disorders and chronic psychological stress are associated with Tako-Tsubo cardiomyopathy- new physiopathological hypothesis. *Circular Journal, 77*(1), 175–180.

Deshmukh, A., Kumar, G., Pant, S., Rihal, C., Murugiah, K., & Mehta, J. L. (2012). Prevalence of Takotsubo cardiomyopathy in the United States. *American Heart Journal, 164*(1), 66–71 e61. doi:10.1016/j.ahj.2012.03.020.

Dias, A., Franco, E., Figueredo, V. M., Hebert, K., & Quevedo, H. C. (2014). Occurrence of Takotsubo cardiomyopathy and use of antidepressants. *International Journal of Cardiology, 174*(2), 433–436. doi:10.1016/j.ijcard.2014.04.028.

Dote, K., Sato, H., Tateishi, H., Uchida, T., & Ishihara, M. (1991). Myocardial stunning due to simultaneous multivessel coronary spasms: A review of 5 cases. *Journal of Cardiology, 21*(2), 203–214.

Doyen, D., Moceri, P., Chiche, O., Schouver, E., Cerboni, P., Chaussade, C., . . . Ferrari, E. (2014). Cardiac biomarkers in Takotsubo cardiomyopathy. *International Journal Cardiology, 174*(3), 798–801. doi:10.1016/j.ijcard.2014.04.120.

Eitel, I., von Knobelsdorff-Brenkenhoff, F., Bernhardt, P., Carbone, I., Muellerleile, K., Aldrovandi, A., . . . Friedrich, M. G. (2011). Clinical characteristics and cardiovascular

magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA, 306*(3), 277–286. doi:10.1001/jama.2011.992.

Elesber, A., Lerman, A., Bybee, K. A., Murphy, J. G., Barsness, G., Singh, M., . . . Prasad, A. (2006). Myocardial perfusion in apical ballooning syndrome correlate of myocardial injury. *American Heart Journal, 152*(3), 469. e469–413. doi:10.1016/j.ahj.2006.06.007.

Elesber, A. A., Prasad, A., Bybee, K. A., Valeti, U., Motiei, A., Lerman, A., . . . Rihal, C. S. (2006). Transient cardiac apical ballooning syndrome: Prevalence and clinical implications of right ventricular involvement. *Journal American College Cardiology, 47*(5), 1082–1083. doi:10.1016/j.jacc.2005.12.004.

Elesber, A. A., Prasad, A., Lennon, R. J., Wright, R. S., Lerman, A., & Rihal, C. S. (2007). Four-year recurrence rate and prognosis of the apical ballooning syndrome. *Journal of the American College of Cardiology, 50*(5), 448–452. doi:10.1016/j.jacc.2007.03.050.

Elian, D., Osherov, A., Matetzky, S., Hod, H., Guetta, V., Feinberg, M. S., & Di Segni, E. (2006). Left ventricular apical ballooning: Not an uncommon variant of acute myocardial infarction in women. *Clinical Cardiology, 29*(1), 9–12.

Ellison, G. M., Torella, D., Karakikes, I., Purushothaman, S., Curcio, A., Gasparri, C., . . . Nadal-Ginard, B. (2007). Acute beta-adrenergic overload produces myocyte damage through calcium leakage from the ryanodine receptor 2 but spares cardiac stem cells. *Journal Biology Chemistry, 282*(15), 11397–11409. doi:10.1074/jbc.M607391200.

El-Sayed, A. M., Brinjikji, W., & Salka, S. (2012). Demographic and co-morbid predictors of stress (takotsubo) cardiomyopathy. *American Journal of Cardiology, 110*(9), 1368–1372. doi:10.1016/j.amjcard.2012.06.041.

Eshtehardi, P., Koestner, S. C., Adorjan, P., Windecker, S., Meier, B., Hess, O. M., . . . Cook, S. (2009). Transient apical ballooning syndrome – clinical characteristics, ballooning pattern, and long-term follow-up in a Swiss population. *International Journal Cardiology, 135*(3), 370–375. doi:10.1016/j.ijcard.2008.03.088.

Falola, M., Fonbah, W., & McGwin, G., Jr. (2013). Takotsubo cardiomyopathy versus ST-elevation myocardial infarction in a large case-control study: Proposing a new mechanism. *International Journal of Cardiology, 167*(3), 1079–1081. doi:10.1016/j.ijcard.2012.10.059.

Feola, M., Rosso, G. L., Casasso, F., Morena, L., Biggi, A., Chauvie, S., . . . Uslenghi, E. (2006). Reversible inverse mismatch in transient left ventricular apical ballooning: Perfusion/metabolism positron emission tomography imaging. *Journal Nuclear Cardiology, 13*(4), 587–590. doi:10.1016/j.nuclcard.2006.05.004.

Figtree, G. A., Bagnall, R. D., Abdulla, I., Buchholz, S., Galougahi, K. K., Yan, W., . . . Ward, M. R. (2013). No association of G-protein-coupled receptor kinase 5 or beta-adrenergic receptor polymorphisms with Takotsubo cardiomyopathy in a large Australian cohort. *Europe Journal Heart Fail, 15*(7), 730–733. doi:10.1093/eurjhf/hft040.

Finsterer, J., & Wahbi, K. (2014). CNS disease triggering Takotsubo stress cardiomyopathy. *International Journal of Cardiology, 177*(2), 322–329. doi:10.1016/j.ijcard.2014.08.101.

Fiol, M., Carrillo, A., Rodriguez, A., Herrero, J., & Garcia-Niebla, J. (2012). Left ventricular ballooning syndrome due to vasospasm of the middle portion of the left anterior descending coronary artery. *Cardiology Journal, 19*(3), 314–316.

Frohlich, G. M., Schoch, B., Schmid, F., Keller, P., Sudano, I., Luscher, T. F., . . . Enseleit, F. (2012). Takotsubo cardiomyopathy has a unique cardiac biomarker profile: NT-proBNP/myoglobin and NT-proBNP/troponin T ratios for the differential diagnosis of acute coronary syndromes and stress induced cardiomyopathy. *International Journal Cardiology, 154*(3), 328–332. doi:10.1016/j.ijcard.2011.09.077.

Gach, O., Lempereur, M., Pierard, L. A., & Lancellotti, P. (2012). Recurrent stress cardiomyopathy with variable pattern of left ventricle contraction abnormality. *Journal of the American College of Cardiology, 60*(3), e5. doi:10.1016/j.jacc.2011.10.911.

Ghadri, J. R., Dougoud, S., Maier, W., Kaufmann, P. A., Gaemperli, O., Prasad, A., . . . Templin, C. (2014). A PET/CT-follow-up imaging study to differentiate takotsubo cardiomyopathy from

acute myocardial infarction. *International Journal Cardiovascular Imaging, 30*(1), 207–209. doi:10.1007/s10554-013-0311-x.

Gianni, M., Dentali, F., Grandi, A. M., Sumner, G., Hiralal, R., & Lonn, E. (2006). Apical ballooning syndrome or takotsubo cardiomyopathy: A systematic review. *European Heart Journal, 27*(13), 1523–1529. doi:10.1093/eurheartj/ehl032.

Haghi, D., Athanasiadis, A., Papavassiliu, T., Suselbeck, T., Fluechter, S., Mahrholdt, H., . . . Sechtem, U. (2006). Right ventricular involvement in Takotsubo cardiomyopathy. *Europe Heart Journal, 27*(20), 2433–2439. doi:10.1093/eurheartj/ehl274.

Haghi, D., Fluechter, S., Suselbeck, T., Kaden, J. J., Borggrefe, M., & Papavassiliu, T. (2007). Cardiovascular magnetic resonance findings in typical versus atypical forms of the acute apical ballooning syndrome (Takotsubo cardiomyopathy). *International Journal of Cardiology, 120*(2), 205–211. doi:10.1016/j.ijcard.2006.09.019.

Haghi, D., Roehm, S., Hamm, K., Harder, N., Suselbeck, T., Borggrefe, M., & Papavassiliu, T. (2010). Takotsubo cardiomyopathy is not due to plaque rupture: An intravascular ultrasound study. *Clinical Cardiology, 33*(5), 307–310. doi:10.1002/clc.20747.

Hoyt, J., Lerman, A., Lennon, R. J., Rihal, C. S., & Prasad, A. (2010). Left anterior descending artery length and coronary atherosclerosis in apical ballooning syndrome (Takotsubo/stress induced cardiomyopathy). *International Journal of Cardiology, 145*(1), 112–115. doi:10.1016/j.ijcard.2009.06.018.

Hurst, R. T., Askew, J. W., Reuss, C. S., Lee, R. W., Sweeney, J. P., Fortuin, F. D., . . . Tajik, A. J. (2006). Transient midventricular ballooning syndrome: A new variant. *Journal American College Cardiology, 48*(3), 579–583. doi:10.1016/j.jacc.2006.06.015.

Isogai, T., Yasunaga, H., Matsui, H., Tanaka, H., Ueda, T., Horiguchi, H., & Fushimi, K. (2014). Out-of-hospital versus in-hospital Takotsubo cardiomyopathy: Analysis of 3719 patients in the diagnosis procedure combination database in Japan. *International Journal of Cardiology, 176*(2), 413–417. doi:10.1016/j.ijcard.2014.07.110.

Izumo, M., Nalawadi, S., Shiota, M., Das, J., Dohad, S., Kuwahara, E., . . . Shiota, T. (2011). Mechanisms of acute mitral regurgitation in patients with takotsubo cardiomyopathy: An echocardiographic study. *Circular Cardiovascular Imaging, 4*(4), 392–398. doi:10.1161/CIRCIMAGING.110.962845.

Joe, B. H., Jo, U., Kim, H. S., Park, C. B., Hwang, H. J., Sohn, I. S., . . . Kim, C. J. (2012). APACHE II score, rather than cardiac function, may predict poor prognosis in patients with stress-induced cardiomyopathy. *Journal Korean Medicine Science, 27*(1), 52–57. doi:10.3346/jkms.2012.27.1.52.

Kastaun, S., Schwarz, N. P., Juenemann, M., Yeniguen, M., Nef, H. M., Moellmann, H., . . . Gerriets, T. (2014). Cortisol awakening and stress response, personality and psychiatric profiles in patients with takotsubo cardiomyopathy. *Heart, 100*(22), 1786–1792. doi:10.1136/heartjnl-2014-305745.

Kawai, S., Kitabatake, A., Tomoike, H., & Takotsubo Cardiomyopathy G. (2007). Guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy. *Circulation Journal, 71*(6), 990–992.

Komesaroff, P. A., Esler, M. D., & Sudhir, K. (1999). Estrogen supplementation attenuates glucocorticoid and catecholamine responses to mental stress in perimenopausal women. *Journal of Clinical Endocrinology and Metabolism, 84*(2), 606–610. doi:10.1210/jcem.84.2.5447.

Kop, W. J., Krantz, D. S., Howell, R. H., Ferguson, M. A., Papademetriou, V., Lu, D., . . . Gottdiener, J. S. (2001). Effects of mental stress on coronary epicardial vasomotion and flow velocity in coronary artery disease: Relationship with hemodynamic stress responses. *Journal American College Cardiology, 37*(5), 1359–1366.

Kumar, S., Kaushik, S., Nautiyal, A., Choudhary, S. K., Kayastha, B. L., Mostow, N., & Lazar, J. M. (2011). Cardiac rupture in takotsubo cardiomyopathy: A systematic review. *Clinical Cardiology, 34*(11), 672–676. doi:10.1002/clc.20957.

Kume, T., Akasaka, T., Kawamoto, T., Yoshitani, H., Watanabe, N., Neishi, Y., . . . Yoshida, K. (2005). Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. *Circular Journal, 69*(8), 934–939.

Kume, T., Kawamoto, T., Okura, H., Toyota, E., Neishi, Y., Watanabe, N., . . . Yoshida, K. (2008). Local release of catecholamines from the hearts of patients with tako-tsubo-like left ventricular dysfunction. *Circular Journal, 72*(1), 106–108.

Kwon, S. W., Kim, B. O., Kim, M. H., Lee, S. J., Yoon, J. H., Chung, H., . . . Hong, B. K. (2013). Diverse left ventricular morphology and predictors of short-term outcome in patients with stress-induced cardiomyopathy. *International Journal Cardiology, 168*(1), 331–337. doi:10.1016/j.ijcard.2012.09.050.

Lacey, C., Mulder, R., Bridgman, P., Kimber, B., Zarifeh, J., Kennedy, M., & Cameron, V. (2014). Broken heart syndrome – is it a psychosomatic disorder? *Journal of Psychosomatic Research, 77*(2), 158–160. doi:10.1016/j.jpsychores.2014.05.003.

Lavi, S., Nevo, O., Thaler, I., Rosenfeld, R., Dayan, L., Hirshoren, N., . . . Jacob, G. (2007). Effect of aging on the cardiovascular regulatory systems in healthy women. *American Journal Physiology Regulatory Integration Comparative Physiology, 292*(2), R788–793. doi:10.1152/ajpregu.00352.2006.

Lee, P. H., Song, J. K., Sun, B. J., Choi, H. O., Seo, J. S., Na, J. O., . . . Park, S. W. (2010). Outcomes of patients with stress-induced cardiomyopathy diagnosed by echocardiography in a tertiary referral hospital. *Journal American Society Echocardiography, 23*(7), 766–771. doi:10.1016/j.echo.2010.05.002.

Leor, J., Poole, W. K., & Kloner, R. A. (1996). Sudden cardiac death triggered by an earthquake. *New England Journal of Medicine, 334*(7), 413–419. doi:10.1056/nejm199602153340701.

Looi, J. L., Wong, C. W., Khan, A., Webster, M., & Kerr, A. J. (2012). Clinical characteristics and outcome of apical ballooning syndrome in Auckland, New Zealand. *Heart, Lung & Circulation, 21*(3), 143–149. doi:10.1016/j.hlc.2011.11.010.

Madhavan, M., Borlaug, B. A., Lerman, A., Rihal, C. S., & Prasad, A. (2009). Stress hormone and circulating biomarker profile of apical ballooning syndrome (Takotsubo cardiomyopathy): Insights into the clinical significance of B-type natriuretic peptide and troponin levels. *Heart, 95*(17), 1436–1441. doi:10.1136/hrt.2009.170399.

Madhavan, M., Rihal, C. S., Lerman, A., & Prasad, A. (2011). Acute heart failure in apical ballooning syndrome (TakoTsubo/stress cardiomyopathy): Clinical correlates and Mayo Clinic risk score. *Journal of the American College of Cardiology, 57*(12), 1400–1401. doi:10.1016/j.jacc.2010.10.038.

Mann, D. L., Kent, R. L., Parsons, B., & Cooper, G. t. (1992). Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation, 85*(2), 790–804.

Maron, B. J., Towbin, J. A., Thiene, G., Antzelevitch, C., Corrado, D., Arnett, D., . . . Prevention. (2006). Contemporary definitions and classification of the cardiomyopathies: An American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation, 113*(14), 1807–1816. doi:10.1161/CIRCULATIONAHA.106.174287.

Martin, E. A., Prasad, A., Rihal, C. S., Lerman, L. O., & Lerman, A. (2010). Endothelial function and vascular response to mental stress are impaired in patients with apical ballooning syndrome. *Journal of the American College of Cardiology, 56*(22), 1840–1846. doi:10.1016/j.jacc.2010.03.107.

Martinez-Selles, M., Datino, T., Pello, A. M., & Fernandez-Aviles, F. (2010). Ergonovine provocative test in Caucasian patients with left ventricular apical ballooning syndrome. *International Journal of Cardiology, 145*(1), 89–91. doi:10.1016/j.ijcard.2009.05.040.

Mausbach, B. T., Dimsdale, J. E., Ziegler, M. G., Mills, P. J., Ancoli-Israel, S., Patterson, T. L., & Grant, I. (2005). Depressive symptoms predict norepinephrine response to a psychological stressor task in Alzheimer's caregivers. *Psychosomatic Medicine, 67*(4), 638–642. doi:10.1097/01.psy.0000173312.90148.97.

Meimoun, P., Malaquin, D., Sayah, S., Benali, T., Luycx-Bore, A., Levy, F., . . . Tribouilloy, C. (2008). The coronary flow reserve is transiently impaired in tako-tsubo cardiomyopathy:

A prospective study using serial Doppler transthoracic echocardiography. *Journal American Society Echocardiography, 21*(1), 72–77. doi:10.1016/j.echo.2007.05.024.

Meisel, S. R., Kutz, I., Dayan, K. I., Pauzner, H., Chetboun, I., Arbel, Y., & David, D. (1991). Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. *Lancet, 338*(8768), 660–661.

Mitsuma, W., Kodama, M., Ito, M., Tanaka, K., Yanagawa, T., Ikarashi, N., . . . Aizawa, Y. (2007). Serial electrocardiographic findings in women with Takotsubo cardiomyopathy. *American Journal Cardiology, 100*(1), 106–109. doi:10.1016/j.amjcard.2007.02.062.

Mittleman, M. A., Maclure, M., Sherwood, J. B., Mulry, R. P., Tofler, G. H., Jacobs, S. C., . . . Muller, J. E. (1995). Triggering of acute myocardial infarction onset by episodes of anger. Determinants of myocardial infarction onset study investigators. *Circulation, 92*(7), 1720–1725.

Murakami, T., Yoshikawa, T., Maekawa, Y., Ueda, T., Isogai, T., Konishi, Y., . . . Takayama, M. (2014). Characterization of predictors of in-hospital cardiac complications of takotsubo cardiomyopathy: Multi-center registry from Tokyo CCU Network. *Journal Cardiology, 63*(4), 269–273. doi:10.1016/j.jjcc.2013.09.003.

Nef, H. M., Mollmann, H., Troidl, C., Kostin, S., Voss, S., Hilpert, P., . . . Elsasser, A. (2009). Abnormalities in intracellular Ca2+ regulation contribute to the pathomechanism of Tako-Tsubo cardiomyopathy. *Europe Heart Journal, 30*(17), 2155–2164. doi:10.1093/eurheartj/ehp240.

Nishida, J., Kouzu, H., Hashimoto, A., Fujito, T., Kawamukai, M., Mochizuki, A., . . . Miura, T. (2014). "Ballooning" patterns in takotsubo cardiomyopathy reflect different clinical backgrounds and outcomes: A BOREAS-TCM study. *Heart Vessels*. doi:10.1007/s00380-014-0548-x.

Novo, G., Giambanco, S., Guglielmo, M., Arvigo, L., Sutera, M. R., Giambanco, F., . . . Novo, S. (2014). G-protein-coupled receptor kinase 5 polymorphism and Takotsubo cardiomyopathy. *Journal Cardiovascular Medicine (Hagerstown)*. doi:10.2459/jcm.0000000000000120.

Nunez Gil, I. J., Andres, M., Almendro Delia, M., Sionis, A., Martin, A., Bastante, T., . . . Sanchez-Grande Flecha, A. (2015). Characterization of Tako-tsubo cardiomyopathy in Spain: Results from the RETAKO National Registry. *Review Espanola Cardiology (England Ed), 68*(6), 505–512. doi:10.1016/j.rec.2014.07.026.

Ogura, R., Hiasa, Y., Takahashi, T., Yamaguchi, K., Fujiwara, K., Ohara, Y., . . . Ohtani, R. (2003). Specific findings of the standard 12-lead ECG in patients with 'Takotsubo' cardiomyopathy: Comparison with the findings of acute anterior myocardial infarction. *Circular Journal, 67*(8), 687–690.

Ortak, J., Khattab, K., Barantke, M., Wiegand, U. K., Bansch, D., Ince, H., . . . Bonnemeier, H. (2009). Evolution of cardiac autonomic nervous activity indices in patients presenting with transient left ventricular apical ballooning. *Pacing Clinical Electrophysiology, 32*(Suppl 1), S21–25. doi:10.1111/j.1540-8159.2008.02221.x.

Palla, A. R., Dande, A. S., Petrini, J., Wasserman, H. S., & Warshofsky, M. K. (2012). Pretreatment with low-dose beta-adrenergic antagonist therapy does not affect severity of Takotsubo cardiomyopathy. *Clinical Cardiology, 35*(8), 478–481. doi:10.1002/clc.21983.

Park, J. H., Kang, S. J., Song, J. K., Kim, H. K., Lim, C. M., Kang, D. H., & Koh, Y. (2005). Left ventricular apical ballooning due to severe physical stress in patients admitted to the medical ICU. *Chest, 128*(1), 296–302. doi:10.1378/chest.128.1.296.

Parodi, G., Del Pace, S., Carrabba, N., Salvadori, C., Memisha, G., Simonetti, I., . . . Gensini, G. F. (2007). Incidence, clinical findings, and outcome of women with left ventricular apical ballooning syndrome. *American Journal Cardiology, 99*(2), 182–185. doi:10.1016/j.amjcard.2006.07.080.

Parodi, G., Bellandi, B., Del Pace, S., Barchielli, A., Zampini, L., Velluzzi, S., . . . Tuscany Registry of Tako-Tsubo, C. (2011). Natural history of tako-tsubo cardiomyopathy. *Chest, 139*(4), 887–892. doi:10.1378/chest.10-1041.

Parodi, G., Citro, R., Bellandi, B., Provenza, G., Marrani, M., & Bossone, E. (2014). Revised clinical diagnostic criteria for Tako-tsubo syndrome: The Tako-tsubo Italian network proposal. *International Journal of Cardiology, 172*(1), 282–283. doi:10.1016/j.ijcard.2013.12.239.

Patel, S. M., Lerman, A., Lennon, R. J., & Prasad, A. (2013). Impaired coronary microvascular reactivity in women with apical ballooning syndrome (Takotsubo/stress cardiomyopathy). *Europe Heart Journal Acute Cardiovascular Care, 2*(2), 147–152. doi:10.1177/2048872613475891.

Paur, H., Wright, P. T., Sikkel, M. B., Tranter, M. H., Mansfield, C., O'Gara, P., . . . Harding, S. E. (2012). High levels of circulating epinephrine trigger apical cardiodepression in a beta2-adrenergic receptor/Gi-dependent manner: A new model of Takotsubo cardiomyopathy. *Circulation, 126*(6), 697–706. doi:10.1161/CIRCULATIONAHA.112.111591.

Pelliccia, F., Parodi, G., Greco, C., Antoniucci, D., Brenner, R., Bossone, E., . . . Kaski, J. C. (2015). Comorbidities frequency in takotsubo syndrome: An international collaborative systematic review including 1109 patients. *American Journal Medicine, 128*(6), 654 e611–659. doi:10.1016/j.amjmed.2015.01.016.

Pilgrim, T. M., & Wyss, T. R. (2008). Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: A systematic review. *International Journal of Cardiology, 124*(3), 283–292. doi:10.1016/j.ijcard.2007.07.002.

Pison, L., De Vusser, P., & Mullens, W. (2004). Apical ballooning in relatives. *Heart, 90*(12), e67. doi:10.1136/hrt.2004.046813.

Prasad, A., Lerman, A., & Rihal, C. S. (2008). Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. *American Heart Journal, 155*(3), 408–417. doi:10.1016/j.ahj.2007.11.008.

Previtali, M., Repetto, A., Panigada, S., Camporotondo, R., & Tavazzi, L. (2009). Left ventricular apical ballooning syndrome: Prevalence, clinical characteristics and pathogenetic mechanisms in a European population. *International Journal of Cardiology, 134*(1), 91–96. doi:10.1016/j.ijcard.2008.01.037.

Previtali, M., Repetto, A., Camporotondo, R., Citro, R., Faggiano, P., Bovelli, D., . . . Klersy, C. (2011). Clinical characteristics and outcome of left ventricular ballooning syndrome in a European population. *American Journal Cardiology, 107*(1), 120–125. doi:10.1016/j.amjcard.2010.08.055.

Redfors, B., Ali, A., Shao, Y., Lundgren, J., Gan, L. M., & Omerovic, E. (2014a). Different catecholamines induce different patterns of takotsubo-like cardiac dysfunction in an apparently afterload dependent manner. *International Journal of Cardiology, 174*(2), 330–336. doi:10.1016/j.ijcard.2014.04.103.

Redfors, B., Shao, Y., Lyon, A. R., & Omerovic, E. (2014b). Diagnostic criteria for takotsubo syndrome: A call for consensus. *International Journal of Cardiology, 176*(1), 274–276. doi:10.1016/j.ijcard.2014.06.094.

Redfors, B., Vedad, R., Angeras, O., Ramunddal, T., Petursson, P., Haraldsson, I., . . . Omerovic, E. (2015). Mortality in takotsubo syndrome is similar to mortality in myocardial infarction – a report from the SWEDEHEART registry. *International Journal Cardiology, 185*, 282–289. doi:10.1016/j.ijcard.2015.03.162.

Regnante, R. A., Zuzek, R. W., Weinsier, S. B., Latif, S. R., Linsky, R. A., Ahmed, H. N., & Sadiq, I. (2009). Clinical characteristics and four-year outcomes of patients in the Rhode Island Takotsubo cardiomyopathy registry. *American Journal of Cardiology, 103*(7), 1015–1019. doi:10.1016/j.amjcard.2008.12.020.

Reuss, C. S., Lester, S. J., Hurst, R. T., Askew, J. W., Nager, P., Lusk, J., . . . Tajik, A. J. (2007). Isolated left ventricular basal ballooning phenotype of transient cardiomyopathy in young women. *American Journal Cardiology, 99*(10), 1451–1453. doi:10.1016/j.amjcard.2006.12.078.

Rigo, F., Sicari, R., Citro, R., Ossena, G., Buja, P., & Picano, E. (2009). Diffuse, marked, reversible impairment in coronary microcirculation in stress cardiomyopathy: A Doppler

transthoracic echo study. *Annals of Medicine, 41*(6), 462–470. doi:10.1080/07853890903022793.

Sader, M. A., & Celermajer, D. S. (2002). Endothelial function, vascular reactivity and gender differences in the cardiovascular system. *Cardiovascular Research, 53*(3), 597–604.

Santoro, F., Ieva, R., Musaico, F., Ferraretti, A., Triggiani, G., Tarantino, N., . . . Brunetti, N. D. (2014). Lack of efficacy of drug therapy in preventing takotsubo cardiomyopathy recurrence: A meta-analysis. *Clinical Cardiology, 37*(7), 434–439. doi:10.1002/clc.22280.

Sato, A., Aonuma, K., Nozato, T., Sekiguchi, Y., Okazaki, O., Kubota, K., & Hiroe, M. (2008). Stunned myocardium in transient left ventricular apical ballooning: A serial study of dual I-123 BMIPP and Tl-201 SPECT. *Journal of Nuclear Cardiology, 15*(5), 671–679. doi:10.1016/j.nuclcard.2008.03.010.

Scantlebury, D. C., Prasad, A., Rabinstein, A. A., & Best, P. J. (2013). Prevalence of migraine and Raynaud phenomenon in women with apical ballooning syndrome (Takotsubo or stress cardiomyopathy). *American Journal of Cardiology, 111*(9), 1284–1288. doi:10.1016/j.amjcard.2013.01.269.

Schultz, T., Shao, Y., Redfors, B., Sverrisdottir, Y. B., Ramunddal, T., Albertsson, P., . . . Omerovic, E. (2012). Stress-induced cardiomyopathy in Sweden: Evidence for different ethnic predisposition and altered cardio-circulatory status. *Cardiology, 122*(3), 180–186. doi:10.1159/000338814.

Sharkey, S. W., Lesser, J. R., Zenovich, A. G., Maron, M. S., Lindberg, J., Longe, T. F., & Maron, B. J. (2005). Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation, 111*(4), 472–479. doi:10.1161/01.CIR.0000153801.51470.EB.

Sharkey, S. W., Lesser, J. R., Menon, M., Parpart, M., Maron, M. S., & Maron, B. J. (2008). Spectrum and significance of electrocardiographic patterns, troponin levels, and thrombolysis in myocardial infarction frame count in patients with stress (tako-tsubo) cardiomyopathy and comparison to those in patients with ST-elevation anterior wall myocardial infarction. *American Journal of Cardiology, 101*(12), 1723–1728. doi:10.1016/j.amjcard.2008.02.062.

Sharkey, S. W., Maron, B. J., Nelson, P., Parpart, M., Maron, M. S., & Bristow, M. R. (2009). Adrenergic receptor polymorphisms in patients with stress (tako-tsubo) cardiomyopathy. *Journal of Cardiology, 53*(1), 53–57. doi:10.1016/j.jjcc.2008.08.006.

Sharkey, S. W., Windenburg, D. C., Lesser, J. R., Maron, M. S., Hauser, R. G., Lesser, J. N., . . . Maron, B. J. (2010). Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *Journal American College Cardiology, 55*(4), 333–341. doi:10.1016/j.jacc.2009.08.057.

Sharkey, S. W., Lesser, J. R., Garberich, R. F., Pink, V. R., Maron, M. S., & Maron, B. J. (2012). Comparison of circadian rhythm patterns in Tako-tsubo cardiomyopathy versus ST-segment elevation myocardial infarction. *American Journal of Cardiology, 110*(6), 795–799. doi:10.1016/j.amjcard.2012.04.060.

Sharkey, S. W., Lips, D. L., Pink, V. R., & Maron, B. J. (2013). Daughter-mother tako-tsubo cardiomyopathy. *American Journal of Cardiology, 112*(1), 137–138. doi:10.1016/j.amjcard.2013.02.063.

Showkathali, R., Patel, H., Ramoutar, A., Kabir, A. M., Sayer, J. W., Clesham, G. J., . . . Kelly, P. A. (2014). Typical takotsubo cardiomyopathy in suspected ST elevation myocardial infarction patients admitted for primary percutaneous coronary intervention. *Europe Journal International Medicine, 25*(2), 132–136. doi:10.1016/j.ejim.2013.09.004.

Singh, N. K., Rumman, S., Mikell, F. L., Nallamothu, N., & Rangaswamy, C. (2010). Stress cardiomyopathy: Clinical and ventriculographic characteristics in 107 North American subjects. *International Journal of Cardiology, 141*(3), 297–303. doi:10.1016/j.ijcard.2008.12.043.

Singh, K., Carson, K., Shah, R., Sawhney, G., Singh, B., Parsaik, A., . . . Horowitz, J. (2014). Meta-analysis of clinical correlates of acute mortality in takotsubo cardiomyopathy. *American Journal Cardioogyl, 113*(8), 1420–1428. doi:10.1016/j.amjcard.2014.01.419.

Singh, K., Carson, K., Usmani, Z., Sawhney, G., Shah, R., & Horowitz, J. (2014b). Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo

cardiomyopathy. *International Journal of Cardiology, 174*(3), 696–701. doi:10.1016/j.ijcard.2014.04.221.

Song, B. G., Hahn, J. Y., Cho, S. J., Park, Y. H., Choi, S. M., Park, J. H., . . . Gwon, H. C. (2010). Clinical characteristics, ballooning pattern, and long-term prognosis of transient left ventricular ballooning syndrome. *Heart Lung, 39*(3), 188–195. doi:10.1016/j.hrtlng.2009.07.006.

Song, B. G., Chun, W. J., Park, Y. H., Kang, G. H., Oh, J., Lee, S. C., . . . Oh, J. K. (2011). The clinical characteristics, laboratory parameters, electrocardiographic, and echocardiographic findings of reverse or inverted takotsubo cardiomyopathy: Comparison with mid or apical variant. *Clinical Cardiology, 34*(11), 693–699. doi:10.1002/clc.20953.

Song, B. G., Yang, H. S., Hwang, H. K., Kang, G. H., Park, Y. H., Chun, W. J., & Oh, J. H. (2012). The impact of stressor patterns on clinical features in patients with tako-tsubo cardiomyopathy: Experiences of two tertiary cardiovascular centers. *Clinical Cardiology, 35*(11), E6–E13. doi:10.1002/clc.22053.

Song, B. G., Oh, J. H., Kim, H. J., Kim, S. H., Chung, S. M., Lee, M., . . . Chun, W. J. (2013). Chronobiological variation in the occurrence of Tako-tsubo cardiomyopathy: Experiences of two tertiary cardiovascular centers. *Heart Lung, 42*(1), 40–47. doi:10.1016/j.hrtlng.2012.09.004.

Spinelli, L., Trimarco, V., Di Marino, S., Marino, M., Iaccarino, G., & Trimarco, B. (2010). L41Q polymorphism of the G protein coupled receptor kinase 5 is associated with left ventricular apical ballooning syndrome. *European Journal of Heart Failure, 12*(1), 13–16. doi:10.1093/eurjhf/hfp173.

Steinberg, J. S., Arshad, A., Kowalski, M., Kukar, A., Suma, V., Vloka, M., . . . Rozanski, A. (2004). Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. *Journal American College Cardiology, 44*(6), 1261–1264. doi:10.1016/j.jacc.2004.06.032.

Steptoe, A., Strike, P. C., Perkins-Porras, L., McEwan, J. R., & Whitehead, D. L. (2006). Acute depressed mood as a trigger of acute coronary syndromes. *Biological Psychiatry, 60*(8), 837–842. doi:10.1016/j.biopsych.2006.03.041.

Sugimoto, K., Inamasu, J., Hirose, Y., Kato, Y., Ito, K., Iwase, M., . . . Ozaki, Y. (2012). The role of norepinephrine and estradiol in the pathogenesis of cardiac wall motion abnormality associated with subarachnoid hemorrhage. *Stroke, 43*(7), 1897–1903. doi:10.1161/strokeaha.111.646893.

Summers, M. R., Lennon, R. J., & Prasad, A. (2010). Pre-morbid psychiatric and cardiovascular diseases in apical ballooning syndrome (tako-tsubo/stress-induced cardiomyopathy): Potential pre-disposing factors? *Journal of the American College of Cardiology, 55*(7), 700–701. doi:10.1016/j.jacc.2009.10.031.

Sung, B. H., Ching, M., Izzo, J. L., Jr., Dandona, P., & Wilson, M. F. (1999). Estrogen improves abnormal norepinephrine-induced vasoconstriction in postmenopausal women. *Journal of Hypertension, 17*(4), 523–528.

Sy, F., Basraon, J., Zheng, H., Singh, M., Richina, J., & Ambrose, J. A. (2013). Frequency of Takotsubo cardiomyopathy in postmenopausal women presenting with an acute coronary syndrome. *American Journal of Cardiology, 112*(4), 479–482. doi:10.1016/j.amjcard.2013.04.010.

Takizawa, M., Kobayakawa, N., Uozumi, H., Yonemura, S., Kodama, T., Fukusima, K., . . . Aoyagi, T. (2007). A case of transient left ventricular ballooning with pheochromocytoma, supporting pathogenetic role of catecholamines in stress-induced cardiomyopathy or takotsubo cardiomyopathy. *International Journal Cardiology, 114*(1), e15–e17. doi:10.1016/j.ijcard.2006.07.125.

Tsuchihashi, K., Ueshima, K., Uchida, T., Oh-mura, N., Kimura, K., Owa, M., . . . Angina Pectoris-Myocardial Infarction Investigations in, J. (2001). Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. *Journal American College Cardiology, 38*(1), 11–18.

Uchida, Y., Egami, H., Uchida, Y., Sakurai, T., Kanai, M., Shirai, S., . . . Oshima, T. (2010). Possible participation of endothelial cell apoptosis of coronary microvessels in the genesis of Takotsubo cardiomyopathy. *Clinical Cardiology, 33*(6), 371–377. doi:10.1002/clc.20777.

Ueyama, T., Kasamatsu, K., Hano, T., Yamamoto, K., Tsuruo, Y., & Nishio, I. (2002). Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: A possible animal model of 'tako-tsubo' cardiomyopathy. *Circulation Journal, 66*(7), 712–713.

Ueyama, T., Ishikura, F., Matsuda, A., Asanuma, T., Ueda, K., Ichinose, M., . . . Beppu, S. (2007). Chronic estrogen supplementation following ovariectomy improves the emotional stress-induced cardiovascular responses by indirect action on the nervous system and by direct action on the heart. *Circular Journal, 71*(4), 565–573.

Vaccaro, A., Despas, F., Delmas, C., Lairez, O., Lambert, E., Lambert, G., . . . Pathak, A. (2014). Direct evidences for sympathetic hyperactivity and baroreflex impairment in Tako Tsubo cardiopathy. *PLoS One, 9*(3), e93278. doi:10.1371/journal.pone.0093278.

Vasilieva, E., Vorobyeva, I., Lebedeva, A., Urazovskaya, I., Kalinskaya, A., Skrypnik, D., & Shpektor, A. (2011). Brachial artery flow-mediated dilation in patients with Tako-tsubo cardiomyopathy. *American Journal of Medicine, 124*(12), 1176–1179. doi:10.1016/j.amjmed.2011.05.033.

Verberne, H. J., van der Heijden, D. J., van Eck-Smit, B. L., & Somsen, G. A. (2009). Persisting myocardial sympathetic dysfunction in takotsubo cardiomyopathy. *Journal of Nuclear Cardiology, 16*(2), 321–324. doi:10.1007/s12350-008-9017-1.

Vriz, O., Minisini, R., Citro, R., Guerra, V., Zito, C., De Luca, G., . . . Bossone, E. (2011). Analysis of beta 1 and beta 2-adrenergic receptors polymorphism in patients with apical ballooning cardiomyopathy. *Acta Cardiology, 66*(6), 787–790. doi:10.2143/Ac.66.6.2136964.

Wedekind, H., Moller, K., & Scholz, K. H. (2006). Tako-tsubo cardiomyopathy. Incidence in patients with acute coronary syndrome. *Herz, 31*(4), 339–346. doi:10.1007/s00059-006-2822-x.

Weihs, V., Szucs, D., Fellner, B., Eber, B., Weihs, W., Lambert, T., . . . Huber, K. (2013). Stress-induced cardiomyopathy (Tako-Tsubo syndrome) in Austria. *Europe Heart Journal Acute Cardiovascular Care, 2*(2), 137–146. doi:10.1177/2048872613483592.

Winchester, D. E., Ragosta, M., & Taylor, A. M. (2008). Concurrence of angiographic coronary artery disease in patients with apical ballooning syndrome (tako-tsubo cardiomyopathy). *Catheterization and Cardiovascular Interventions, 72*(5), 612–616. doi:10.1002/ccd.21738.

Wittstein, I. S. (2012). Stress cardiomyopathy: A syndrome of catecholamine-mediated myocardial stunning? *Cellular and Molecular Neurobiology, 32*(5), 847–857. doi:10.1007/s10571-012-9804-8.

Wittstein, I. S., Thiemann, D. R., Lima, J. A., Baughman, K. L., Schulman, S. P., Gerstenblith, G., . . . Champion, H. C. (2005). Neurohumoral features of myocardial stunning due to sudden emotional stress. *New England Journal Medicine, 352*(6), 539–548. doi:10.1056/NEJMoa043046.

Yoshida, T., Hibino, T., Kako, N., Murai, S., Oguri, M., Kato, K., . . . Kimura, G. (2007). A pathophysiologic study of tako-tsubo cardiomyopathy with F-18 fluorodeoxyglucose positron emission tomography. *Europe Heart Journal, 28*(21), 2598–2604. doi:10.1093/eurheartj/ehm401.

Zaroff, J. G., Pawlikowska, L., Miss, J. C., Yarlagadda, S., Ha, C., Achrol, A., . . . Young, W. L. (2006). Adrenoceptor polymorphisms and the risk of cardiac injury and dysfunction after subarachnoid hemorrhage. *Stroke, 37*(7), 1680–1685. doi:10.1161/01.STR.0000226461.52423.dd.

Zeballos, C., Moraca, R. J., Bailey, S. H., & Magovern, G. J., Jr. (2012). Temporary mechanical circulatory support for Takotsubo cardiomyopathy secondary to primary mediastinal B-cell lymphoma. *Journal of Cardiac Surgery, 27*(1), 119–121. doi:10.1111/j.1540-8191.2011.01391.x.

Congenital Heart Diseases

Massimo Chessa and Fatma Aboalsoud Taha

Contents

Abstract

– Introduction: Congenital heart defect (CHD) may be defined as an anatomic malformation of the heart or great vessels which occurs during intrauterine development. CHDs are serious and chronic illnesses. Congenital heart defects

M. Chessa (✉)
Pediatric and Adult Congenital Heart Centre, IRCCS-Policlinico San Donato-University Hospital, San Donato Milanese (Milan), Lombardy, Italy
e-mail: massimo.chessa@grupposandonato.it

F.A. Taha
Faculty of Medicine, Tanta University, Tanta, Egypt
e-mail: fatma.taha@med.tanta.edu.eg; fatmastaha@yahoo.com

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_22

may be classified into acyanotic and cyanotic depending on the presence or absence of cyanosis. As survival has improved, evidence has accumulated that CHD touches many aspects of the lives of those affected. Children and adults with CHDs report difficulties in physical, behavioral, and psychiatric abnormalities.
– Aim: To emphasize that people with CHDs often need treatment over their life and therefore require specialist review during childhood and adulthood. This is because people with complex heart problems can develop further problems with their heart rhythm or valves over time. Also they may report physical, psychological, and behavioral abnormalities.
– Conclusion: A significant proportion of survivors of open-heart surgery for CHD are at risk for physical and psychological maladjustment. This calls for an integrated approach to family support, taking the child's individual needs into account as well as the needs of the parents.

Keywords
Congenital heart diseases (CHDs) • Atrial and ventricular septal defects • Patent ductus arteriosus (PDA) • Stenotic cardiac lesions • Coarctation and interruption of the aorta • Tetralogy of Fallot (ToF)/pulmonary atresia (PA) • Transposition of the great arteries (TGA) • Truncus arteriosus • Anomalous pulmonary venous return (APVR) • Ebstein anomaly

Introduction

Congenital heart defect (CHD) may be defined as an anatomic malformation of the heart or great vessels which occurs during intrauterine development, irrespective of the age at presentation (Syamasundar 2012).

CHDs are among the most pervasive and serious chronic illnesses found in children (Behrman et al. 1992).

Congenital heart defects may be classified into acyanotic and cyanotic depending upon whether the patients clinically exhibit cyanosis (Taber and Venes 2009).

As survival has improved, evidence has accumulated that CHD touches many aspects of the lives of those affected. Children and adults report difficulties with physical growth and/or stature. Gross motor abnormalities are common in both groups, and significantly reduced exercise tolerance is reported in adults with CHD, including those with minor defects. Behavioral and psychiatric abnormalities are reported in adolescents and young adults, including a significant incidence of depression and anxiety disorders. Also, a significant proportion of children with CHD experience psychological maladjustment following cardiopulmonary bypass surgery. Children with more severe heart defects or those in need of future surgical

interventions and children with neurodevelopmental impairment are at particular risk for maladjustment (Green 2004).

People with congenital heart disease often do need treatment over their life and therefore require specialist review during childhood and adulthood. This is because people with complex heart problems can develop further problems with their heart rhythm or valves over time. This calls for an integrated approach to family support, taking the child's individual needs into account as well as the needs of the parents (Green 2004).

Normal Heart

Anatomy of the Normal Heart

Definition

The human heart is a vital organ that functions as a pump, providing a continuous circulation of blood through the body, by way of the cardiac cycles (Taber and Venes 2009).

Development

The heart is the first functional organ to develop in the embryo. The human embryonic heart begins beating at around 21 days or at 5 weeks after conception (DuBose et al. 2010) (Figs. 1 and 2).

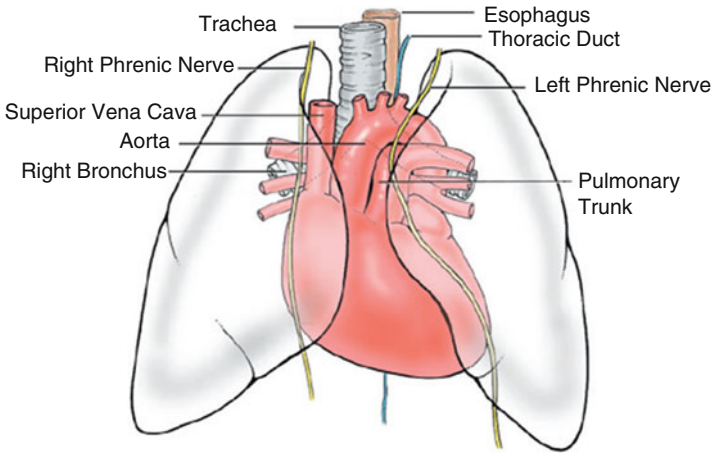


Fig. 1 Location of the normal heart

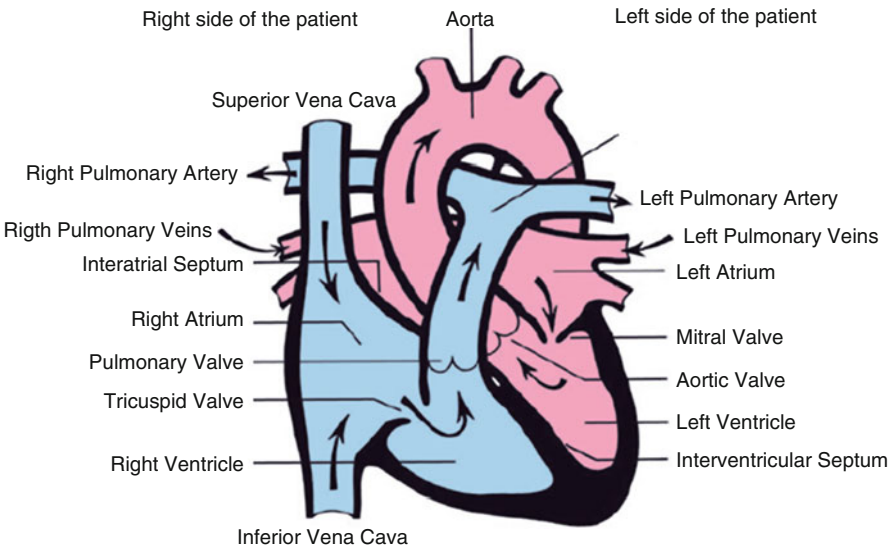


Fig. 2 Anatomy of the normal Heart

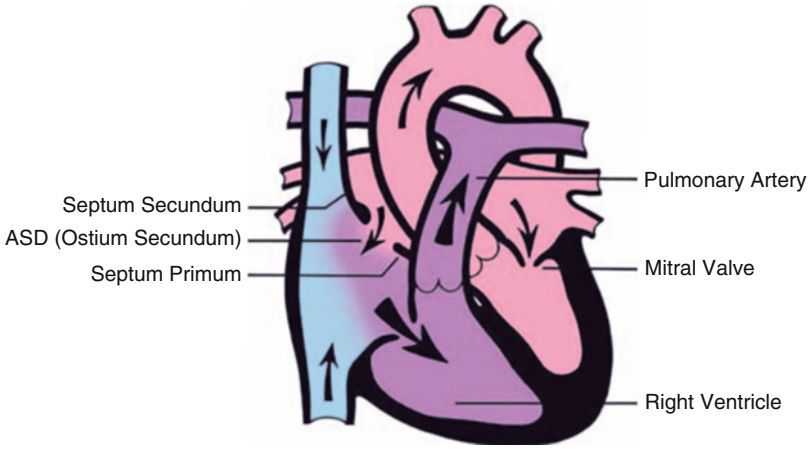


Fig. 3 Atrial septal defect

Location and Site

- The heart is located in the middle mediastinum in the thoracic cavity. The heart is at the level of the thoracic vertebrae T5-8. It rests on the diaphragm, beneath the sternum and ribs, and has two sides adjacent to the right and left lungs (Drake et al. 2005) as shown in Fig. 3.
- The heart is enclosed in a protective sac, the pericardium which also contains a lubricating pericardial fluid. This enables the heart to move in response to its own

contractions and to the movements of adjacent structures as the diaphragm and lungs. It also serves as protection from infection and knocks (Levine and Miller 2002).

Structure (Walls and Chambers)

- The outer wall of the heart is made up of three layers, the epicardium, the myocardium (the muscle layer), and the endocardium. The endocardium merges with the inner lining (endothelium) of the blood vessels and covers the heart valves (Heart 2010).
- The heart is divided into four main chambers: the two upper chambers are called the left atrium and the right atrium (receiving chambers), and the two lower chambers are called the right and the left ventricles (discharging chambers) (Starr et al. 2009).
- There is a dividing wall of muscle, called the septum, which separates the right side from the left side of the heart. The interatrioventricular septum gives two functionally and anatomically distinct units. The ventricular septum is thicker than the atrial septum (Starr et al. 2009) as shown in Fig. 2.

Blood Supply

As well as the blood being pumped within the heart, the heart has its own blood supply that surrounds it. This is the coronary circulation (Taber and Venes 2009).

Conduction System

Signals arising in the SA node stimulate the atria to contract and travel to the AV node. After a delay, the stimulus is conducted through the bundle of His to the Purkinje fibers and the endocardium at the apex of the heart, then finally to the ventricular epicardium (Anatomy and Function of the Heart's Electrical System 2013).

Physiology of the Normal Heart: (Cardiac Cycle)

- The pathways of blood through the human heart are part of the pulmonary and systemic circuits. These pathways include the tricuspid valve and the mitral valve (the atrioventricular (AV) valves) and the aortic valve and the pulmonary valve (the semilunar valves) (Marieb 2003).
- Physicians commonly refer to the right atrium and right ventricle together as the right heart and to the left atrium and left ventricle as the left heart (Phibbs 2007).
- The lower ventricles are thicker and stronger than the upper atria. The muscle wall surrounding the left ventricle is thicker than the wall surrounding the right ventricle due to the higher force needed to pump the blood through the systemic circulation (Anderson 2012).
- Normally with each heartbeat, blood flows through the heart in one direction, from the atria to the ventricles; the right ventricle pumps the same amount of blood into the lungs that the left ventricle pumps out into the body. Blood is prevented from flowing backwards by the tricuspid, mitral, aortic, and pulmonary valves (Anderson 2012).

- The heart acts as a double pump. The function of the right heart is to collect deoxygenated blood, in the right atrium, from the body (via the superior and inferior venae cavae) and pump it, via the right ventricle, into the lungs (pulmonary circulation) where carbon dioxide can be exchanged for oxygen. This happens through the passive process of diffusion. From there, blood flows back through the pulmonary vein to the left atrium (Anderson 2012).
- The left heart collects oxygenated blood from the lungs into the left atrium. From the left atrium the blood flows to the left ventricle which pumps it out to the rest of the body (via the aorta). The (relatively) deoxygenated blood finally returns to the heart through the superior and inferior venae cavae (Anderson 2012).

Congenital Heart Diseases (CHDs)

Definition of CHD

Congenital heart defect (CHD) may be defined as an anatomic malformation of the heart or great vessels which occurs during intrauterine development, irrespective of the age at presentation (Syamasundar 2012).

Incidence of CHD

CHDs are among the most pervasive and serious chronic illnesses found in children. It is estimated that 8 of every 1,000 babies are born with a congenital heart defect (Behrman et al. 1992).

Classification of CHD

Congenital heart defects may be classified into acyanotic and cyanotic depending upon whether the patients clinically exhibit cyanosis. The acyanotic defects may further be subdivided into obstructive lesions and left-to-right shunt lesions. The cyanotic defects, by definition, have right-to-left shunt (Syamasundar 2012).

Acyanotic Conditions

Patent Foramen Ovale (PFO)

- Definition: An interatrial communication that exists normally in the fetus where it allows blood to bypass the pulmonary circulation. Normally this opening closes at birth when the lungs function (Yun 2011).
- Incidence: A PFO is seen in almost all newborns; frequency decreases with age (Hagen et al. 1984; Kasasbeh et al. 2013).
- Management: Percutaneous device closure is required in patients who have had a stroke or TIA (Romfh et al. 2012).

- Natural history and prognosis: Complete anatomic closure of the foramen ovale occurs in 70–75 % of adults. It assumes clinical importance in certain congenital heart defects and in older patients with paradoxical emboli and stroke (Schneider et al. 1996).

Atrial Septal Defect (ASD)

- Definition: An interatrial communication that results from opening in the atrial septum (Brickner et al. 2000; Feldt et al. 1971).
- Incidence: It accounts for about one-third of CHD and most likely to be detected in adults. It occurs in women two to three times as often as in men (Brickner et al. 2000; Feldt et al. 1971).
- Types: Anatomically, it may take the form of ostium secundum, in the region of the fossa ovalis (75 %); ostium primum, in the lower part of the atrial septum (15 %); or sinus venosus, in the upper atrial septum (10 %) (Brickner et al. 2000).
- Associated cardiac abnormalities: Include mitral valve prolapse (with ostium secundum defects), mitral regurgitation (due to a cleft in the anterior mitral valve leaflet, which occurs with ostium primum defects), and partial anomalous pulmonary venous drainage into the right atrium or venae cavae (with sinus venosus) (Brickner et al. 2000; Leachman et al. 1976; Van Praagh et al. 1994).
- Pathophysiology: Regardless of its anatomical location, there is shunting of blood from left atrium to the right atrium (Fig. 3); the direction and magnitude of shunting are determined by the size of the defect and the relative compliance of the ventricles, causing increased pulmonary blood flow and dilatation of the atria, right ventricle, and pulmonary arteries. Eventually, if the right ventricle fails or its compliance declines, the left-to-right shunting diminishes in magnitude, and right-to-left shunting may occur (Brickner et al. 2000).
- Management: An atrial septal defect with a ratio of pulmonary to systemic flow of 1.5 or more diagnosed by catheterization should be closed percutaneously (Butera et al. 2008) or surgically (Konstantinides et al. 1995). Surgical closure is not recommended for patients with irreversible pulmonary vascular disease and pulmonary hypertension (Steele et al. 1987). Prophylaxis against infective endocarditis is not recommended (Brickner et al. 2000).
- Natural history and prognosis:
  - Initially ASDs produce no symptoms and remain undetected for years (Brickner et al. 2000; Craig and Selzer 1968). Over the years, the increased volume of blood through the right side of the heart usually causes right ventricular dilatation and failure (Brickner et al. 2000; Craig and Selzer 1968).
  - Obstructive pulmonary vascular disease (Eisenmenger's syndrome) occurs rarely in adults with atrial septal defect (Craig and Selzer 1968).
  - A patient with an atrial septal defect usually has normal sinus rhythm for the first three decades of life; after which atrial arrhythmias, including atrial fibrillation and supraventricular tachycardia, may appear (Perloff 1998).
  - Also paradoxical embolism or recurrent pulmonary infections may prompt the patient to seek medical attention (Brickner et al. 2000).

Atrioventricular Defect (Endocardial Cushion Defect) (AV Canal)

- Definition: A spectrum of cardiac malformations derived from defects in the formation of the endocardial cushions. Developmentally, the endocardial cushions contribute to the lower portion of the atrial septum (septum primum), the upper portion of the ventricular septum, and the mitral and tricuspid valves (Brickner et al. 2000).
- Types:
  - Ostium primum defect or incomplete AV canal (Fig. 4) consists of an atrial septal defect located low in the atrial septum, which is often associated with a cleft in the anterior leaflet of the mitral valve leading to mitral insufficiency (Brickner et al. 2000).
  - Complete AV canal (Fig. 5) consists of ostium primum type of defect which is continuous with a larger defect in the adjacent ventricular septum. In these instances the defect crosses both the mitral and tricuspid valvular annulus, causing deficiencies of the septal leaflets of both valves (Gatzoulis et al. 1999).
- Pathophysiology: Two major hemodynamic abnormalities are found. The first is the volume overload on the right atrium and right ventricle and pulmonary overcirculation, as in patients with ASD. The second abnormality is mitral insufficiency, which increases left ventricular volume (Brickner et al. 2000).
- Management:
  - In asymptomatic patients with an ostium primum type of defect and a cleft mitral valve, operation can be delayed. The defect is closed and the cleft mitral valve is sutured (Brickner et al. 2000).

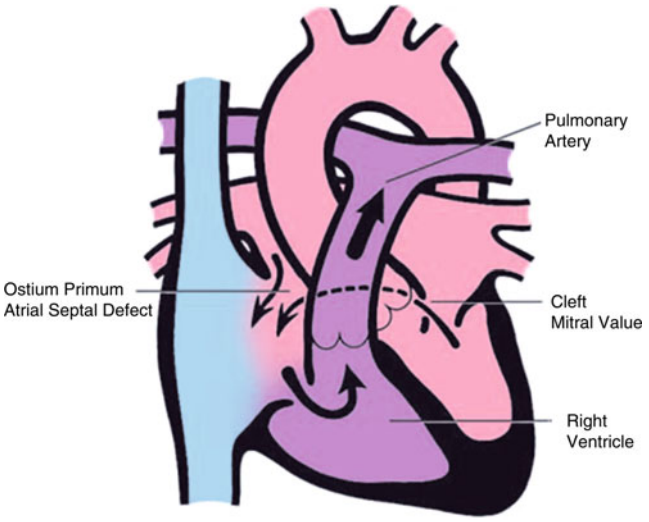


Fig. 4 Partial AV canal

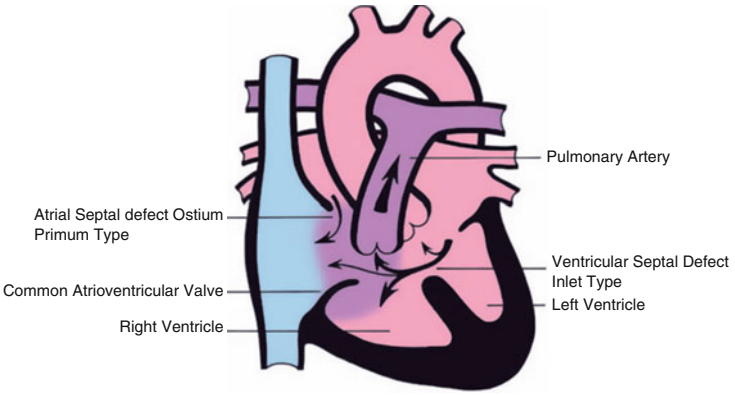


Fig. 5 Complete AV canal

  - In patients with complete AV canal, corrective operation can be indicated in very young symptomatic infants. Infants are routinely sent for operation at 2–3 months of age (Gatzoulis et al. 1999).
- Natural history and prognosis:
  - The risk of pulmonary vascular disease developing within the first 6–9 months of life is high, in complete form especially in Down syndrome (Craig 2006).
  - Some postoperative patients require prosthetic replacement of the mitral valve (Burke et al. 1996; Somerville 1965).
  - Surgically induced AV block is uncommon but is more likely with this lesion than in closure of perimembranous ventricular septal defect (Burke et al. 1996; Somerville 1965).
  - Arrhythmias appear to have an earlier age of onset in patients with ASD ostium primum defect or repair AV canal defect than in other atrial shunts, due to concomitant left AV valve regurgitation (Burke et al. 1996; Somerville 1965).

Ventricular Septal Defect (VSD)

- Definition: A VSD is a defect in the interventricular septum between both ventricles (Mas and Bricker 1990).
- Incidence: VSD is the most common CHD in infants and children. It occurs with similar frequency in boys and girls. Spontaneous closure of small VSD may occur (Brickner et al. 2000; Perloff 1998).
- Etiology: Certainly, VSDs are prevalent in association with genetic abnormalities, especially in trisomies 13, 18, and 21 as well as other less common syndromes (Mas and Bricker 1990).
- Types: Anatomically, 70 % are perimembranous located in the membranous portion of the interventricular septum, 20 % are muscular in the muscular portion of the septum, 5 % are inlet (atrioventricular canal defects) near the junction of the mitral and tricuspid valves and 5 % below the aortic valve which usually leads to

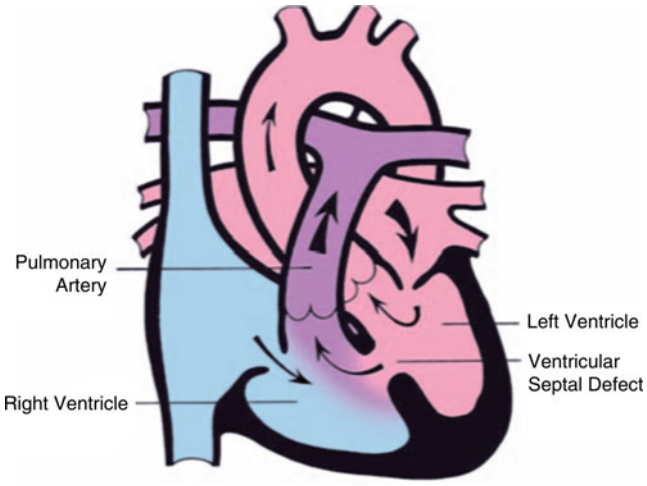


Fig. 6 Ventricular septal defect

prolapse of one or more aortic valve leaflets into the defect during systole leads to aortic regurgitation (AR) (Brickner et al. 2000; Graham and Gutgesell 1995).

- Associated anomalies: It may occur in isolation or, less commonly, as a part of a complex cardiac malformation (Brickner et al. 2000).
- Pathophysiology: The physiologic consequences of a VSD are determined by the size of the defect and the relative resistance in the systemic and pulmonary vascular beds. Left-to-right shunting predominates (Fig. 6). Over time, the pulmonary vascular resistance usually increases, and the magnitude of left-to-right shunting declines. The pulmonary vascular resistance equals or exceeds the systemic resistance, and right-to left shunting begins (Brickner et al. 2000).
- Management: Catheterization and angiography confirm the presence and location of the defect, as well as the magnitude of shunting and the pulmonary vascular resistance. Surgical closure of the defect is recommended, if the magnitude of pulmonary vascular obstructive disease is not prohibitive (Brickner et al. 2000; Boehrer et al. 1992).
- Natural history and prognosis:
  - It depends on the size of the defect and the pulmonary vascular resistance. Adults with small defects and normal pulmonary arterial pressure are generally asymptomatic, and pulmonary vascular disease is unlikely to develop (Kidd et al. 1993). Such patients do not require surgical closure, but they are at risk for infective endocarditis and should receive antibiotic prophylaxis (Brickner et al. 2000; Kidd et al. 1993).
  - Patients with large defects who survive to adulthood usually have left ventricular failure or pulmonary hypertension with associated right ventricular failure (Perloff 1998).
  - Complete heart block secondary to injury to the conduction system during repair of a VSD may require a postoperative pacemaker. Now, awareness of

the location of the conductive system in relationship to the defect makes this a rare complication (Perloff 1998; Kidd et al. 1993).

Patent Ductus Arteriosus (PDA)

- Definition: It connects the descending aorta (just distal to the left subclavian artery) to the left pulmonary artery. In the fetus, it permits pulmonary arterial blood to bypass the unexpanded lungs and enter the descending aorta for oxygenation in the placenta. It normally closes soon after birth (Brickner et al. 2000).
- Incidence: PDA accounts for about 10 % of cases of CHDs (Brickner et al. 2000).
- Etiology: Its incidence is higher in pregnancies complicated by persistent perinatal hypoxemia or maternal rubella infection and in infants born prematurely (Brickner et al. 2000).
- Pathophysiology: With larger shunts, flow is markedly increased, which may lead to left ventricular failure, pulmonary vascular obstruction, and finally the reverse of shunting (Brickner et al. 2000; Campbell 1955).
- Management:
  - Catheterization and angiography make it possible to quantify the magnitude of shunting and the pulmonary vascular resistance as well as visualize the ductus arteriosus (Boehrer et al. 1992).
  - Percutaneous device closure and surgical ligation or resection of patent ductus arteriosus are required (Brickner et al. 2000; Fisher et al. 1986).
  - Once severe pulmonary vascular obstructive disease develops, surgical ligation or percutaneous closure is contraindicated (Fisher et al. 1986).
- Natural history and prognosis:
  - A patent ductus arteriosus rarely closes spontaneously after infancy (Brickner et al. 2000; Fisher et al. 1986).
  - A small patent ductus arteriosus is asymptomatic; however, it entails the risk of infective endocarditis and septic pulmonary emboli (Brickner et al. 2000).
  - A moderate patent ductus arteriosus may be asymptomatic during infancy, during childhood, or adulthood (Campbell 1955; Idem 1968).
  - A large unrepaired patent ductus arteriosus may have heart failure or pulmonary hypertension (Perloff 1998; Idem 1968).
  - The ductus arteriosus may become aneurysmal and calcified, which may lead to its rupture (Fisher et al. 1986).

Aortic Stenosis (AS)

- Definition: It is an obstruction to left ventricular outflow (Brickner et al. 2000).
- Types:
  - Valvular AS as restriction of blood flow through the aortic valve (Fig. 7). The area of the aortic orifice in a normal adult is 3.0–4.0 cm^2. Valvular aortic stenosis is considered important with valve area of approximately 1.0 cm^2.
  - Subvalvular aortic stenosis.
  - Supravalvar aortic stenosis (Brickner et al. 2000).

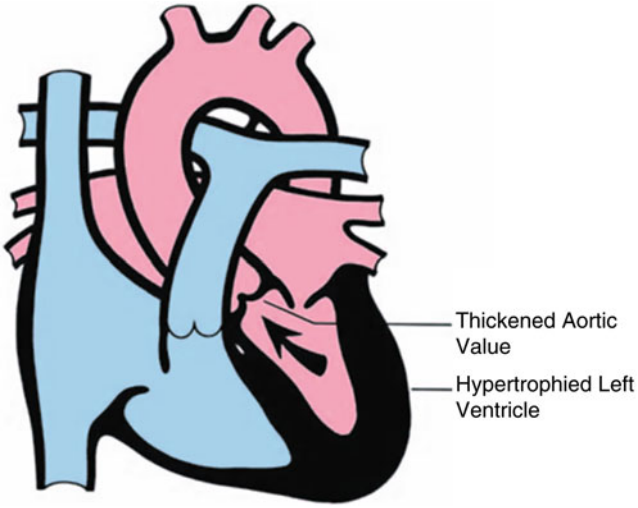


Fig. 7 Aortic stenosis

- Etiology:
  - In valvular AS, the most common pathological finding in patients who are younger than 65 years of age is a bicuspid aortic valve.
  - In subvalvular aortic stenosis there is either an isolated fibrous ring (membranous subaortic stenosis) or a septal hypertrophy (idiopathic hypertrophic cardiomyopathy).
  - In supravalvar aortic stenosis, there is either Williams syndrome, in which a defect in the elastin gene is present, or familial supravalvar aortic stenosis, which probably carries a mutated elastin gene (Brickner et al. 2000; Friedman 1995).
- Incidence: Aortic stenosis represents about 6 % of CHD. Bicuspid aortic valve is found in 2–3 % of the population. It is four times as common in men as in women. Twenty percent of patients with bicuspid aortic valve have an associated cardiovascular abnormality, such as patent ductus arteriosus or aortic coarctation (Brickner et al. 2000; Friedman 1995).
- Pathophysiology:
  - In patients with bicuspid aortic valve, the bicuspid valve has a single fused commissure. Although the deformed valve is not stenotic at birth, it is subjected to thickening and calcification of the leaflets, with resultant immobility. In many patients, there is a coexisting abnormality of the medial layer of the aorta above the valve, which predisposes to dilatation of the aortic root. Left ventricular hypertrophy results from gradually worsening aortic stenosis (Brickner et al. 2000).
  - In patients with fibromuscular membrane with a small central orifice located in the left ventricle, a jet of blood passes through the orifice and strikes the aortic valve. The energy of the jet results in alterations in the aortic valve and aortic insufficiency (Friedman 1995).

  - Cardiac catheterization is performed to determine the severity of aortic stenosis in cases in which it cannot be assessed noninvasively and to determine whether concomitant coronary artery disease is present (Brickner et al. 2000).
- Management:
  - In valvular type, symptomatic patients should undergo valvotomy through surgery or transcatheter methods, homograft or Ross procedure in young age and valve replacement in adults (Brickner et al. 2000; Teupe et al. 1997).
  - In subvalvular type, excision of the membrane is indicated in all patients (Lopes et al. 2011).
  - In supravalvular type, operative relief of the obstruction in the ascending aorta can be accomplished by surgical widening of the narrowing with a patch (Johnson and Moller 2014).
- Natural history and prognosis:
  - Asymptomatic adults with valvular aortic stenosis have a normal life expectancy; they should receive antibiotic prophylaxis against infective endocarditis. Once symptoms appear, survival is limited: the median survival is only 5 years after angina develops, 3 years after syncope occurs, and 2 years after symptoms of heart failure appear (Brickner et al. 2000).
  - Postoperative risks include that valvotomy may require a prosthesis or homograft in adulthood if the valve becomes calcified or rigid, or if the valve insufficiency develops. No currently available replacement valve is perfect: mechanical prostheses are long lived but thrombogenic, so anticoagulation is required; homograft valves, although free from thrombogenic complications, are often shorter lived because of destruction by calcification. Ross autograft can affect coronaries due to reimplantation of coronaries in pulmonary autograft (neoaorta) (Lopes et al. 2011; Geva et al. 2007).
  - The major hazard of subaortic membrane excision is the possibility of damage to the septal leaflet of the mitral valve, since the membrane is often attached to this leaflet and the risk of high recurrence rate (Lopes et al. 2011; Geva et al. 2007).
  - The hazard of post-patch correction of supravalvular stenosis with a patch is reobstruction because of progressive medial thickening of affected vessels in long term (Johnson and Moller 2014).

Pulmonary Stenosis (PS)

- Incidence: It constitutes 10–12 % of CHDs in adults. Obstruction of right ventricular outflow is valvular in 90 % of patients and supravalvular or subvalvular in the remainder (Brickner et al. 2000).
- Etiology: Valvular PS typically is an isolated abnormality (Fig. 8), but it may occur in association with VSD. About two-thirds of patients with Noonan syndrome have PS due to valve dysplasia. Supravalvular PS often coexists with other congenital cardiac abnormalities (valvular PS, ASD, VSD, PDA, or ToF). It is a common feature of Williams syndrome (Zalzstein et al. 1991). Subvalvular PS usually occurs in association with VSD (Brickner et al. 2000). Peripheral pulmonary artery stenosis occurs in children with supravalvar aortic stenosis,

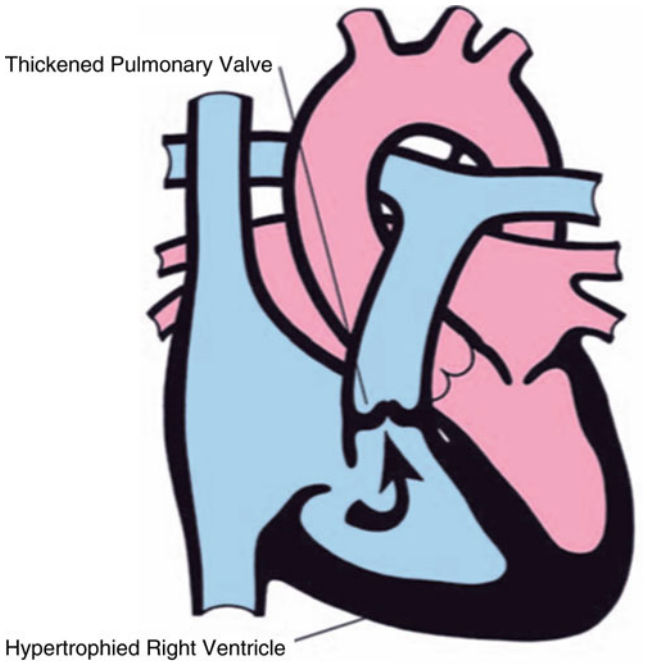


Fig. 8 Pulmonary Stenosis

particularly those with Williams syndrome, occurs with Alagille syndrome, or appears without apparent cause. Hypoplastic pulmonary arteries frequently accompany tetralogy of Fallot with pulmonary valve atresia; these patients often have DiGeorge syndrome (Johnson and Moller 2014).

- Pathophysiology: The commissures are fused, so that during ventricular systole the valve is dome shaped with a small central orifice. In dysplastic valve like in Noonan syndrome, the commissures are rather open, but each leaflet is greatly thickened and redundant. The area of the pulmonary valve orifice in a normal adult is about 2.0 cm^2 per square meter of body surface area, and there is no systolic pressure gradient across the valve. When the valve becomes stenotic, the right ventricular systolic pressure increases, and a systolic pressure gradient is observed between the right ventricle and the pulmonary artery (Brickner et al. 2000; Johnson and Moller 2014).
- Management:
  - Valvular PS: Prophylaxis against infective endocarditis. Percutaneous balloon valvuloplasty, the procedure of choice, is usually successful, provided the valve is mobile and pliant; its long-term results are excellent (Brickner et al. 2000; Teupe et al. 1997; Fawzy et al. 1990). Valve replacement is required if the leaflets are dysplastic or calcified or if marked regurgitation is present (Johnson and Moller 2014).

  - Supravalvular PS: Treatment with catheter balloon dilation, sometimes with placement of endovascular metal stents, is widely used, although with variable results depend on the etiology and severity of the stenosis (Johnson and Moller 2014).
  - The neonate with critical stenosis and an extremely hypoplastic pulmonary annulus requires outflow tract widening by use of a patch (Johnson and Moller 2014).
- Natural history and prognosis:
  - Adults with valvular pulmonary stenosis are often asymptomatic (Brickner et al. 2000).
  - When the stenosis is severe, dyspnea on exertion or fatigability may occur. Eventually, right ventricular failure may develop, with resultant peripheral edema and abdominal swelling. Finally, if the foramen ovale is patent, shunting of blood from the right to the left atrium may occur, causing cyanosis and clubbing (Brickner et al. 2000).

Coarctation of the Aorta (COA)

- Definition: It typically consists of a discrete, diaphragm-like ridge extending into the aortic lumen usually just distal to the left subclavian artery at the site of the aortic ductal attachment (the ligamentum arteriosum) (Brickner et al. 2000), as shown in Fig. 9. This condition results in hypertension in the arms. Less commonly, the coarctation is immediately proximal to the left subclavian artery, in which case a difference in arterial pressure is noted between the arms. Extensive collateral arterial circulation to the distal body develops. It is often accompanied by hypoplasia or diffuse narrowing of the aortic arch (Yun 2011).
- Incidence: COA represents 8–10 % of CHD. Two to five times as frequent in men as in women (Yun 2011).

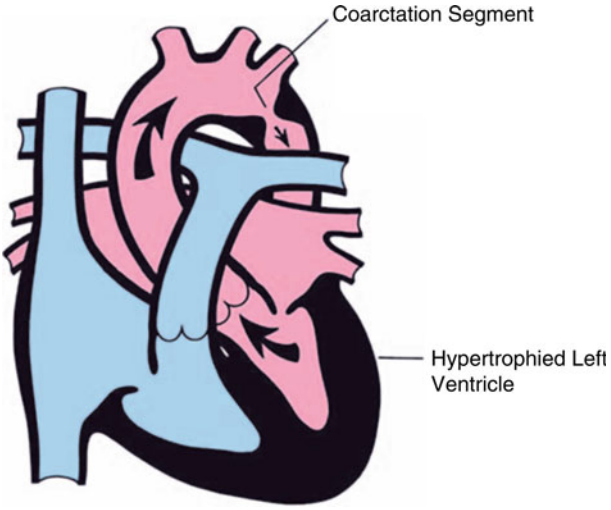


Fig. 9 Aortic coarctation

- Etiology: It may occur in conjunction with gonadal dysgenesis (e.g., Turner syndrome), bicuspid aortic valve, VSD, PDA, mitral stenosis or regurgitation, or aneurysms of the circle of Willis (Perloff 1998; Mazzanti et al. 1988).
- Pathophysiology: In this case usually the lower half of the body is a ductus dependent (Penny and Shekerdemian 2001).
- Management:
  - Computed tomography, magnetic resonance imaging, and contrast aortography provide precise anatomical information regarding the location and length of the coarctation and collateral circulation (Brickner et al. 2000).
  - If ductal-dependent clinical presentations are detected early, infants can survive with prostaglandin E1 (PGE1) treatment (Brickner et al. 2000).
  - Surgical repair should be considered for patients with a transcoarctation pressure gradient of more than 30 mmHg (Brickner et al. 2000).
  - In the young infant, sacrificing the left subclavian artery, and using the transected blood vessel as a graft by turning it down and sewing it into the aortic wall, was popular at one time (Robert and Bekman 2013).
  - There are several surgical techniques used to repair a coarctation of the aorta. If the coarcted segment is short and discrete, resection and end-to-end anastomosis of the proximal and distal ends are possible. If the coarctation is a long tubular obstruction, resection with interposition of a tube graft would be necessary (Robert and Bekman 2013).
  - Percutaneous balloon dilation eventually with stent positioning is indicated for recurrent and or native coarctation in some adult patients with discrete lesions. However, the availability of covered stents and stent grafts has made stent placement the treatment of choice for most adult patients with native or recurrent coarctation (Romfh et al. 2012; Tanous et al. 2009).
- Natural history and prognosis:
  - Most adults with aortic coarctation are asymptomatic. The diagnosis is made during routine examination, when systemic arterial hypertension is observed in the arms, with diminished or absent femoral arterial pulses (Brickner et al. 2000).
  - Complications of aortic coarctation include hypertension, left ventricular failure, aortic dissection, premature coronary artery disease, infective endocarditis, and cerebrovascular accidents (due to the rupture of an intracerebral aneurysm) (Romfh et al. 2012; Perloff 1998; Tanous et al. 2009).
  - Women with coarctation are at high risk for aortic dissection during pregnancy (Brickner et al. 2000).
  - Postoperative complications include residual or recurrent hypertension in up to one-third of patients after successful resolution of coarctation, recurrent coarctation, and the possible sequelae of a bicuspid aortic valve (Romfh et al. 2012; Brickner et al. 2000).
  - The incidence of persistent or recurrent hypertension, as well as the survival rate, is influenced by the patient's age at the time of surgery (Perloff 1998; Musto et al. 2008).

Cyanotic Conditions

Tetralogy of Fallot (ToF)

- Definition: ToF involves four anatomical abnormalities of the heart which are (Syamasundar 2012) malaligned VSD, (Behrman et al. 1992) anterior shift of the aorta over the VSD (overriding aorta), (Taber and Venes 2009) obstruction of the right ventricular outflow tract, and (Green 2004) right ventricular hypertrophy (Fig. 10). Approximately 25 % have a right-sided aortic arch, and about 4 % have a coronary artery anomaly (Lillehei et al. 1986).
- Incidence: It constitutes 4–9 % of CHD and is the most common cyanotic CHD (Lillehei et al. 1986).
- Pathophysiology: The major right ventricular outflow obstruction in ToF is infundibular stenosis. The degree of cyanosis depends on the degree obstruction. This is quite variable, from a slight obstruction, to severe obstruction with pulmonary atresia. With mild pulmonary stenosis, also known as "pink tetralogy of Fallot," ToF behaves as a VSD with pulmonary overflow. As infundibular stenosis increases, progressive cyanosis due to less pulmonary blood flow develops. ToF with pulmonary atresia, also known as pulmonary atresia with VSD, is a ToF severe variant in which there is complete obstruction (atresia) of the right ventricular outflow tract (Marelli and Gurvitz 2011).
- Management: Total surgical correction can now be performed in young infants from 3 to 6 months of age or earlier (Koenig et al. 2004). Surgical treatment of the defect includes patch closure of the VSD and relief of pulmonary outflow obstruction with patch augmentation of the outflow at the expense of creation of free pulmonary regurgitation (PR) (Romfh et al. 2012).

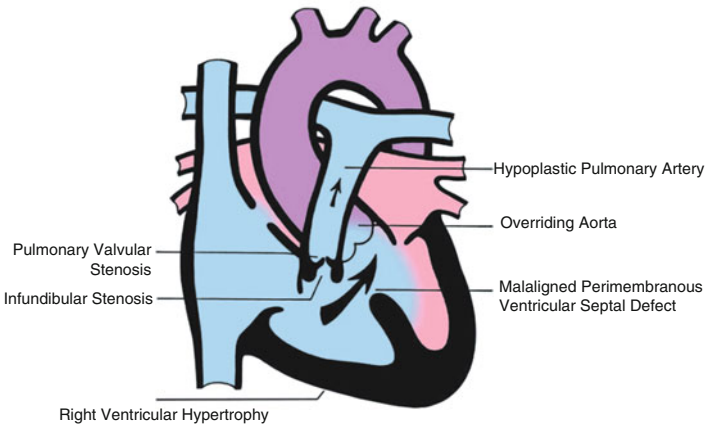


Fig. 10 Tetralogy of Fallot

- Natural history and prognosis:
  - After total repair the majority of patients have normal oxygen saturation and no residual shunt (Romfh et al. 2012; Warnes et al. 2008).
  - The most common late complication is chronic PR. Residual RV outflow obstruction and branch pulmonary artery stenosis are less but important late complications. Late RV dilation and dysfunction are common. Progressive aortic regurgitation, associated with aortic root dilation, has been reported in 15–18 % of patients. Arrhythmias, mostly atrial flutter and fibrillation, are another important late complication. Sudden death due to ventricular arrhythmia is the most common cause of death after surgical repair of ToF. The risk for sudden death is 3–6 % over the 25–30-year follow-up period (Romfh et al. 2012; Warnes et al. 2008).
  - PV replacement is the treatment for chronic PR in patients with severe PR. Surgical valve replacement is the only option currently available for the native RV outflow tract. Atrial arrhythmias can be addressed by a maze procedure at the time of PV replacement. Patients with documented sustained VT or aborted sudden cardiac death should receive an ICD for secondary prevention (Romfh et al. 2012; Warnes et al. 2008).
  - Survival after repair of ToF is less than expected for the general population at all times, and the rate of attrition increases sharply 25 years after surgery (Romfh et al. 2012; Warnes et al. 2008).

Pulmonary Atresia (PA)

- Definition: PA is the absence of a direct connection between the right ventricle and the lungs. Two main types are pulmonary atresia with ventricular septal defect (PA/VSD) and pulmonary atresia with intact ventricular septum (PA/IVS) (Yun 2011; Krishnan 2002).
- Pathophysiology:
  - In PA/VSD, also known as tetralogy of Fallot type pulmonary atresia, there are usually favorable sized two ventricles with large subaortic VSD and variable source of pulmonary arterial supply. Some patients have only ductal structure but more commonly have major aortopulmonary collateral arteries (MAPCAs) arising from the descending aorta (Fig. 11). PA may also be a spectrum of more complex cardiac malformations such as congenitally corrected TGA or heterotaxy syndrome or single ventricle (Yun 2011; Krishnan 2002).
  - In the PA/IVS, tricuspid valve and right ventricle are usually severely underdeveloped, but pulmonary arteries are relatively well developed and supplied by PDA (Fig. 12). Infants with PA/IVS a typical form of “ductus-dependent pulmonary circulation” become more cyanosed and aggravated as the ductal closes and if without prostaglandin infusion, eventually will collapse and perhaps die within first few days of life (Yun 2011; Krishnan 2002; Nadas and Fyler 2006).

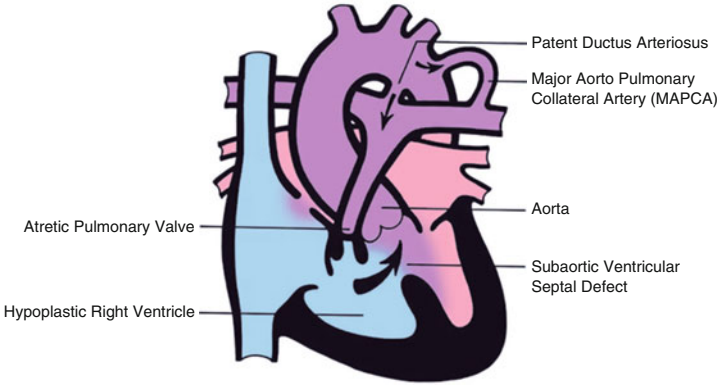


Fig. 11 Pulmonary Atresia + VSD + MAPCAs

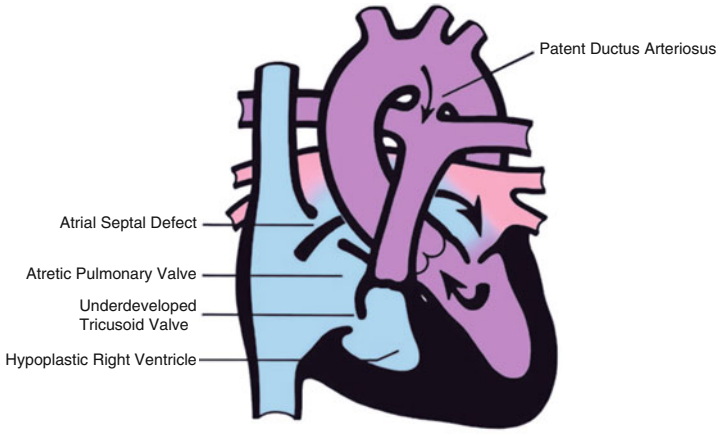


Fig. 12 Pulmonary atresia with intact ventricular septum

- Management:
  - PA/IVS early palliation involves starting on PGE1 infusion to keep widely open the ductus arteriosus until Blalock-Taussig (BT) shunt surgery (Fig. 13), which helps to augment pulmonary flow for PA, and the eventual surgical goal may usually be "Fontan"-type operation (Fig. 14), more often a cavopulmonary shunt achieving a right heart bypass. In selected cases with particular anatomic features, bypass of obstruction can be done using an RV-to-pulmonary artery conduit (Yun 2011; Nadas and Fyler 2006).
  - Management of PA/VSD depends on the pulmonary blood supply. About half of those will be suitable for corrective surgery with VSD closure and connect the right ventricle to the pulmonary arteries using the conduit placement (Yun 2011; Nadas and Fyler 2006; Gewitz and Woolf 2006).

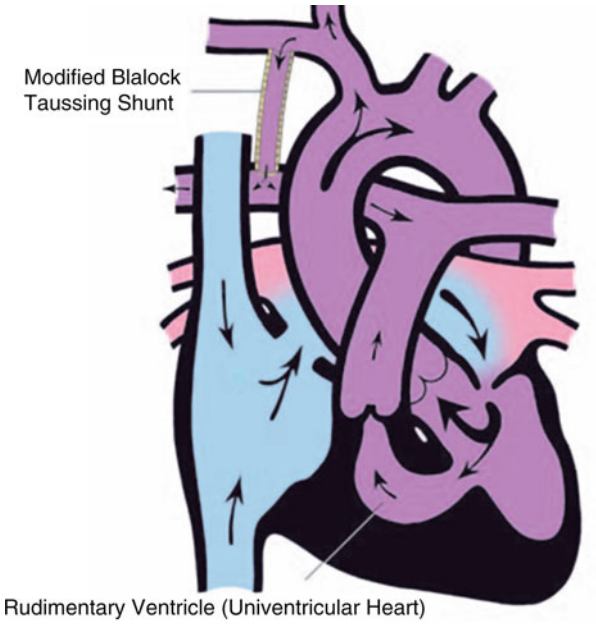


Fig. 13 Univentricular heart

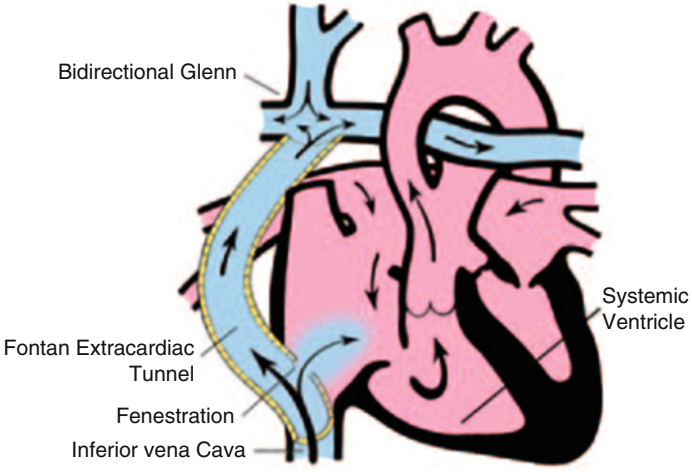


Fig. 14 Fontan correction of univentricular heart

- Natural history and prognosis:
  - Because less ductal dependent than PA/IVS, the natural course of PA/VSD depends on the pulmonary blood supply and other variables. Affected infant with PA/VSD may present cyanosis in the early life, but some can survive into adult life, even without any intervention if the various pulmonary supplies are

appropriate. However other problems develop in later life, leading to poor quality of life and shortened life span (Yun 2011; Krishnan 2002).
  - Treatment options for failure of an RV-to-pulmonary artery conduit include replacement of the conduit, stent implantation to treat stenosis, and percutaneous valve implantation to treat regurgitation (Momenah et al. 2009).
  - Balloon dilation or stenting should be considered for branch PA stenosis if flow in the artery is reduced and especially when accompanied by PR (Romfh et al. 2012; Gatzoulis et al. 2003).

Transposition of the Great Arteries (TGA)

- Definition: The great arteries are placed across the ventricular septum with atrioventricular concordance and ventriculoarterial discordance (the aorta arising from the right ventricle and the PA from the left ventricle) (Hoffman and Christianson 1978).
- Incidence: TGA accounts for 4–5 % of all CHDs (Hoffman and Christianson 1978), and is one of the most common cyanotic heart diseases in the early presentation (Martins and Castela 2008).
- Pathophysiology: This is incompatible with life unless a communication exists between systemic and pulmonary circulation, as the two circulations are in parallel and independent. During the newborn period, the PDA and PFO maintain this communication. As the PDA starts to close and the PFO by itself is inadequate in size, the patient develops intense cyanosis. Its severity and onset depend on the degree of mixing between the two circulations. Eventually progress into obstructive pulmonary vascular disease can occur (Reddy 2002).
- Associated anomalies: In 50 % of the cases, the TGA is an isolated finding. This condition is designated as "simple" or "complete" TGA or TGA/IVS (Fig. 15). By contrast, complex transposition includes all the cases with coexisting malformations, such as VSD (Fig. 16), PS (Fig. 17), left ventricular outflow tract obstruction, aortic arch anomalies, and anomalous venous systemic return (Yun 2011).
- Management:
  - Babies with TGA should be started on PGE1 infusion to maintain ductal patency which increases the pulmonary flow. If the foramen ovale is restricted, PGE1 alone could not achieve clinical improvement, and emergency balloon atrial septostomy (Rashkind balloon septostomy) is the only way to rescue these infants (Yun 2011; Martins and Castela 2008).
  - In surgical repair, the circulations are placed in series either by switching the inflow sources (atrial switch operation) or by switching the outflows (arterial switch operation) (ASO) and placement of the RV-PA conduit (Rastelli operation) (Rastelli et al. 1969). After an atrial switch operation, the RV remains the systemic ventricle while after an ASO the LV becomes the systemic ventricle. Patients born before the early 1980s most likely underwent an atrial switch operation Mustard (1964) or Senning (1959) or a Rastelli et al. (1969) operation. Patients born after the late 1980s were most likely repaired using the ASO.

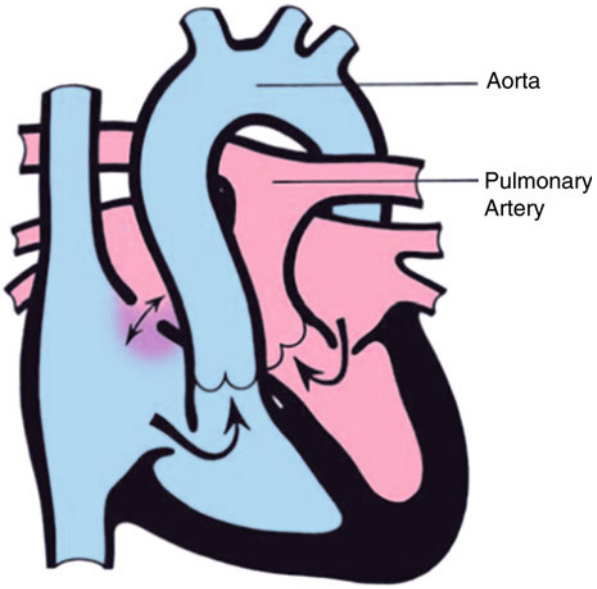


Fig. 15 Transposition of the great arteries without ventricular septal defect

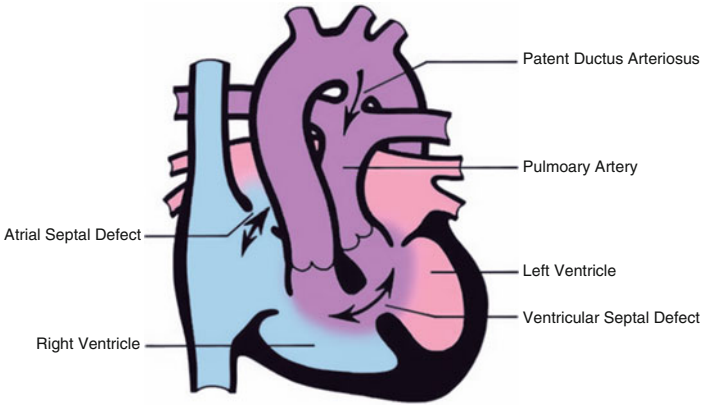


Fig. 16 Transposition of the great arteries with ventricular septal defect

- Natural history and prognosis:
  - Survival without surgery is unlikely. The arterial switch procedure offers the best prognosis with a mortality of about 5 % (Yun 2011).
  - The most frequent complication of an atrial switch operation is sinus node dysfunction. Loss of sinus node function is progressive, and by 20 years only 40 % of patients remain in sinus rhythm. Sinus node dysfunction with tachy or brady syndrome is an indication for pacemaker therapy (Yun 2011).

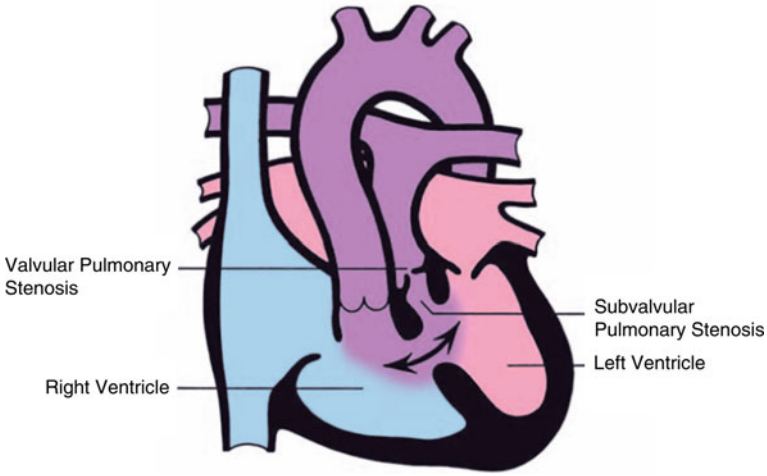


Fig. 17 Transposition of the great arteries with ventricular septal defect and pulmonaru artery stenosis

- Complications related to Rastelli operation are mainly conduit obstruction and subaortic stenosis from inadequate enlargement of the VSD (Yun 2011; Brown et al. 2011).
- The most frequent complication following the ASO is pulmonary artery stenosis. Mechanisms include inadequate growth of the suture line, scarring and retraction of the material used to fill the coronary artery button sites, and tension at the anastomotic site if there is inadequate mobilization of the distal pulmonary arteries. Stent placement is usually effective for branch pulmonary artery stenosis. There is a modest risk for neo-aortic valve regurgitation related in part to neo-aortic root dilatation, especially in patients with a VSD (Prifti et al. 2002). Coronary stenosis or occlusion has been discovered in 5–7 % of patients after the ASO and has been associated with ventricular dysfunction and sudden death (Anderson 2012; Mayer et al. 1990).

Truncus Arteriosus

- Definition: In truncus arteriosus both the ascending aorta and main pulmonary artery or branch pulmonary arteries arise from a common trunk, positioned over a ventricular septal defect that supplies systemic, coronary, and pulmonary circulations (Fig. 18) (Rodefeld and Hanley 2002).
- Incidence: It accounts for about 1–4 % of the congenital heart defects (Rodefeld and Hanley 2002).
- Associated anomalies are common, such as DiGeorge syndrome (Rodefeld and Hanley 2002).

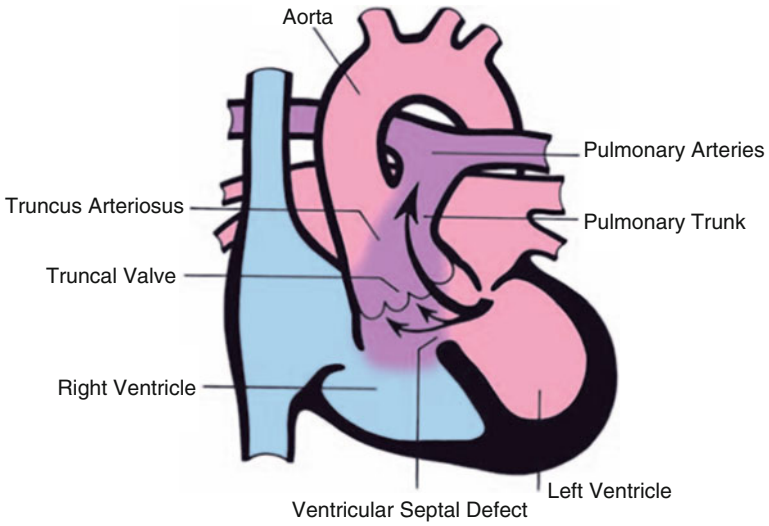


Fig. 18 Truncus

- Management: Treatment of congestive heart failure followed by surgery. Repair of truncus arteriosus includes patch closure of the VSD so that the truncal valve is aligned solely with the left ventricle; separation of the main or branch pulmonary arteries from the truncal root; and establishment of continuity between the pulmonary arteries and the right ventricle, usually by means of a conduit or homograft. The prognosis is poor in untreated cases (Rodefeld and Hanley 2002).
- Natural history and prognosis: After surgery, they will need long-term follow-up as they will eventually need to have the conduit graft replaced (Rodefeld and Hanley 2002).

Total Anomalous Pulmonary Venous Return (TAPVR)

- Definition: All four pulmonary venous directly connect to the right atrium instead of the left atrium. There are four main types according to the connection (Yun 2011): (1) supracardiac type (50 %) to the innominate vein; (2) infradiaphragmatic type (20 %) to the hepatic or portal vein; (3) cardiac type (20 %) to the coronary sinus; and (4) mixed type (10 %) combination of any of type (Fig. 19) (Yun 2011; Seale et al. 2010).
- Incidence: TAPVR represents around 1 % of CHD (Seale et al. 2010).
- Pathophysiology: The timing and mode of presentation depend on the type and degree of obstruction. Infracardiac type is the most commonly obstructed and may have serious manifestations. Fifteen common pulmonary venous channels are delivered to the right atrium, and there the mixing of the pulmonary and systemic circulations occurs. Systemic desaturation occurs as the result of mixing

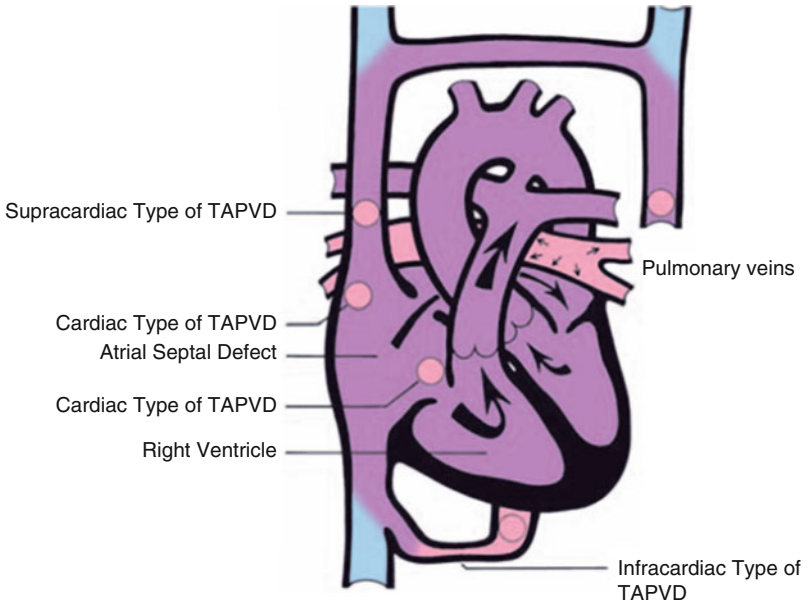


Fig. 19 Total anomalous venous drainage

of two circulations. In patients with TAPVR with obstruction, progressive cyanosis and respiratory distress dominate the presentation (Seale et al. 2010).

- Management:
  - Prostaglandin infusion is not helpful in this case, even harmful. It leads to increase pulmonary blood flow and reduce the pulmonary vascular resistance and may exacerbate the pulmonary venous congestion when obstruction is combined (Yun 2011).
  - Long-term surgical and overall survival outcome is fairly good, although in some cases, there is recurrent and fatal pulmonary venous stenosis. Perioperative mortality is related with the clinical conditions, although it is improved in recent years, but it is still significant (Yun 2011).
- Natural history and prognosis: Survival rate is reported 50 % at 1 month and 0 % at 12 months without treatment (Seale et al. 2010).

Ebstein Anomaly

- Definition: Ebstein anomaly is characterized by downward displacement of the septal and posterior leaflets of the tricuspid valve that are attached to the right ventricular septum. The anterior leaflet is elongated and is displaced downward within the right ventricular cavity causing "atrialization of the right ventricle" (i.e., the right ventricle is small). The "atrialized" ventricle is enlarged and thin, while the functional RV distal to the valve is variably hypoplastic. The result most

often is tricuspid regurgitation (TR), but in some cases tricuspid stenosis is predominant (Romfh et al. 2012; Warnes et al. 2008; Dearani and Danielson 2000).

- Associated lesions include an interatrial communication and less commonly muscular VSD or PDA, pulmonary stenosis or atresia, or left-sided abnormalities such as mitral stenosis or regurgitation can be seen. The conduction system is often abnormal (Warnes et al. 2008).
- Pathophysiology: The functional impairment of the right ventricle and regurgitation of the tricuspid valve retard forward flow of blood through the right heart. The overall effect is right atrium dilation and increased right atrial pressure, thus favoring a right-to-left shunt across the interatrial communication and/or reduced systemic cardiac output. Cyanosis depends up on the right-to-left shunt. The pulmonary valve and pulmonary arteries are often smaller than normal (Romfh et al. 2012; Warnes et al. 2008).
- Management:
  - It is mainly palliative and there are no good surgical options.
  - Medical therapy of Ebstein anomaly is limited to management of complications.
  - In older patients, tricuspid annuloplasty and rarely tricuspid valve replacement may be performed (Romfh et al. 2012; Brown et al. 2008).
- Natural history and prognosis:
  - While fetal or neonatal presentation of Ebstein anomaly is associated with a poor outcome, adults have a much better prognosis. Prognosis depends on the severity of the lesion: it is good with mild lesions and poor with severe lesions with other associated anomalies/malformations. Sudden death is a rare late complication, occurring in about 2 % of patients (Romfh et al. 2012; Attie et al. 2000).
  - Surgical mortality in adult patients is low, under 3 % in the current era (Romfh et al. 2012; Brown et al. 2008).
  - Atrial arrhythmia is the most frequent early complication occurring in one-third of postoperative patients (Romfh et al. 2012; Brown et al. 2008). Recurrent hospitalizations are frequent with arrhythmia being the most common indication for readmission. Transcatheter ablation is the standard treatment of an accessory pathway or other arrhythmia substrate, but success rates tend to be lower and recurrence rates higher than in the structurally normal heart (Chetaille et al. 2004).

Hypoplastic Left Heart Syndrome (HLHS)

- Definition: The left side of the heart is unable to support systemic circulation. It includes aortic valve atresia and some forms of mitral atresia (Yun 2011). Absent forward flow through the left ventricular outlet is characteristic. Left ventricle is markedly underdeveloped and often rudiment. Aortic arch is also hypoplastic, and ascending aorta is very small, acting simply as a passage into the coronary arteries (Yun 2011).

- Incidence: It is rare, accounting for 2–3 % of all CHD (Barron et al. 2009).
- Pathophysiology: Pulmonary venous return can only reach systemic circulation by traversing the patent foramen ovale to reach the right atrium. This implies mixing of pulmonary venous and systemic venous flow, creating a mild cyanotic condition (Yun 2011; Barron et al. 2009). All systemic circulation is absolutely dependent to the ductus arteriosus. After birth, systemic vascular resistance is higher than pulmonary, with the ductal closure after birth; nonfunctioning left ventricle cannot take charge of the cardiac output. This leads to circulatory deterioration and shock (Nadas and Fyler 2006).
- Management: PGE1 infusion is necessary to survive. In previous years HLHS showed high mortality because of the poor interventional outcome. However, in recent years, radical palliative surgery (Norwood and its variants) has become more widespread, and the outcome has improved (Yun 2011).
- Natural history and prognosis: Early death with almost no prospect of prolonged natural survival usually occurs (Yun 2011).

Interruption of the Aortic Arch (IAA)

- Definition: There is no direct connection between ascending and descending aorta due to failure of development in a portion of the aortic arch. The interruption may be distal to the left subclavian artery (type A) or between the left common carotid and the left subclavian artery (type B) or between the innominate artery and the left carotid artery (Type C) (Yun 2011).
- Other associated anomalies: IAA is always associated with other anomalies such as VSD, truncus arteriosus, aortopulmonary window, or other complex anomalies. Type B is commonly associated with 22q11 deletion (DiGeorge syndrome) (Yun 2011).
- Pathophysiology: Lower half of the body has an entirely ductus-dependent circulation. Infants with IAA deteriorate very quickly once their duct begins to close, with congestive heart failure, cardiovascular collapse, and death within few days (Yun 2011).
- Management: Early recognition and intervention will inevitably lead to a better outcome. Surgery is primary repair of the aortic arch and what else is done depends on associated other anomalies (Yun 2011).

Conclusion

People with congenital heart disease often would need treatment over their life and therefore require specialist review during childhood and adulthood. This is because people with complex heart problems can develop further problems with their heart rhythm or valves over time. Psychological assessment and support must be part of the routinely follow-up of these patients.

References

Anatomy and function of the heart's electrical system. Retrieved 7 Aug 2013.

Anderson, R. M. (2012). *The gross physiology of the cardiovascular system*. 2nd ed. See "Chapter 1: Normal physiology." Tucson, AZ: Racquet Press, 1993.

Attie, F., Rosas, M., Rijlaarsdam, M., Buendia, A., Zabal, C., et al. (2000). The adult patient with Ebstein anomaly. Outcome in 72 unoperated patients. *Medicine (Baltimore), 79*, 27–36.

Barron, D. J., Kilby, M. D., Davies, B., Wright, J. G., Jones, T. J., & Brawn, W. J. (2009). Hypoplastic left heart syndrome. *Lancet, 374*, 551–554 [PubMed].

Behrman, R. E., Kliegman, R. M., Nelson, W. E., & Vaughan, V. C. (1992). *Nelson textbook of pediatrics* (14th ed.). Philadelphia: W. B. Saunders Co.

Boehrer, J. D., Lange, R. A., Willard, J. E., Grayburn, P. A., & Hillis, L. D. (1992). Advantages and limitations of methods to detect, localize, and quantitate intracardiac left-to-right shunting. *American Heart Journal, 124*, 448–455.

Brickner, E. M., Hillis, D. L., & Lange, R. A. (2000). Congenital heart disease in adults. *The New England Journal of Medicine, 342*(4), 256–263.

Brown, M. L., Dearani, J. A., Danielson, G. K., Cetta, F., Connolly, H. M., et al. (2008). Functional status after operation for ebstein anomaly: The Mayo Clinic experience. *Journal of the American College of Cardiology, 52*, 460–466.

Brown, J. W., Ruzmetov, M., Huynh, D., Rodefeld, M. D., Turrentine, M. W., et al. (2011). Rastelli operation for transposition of the great arteries with ventricular septal defect and pulmonary stenosis. *The Annals of Thoracic Surgery, 91*, 188–193.

Burke, R. P., Horvath, K., Landzberg, M., Hyde, P., Collins, J. J., et al. (1996). Long-term follow-up after surgical repair of ostium primum atrial septal defects in adults. *Journal of the American College of Cardiology, 27*, 696–699.

Butera, G., Romagnoli, E., Carminati, M., Chessa, M., Piazza, L., et al. (2008). Treatment of isolated secundum atrial septal defects: Impact of age and defect morphology in 1,013 consecutive patients. *American Heart Journal, 156*, 706–712.

Campbell, M. (1955). Patent ductus arteriosus: Some notes on prognosis and on pulmonary hypertension. *British Heart Journal, 17*, 511–533.

Chetaille, P., Walsh, E. P., & Triedman, J. K. (2004). Outcomes of radiofrequency catheter ablation of atrioventricular reciprocating tachycardia in patients with congenital heart disease. *Heart Rhythm, 1*, 168–173.

Craig, B. (2006). Atrioventricular septal defect: From fetus to adult. *Heart, 342*(4), 256–263.

Craig, R. J., & Selzer, A. (1968). Natural history and prognosis of atrial septal defect. *Circulation, 37*, 805–815.

Dearani, J. A., & Danielson, G. K. (2000). Congenital Heart Surgery Nomenclature and Database Project: Ebstein's anomaly and tricuspid valve disease. *The Annals of Thoracic Surgery, 69*, S106–S117.

Drake, R. L., Vogl, W., & Tibbitts, A. W. M. (2005). Mitchell; Illustrations by Richard; Richardson, Paul. In *Gray's anatomy for students* (pp. 157–159). Philadelphia: Elsevier/Churchill Livingstone. Gray's Anatomy, 40th Edition. is an imprint of Elsevier. 2008, Elsevier Limited ISBN 978-0-8089-2306-0.

DuBose, Miller, & Moutos. (2010). Embryonic heart rates compared in assisted and non-assisted pregnancies. Obgyn.net. Retrieved 18 Oct 2010 *22*,10–18.

Fawzy, M. E., Galal, O., Dunn, B., Shaikh, A., Sriram, R., & Duran, C. M. (1990). Regression of infundibular pulmonary stenosis after successful balloon pulmonary valvuloplasty in adults. *Catheterization and Cardiovascular Diagnosis, 21*, 77–81.

Feldt, R. H., Avasthey, P., Yoshimasu, F., Kurland, L. T., & Titus, J. L. (1971). Incidence of congenital heart disease in children born to residents of Olmsted County, Minnesota, 1950–1969. *Mayo Clinic Proceedings, 46*, 794–799.

Fisher, R. G., Moodie, D. S., Sterba, R., & Gill, C. C. (1986). Patent ductus arteriosus in adults—long-term follow-up: Nonsurgical versus surgical treatment. *Journal of the American College of Cardiology, 8*, 280–284.

Friedman, W. F. (1995). Aortic stenosis. In G. C. Emmanouilides, T. A. Riemenschneider, H. D. Allen, & H. P. Gutgesell (Eds.), *Moss and Adams heart disease in infants, children, and adolescents* (pp. 1087–1111). Baltimore: Williams & Wilkins.

Gatzoulis, M. A., Hechter, S., Webb, G. D., & Williams, W. G. (1999). Surgery for partial atrioventricular septal defect in the adult. *The Annals of Thoracic Surgery, 67*, 504–510.

Gatzoulis, M. A., Webb, G. D., & Daubeney, P. E. F. (2003). *Diagnosis and management of adult congenital heart disease*. Toronto: Churchill Livingstone.

Geva, A., McMahon, C. J., Gauvreau, K., Mohammed, L., del Nido, P. J., & Geva, T. (2007). Risk factors for reoperation after repair of discrete subaortic stenosis in children. *Journal of the American College of Cardiology, 50*(15), 1498–1504.

Gewitz, M. H., & Woolf, P. K. (2006). Cardiac emergencies. In G. R. Fleisher & S. Ludwig (Eds.), *Textbook of pediatric emergency medicine* (5th ed., pp. 717–718). Philadelphia: Lippincott Williams and Wilkins.

Graham, T. P., Jr., & Gutgesell, H. P. (1995). Ventricular septal defects. In G. C. Emmanouilides, T. A. Riemenschneider, H. D. Allen, & H. P. Gutgesell (Eds.), *Moss and Adams heart disease in infants, children, and adolescents* (pp. 724–746). Baltimore: Williams & Wilkins.

Green, A. (2004). Outcomes of congenital heart disease: A review. *Journal of Pediatric Nursing, 30* (4), 280–284. Jannetti Publications, Inc.

Hagen, P. T., Scholz, D. G., & Edwards, W. D. (1984). Incidence and size of patent foramen ovale during the first 10 decades of life: An autopsy study of 965 normal hearts. *Mayo Clinic Proceedings, 59*, 17–20.

Hoffman, J. I. E., & Christianson, R. (1978). Congenital heart disease in a cohort of 19,502 births with long-term follow-up. *American Journal of Cardiology, 42*, 461.

Idem. (1968). Natural history of persistent ductus arteriosus. *British Heart Journal, 30*, 4–13.

Johnson, W. H., Moller, J. H. (2014). Conditions obstructing blood flow in children. In *Pediatric cardiology: The essential pocket guide*. Pediatric Cardiology: The Essential Pocket Guide. Copyright © 2014 John Wiley & Sons, Ltd 3rd edn (pp. 148–185). Wiley.

Kasasbeh, E., Peter, K., McPherson, J. A. (2013) Percutaneous closure of patent foramen ovale and atrial septal defect. Medscape http://www.emedicine.medscape.com/article/1839563-overview ¼. Updated 15 Nov 2013.

Kidd, L., Driscoll, D. J., Gersony, W. M., et al. (1993). Second natural history study of congenital heart defects: Results of treatment of patients with ventricular septal defects. *Circulation, 87* (Suppl I), I-38–I-51.

Koenig, P., Hijazi, Z., Zimmerman, F. (2004). *Essential pediatric cardiology.* McGraw-Hill Medical 838 Publishing Division.

Konstantinides, S., Geibel, A., Olschewski, M., et al. (1995). A comparison of surgical and medical therapy for atrial septal defect in adults. *The New England Journal of Medicine, 333*, 469–473.

Krishnan, U. S. (2002). Approach to congenital heart disease in the Neonate. *Indian Journal of Pediatrics, 69*, 501–505 [PubMed].

Leachman, R. D., Cokkinos, D. V., & Cooley, D. A. (1976). Association of ostium secundum atrial septal defects with mitral valve prolapse. *The American Journal of Cardiology, 38*, 167–169.

Levine, J. M., & Miller, K. S. (2002). *Biology.* Upper Saddle River: Pearson Prentice Hall. ISBN 0-13-050730-X.

Lillehei, C. W., Varco, R. L., & Cohen, M. (1986). The first open heart corrections of tetralogy of Fallot. A 26–31 year follow-up of 106 patients. *Annals of Surgery, 204*, 490–502.

Lopes, R., Lourenco, P., Goncalves, A., Cruz, C., & Maciel, M. J. (2011). The natural history of congenital subaortic stenosis. *Congenit Heart Dis, 5*, 417–423.

Marelli, A. J., & Gurvitz, M. (2011). From numbers to guidelines. *Progress in Cardiovascular Diseases, 53*, 239–246.

Marieb, E. N. (2003). *Human anatomy & physiology* (6th ed.). Upper Saddle River: Pearson Education. ISBN 080535462X.

Martins, P., & Castela, E. (2008). Transposition of the great arteries. *Orphanet Journal of Rare Diseases, 3*, 27 [PMC free article] [PubMed].

Mas, M. S., & Bricker, J. T. (1990). Clinical physiology of left-to-right shunts. In A. Garson Jr., J. T. Bricker, & D. G. McNamara (Eds.), *The science and practice of pediatric cardiology* (pp. 999–1001). Philadelphia: Lea and Febiger.

Mayer, J. E., Jr., Sanders, S. P., Jonas, R. A., Castaneda, A. R., & Wernovsky, G. (1990). Coronary artery pattern and outcome of arterial switch operation for transposition of the great arteries. *Circulation, 82*, IV139–IV145.

Mazzanti, L., Prandstraller, D., Tassinari, D., et al. (1988). Heart disease in Turner's syndrome. *Helvetica Paediatrica Acta, 43*, 25–31.

MedicaLook. *Heart*. Medicalook.com. Retrieved 3 May 2010.

Momenah, T. S., El Oakley, R., Al Najashi, K., Khoshhal, S., Al Qethamy, H., et al. (2009). Extended application of percutaneous pulmonary valve implantation. *Journal of the American College of Cardiology, 53*, 1859–1863.

Mustard, W. T. (1964). Successful two-stage correction of transposition of the great vessels. *Surgery, 55*, 469–472.

Musto, C., Cifarelli, A., Pucci, E., Paladini, S., De Felice, F., et al. (2008). Endovascular treatment of aortic coarctation: Long-term effects on hypertension. *International Journal of Cardiology, 130*, 420–425.

Nadas, A. S., & Fyler, D. C. (2006). Hypoxemia. In J. F. Keane, J. E. Lock, & D. C. Fyler (Eds.), *Nada's pediatric cardiology* (2nd ed., pp. 97–101). Philadelphia: Saunders Elsevier.

Penny, D. J., & Shekerdemian, L. S. (2001). Management of the neonate with symptomatic congenital heart disease. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 84*, F141–F145 [PMC free article] [PubMed].

Perloff, J. K. (1998). Survival patterns without cardiac surgery or interventional catheterization: A narrowing base. In J. K. Perloff & J. S. Childs (Eds.), *Congenital heart disease in adults* (2nd ed., pp. 15–53). Philadelphia: W.B. Saunders.

Phibbs, B. (2007). *The human heart: A basic guide to heart disease* (2nd ed., p. 1). Philadelphia: Lippincott Williams & Wilkins. ISBN 9780781767774.

Prifti, E., Crucean, A., Bonacchi, M., Bernabei, M., Murz, B., et al. (2002). Early and long term outcome of the arterial switch operation for transposition of the great arteries: Predictors and functional evaluation. *European Journal of Cardio-Thoracic Surgery, 22*, 864–873.

Rastelli, G. C., McGoon, D. C., & Wallace, R. B. (1969). Anatomic correction of transposition of the great arteries with ventricular septal defect and subpulmonary stenosis. *The Journal of Thoracic and Cardiovascular Surgery, 58*, 545–552.

Reddy, D. V. (2002). Cyanotic congenital heart disease. In *Case based pediatrics for medical students and residents.* Copyright 2004, Department of Pediatrics, University of Hawaii John A. Burns School of Medicine

Robert, H., & Bekman. (2013). Coarctation of the aorta. In Moss and Adams (Eds.), *Heart disease 893 in infants, children, and adolescents including the fetus and young adults* (8th edn). Lippincott 894 Williams & Wilkins.

Rodefeld, M., & Hanley, F. (2002). Neonatal truncus arteriosus repair: Surgical techniques and clinical management. *Seminars in Thoracic and Cardiovascular Surgery Pediatric Cardiac Surgery Annual, 5*(1), 212–217. doi:10.1053/pcsu.2002.31497.

Romfh, A., Pluchinotta, F. R., Porayette, P., Valente, A. M., & Sanders, S. P. (2012). Congenital heart defects in adults: A field guide for cardiologists. *Clinical and Experimental Cardiology, S8*, 007. doi:10.4172/2155-9880.S8-007.

Schneider, B., Zienkiewicz, T., Jansen, V., et al. (1996). Diagnosis of patent foramen ovale by transesophageal echocardiography and correlation with autopsy findings. *The American Journal of Cardiology, 77*, 1202–1209.

Seale, A. N., Uemura, H., Webber, S. A., Partridge, J., Roughton, M., Ho, S. Y., et al. (2010). Total anomalous pulmonary venous connection: Morphology and outcome from an international population-based study. *Circulation, 122*, 2718–2726 [PubMed].

Senning, A. (1959). Surgical correction of transposition of the great vessels. *Surgery, 45*, 966–980.

Somerville, J. (1965). Ostium primum defect: Factors causing deterioration in the natural history. *British Heart Journal, 27*, 413–419.

Starr, C., Evers, C., Starr, L. (2009). Biology: Today and tomorrow with physiology (pp. 422–). Cengage Learning. ISBN 978-0-495-56157-6. Retrieved 7 June 2012.

Steele, P. M., Fuster, V., Cohen, M., Ritter, D. G., & McGoon, D. C. (1987). Isolated atrial septal defect with pulmonary vascular obstructive disease—long term follow-up and prediction of outcome after surgical correction. *Circulation, 76*, 1037–1042.

Syamasundar, P. R. (2012). *Congenital heart defects – a review, congenital heart disease – selected aspects*. Houston: InTech. doi:10.5772/27002. pp. 4. ISBN 978-953-307-472-6.

Taber, C. W., & Venes, D. (2009). *Taber's cyclopedic medical dictionary* (pp. 1018–1023). F a Davis Co. ISBN 0-8036-1559-0.

Tanous, D., Benson, L. N., & Horlick, E. M. (2009). Coarctation of the aorta: Evaluation and management. *Current Opinion in Cardiology, 24*, 509–515.

Teupe, C. H., Burger, W., Schrader, R., & Zeiher, A. M. (1997). Late (five to nine years) follow-up after balloon dilation of valvular pulmonary stenosis in adults. *The American Journal of Cardiology, 80*, 240–242.

Van Praagh, S., Carrera, M. E., Sanders, S. P., Mayer, J. E., & Van Praagh, R. (1994). Sinus venosus defects: Unroofing of the right pulmonary veins—anatomic and echocardiographic findings and surgical treatment. *American Heart Journal, 128*, 365–379.

Warnes, C. A., Williams, R. G., Bashore, T. M., Child, J. S., Connolly, H. M., et al. (2008). ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation, 118*, e714–e833.

Yun, S. W. (2011). Congenital heart disease in the newborn requiring early intervention. *Korean Journal of Pediatrics, 54*(5), 183–191.

Zalzstein, E., Moes, C. A., Musewe, N. N., & Freedom, R. M. (1991). Spectrum of cardiovascular anomalies in Williams-Beuren syndrome. *Pediatric Cardiology, 12*, 219–223.

Psychosocial Aspects of Adults with Congenital Heart Disease

Edward Callus and Emilia Quadri

Contents

Abstract

During the last few decades, the survival rate of adults with congenital heart disease (ConHD) has increased considerably. The psychological characterization of adults with ConHD is very different from patients with acquired cardiac pathologies. Recent guidelines of cardiology associations indicate the necessity for specialized psychosocial support. The majority of the studies in the literature indicate the absence of a relationship between diagnosis, physical functionality, and the presence of residual symptoms and a worse psychological functioning in these patients. The variables which seem to be related to psychological well-being in these patients are the following; negative thoughts, solitude, social support, fear of negative evaluation, imposition of limits, perceived health status, somatic symptoms, perception of an economical difficulty, and restrictions linked to the surgical scar in females. Interestingly, studies, which utilized psychiatric interviews or similar methodologies, outlined that it was common for patients, who were diagnosed with a mood or anxiety disorder, not to have

E. Callus (✉) • E. Quadri
Pediatric and Adult Congenital Heart Disease Centre, IRCCS Policlinico San Donato University Hospital, San Donato Milanese, Lombardy, Italy
e-mail: edward.callus@gmail.com

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_23

received any appropriate treatment and often they were assumed to be well psychologically. When it comes to the life experiences of adults with ConHD, it has been outlined how these patients feel different from their healthy peers. It has been seen that often there is a struggle to feel normal and also to be perceived by others as being normal. This could lead to denial of the conditions and also efforts to exceed their physical boundaries imposed by their condition. Three main domains in which clinical health psychologists can contribute in the handling of adults with ConHD were identified: provision of clinical services, multidisciplinary research, and professional education.

Keywords
Congenital heart disease • Psychology • Clinical psychology • Psychosocial • Life experiences • Anxiety • Depression

Introduction

The global prevalence of congenital heart disease (ConHD) is estimated to be 9.3 per 1,000 newborns making it the most common birth defect (van der Linde et al. 2011), even though interestingly this condition is not very well known in the general population. During the last few decades, the survival rate of adults with ConHD has increased considerably as almost 90 % of children with ConHD currently survive into adulthood (Marelli et al. 2007; Moons et al. 2010), and when considering the whole ConHD population, the percentage of adults has risen to 60 % (Marelli et al. 2014).

The term ConHD comprises many different conditions of varying severity, but many of these patients have a complex condition which requires lifelong medical assistance (Gatzoulis et al. 2005). In fact, about one-third of this population is born with a critical heart disease which entails having a malformation which is life threatening and which necessitates corrective or palliative surgery in the first years of their lives (Marino et al. 2001; Samanek 2000). For a more detailed description of congenital heart disease, please refer to Dr. Chessa's chapter "▶ Congenital Heart Diseases," in the manual.

The psychological characterization of adults with congenital heart disease is very different from patients with acquired cardiac pathologies. Becoming aware of having a cardiac condition during one's childhood has a very different impact from acquiring an illness, to which the general population is familiar to, at a much later stage in life.

When it comes to acquired cardiac illness, it is well known that a cardiac rehabilitation is of great benefit, even with it comes to overall psychosocial well-being (Mampuya 2012). It is very interesting to note that there are still no precise indications when it comes to cardiac rehabilitation with ConHD patients. When conducting a literature review regarding this, only a letter to an editor can be found (Holloway et al. 2011) where there is encouragement for the participation of these

patients to cardiac rehabilitation programs. In this letter it is specified that historically ConHD patients have not participated in traditional cardiac rehabilitation programs.

Since it has been demonstrated that the capacity of physical exercise diminishes with the advancement of age in ConHD (Diller et al. 2005), it would be advisable that these patients participated in cardiac rehabilitation programs since they are effective at improving the capacity for physical exercise in chronic heart failure patients. This group of patients has many factors leading to low physical exercise which are in common with adults with ConHD (Giannakoulas and Dimopoulos 2010).

It is important to consider the fact that the education regarding physical exercise is not optimal in specialized clinics (Swan and Hillis 2000). In addition, the majority of adult patients with ConHD report having from a moderate to an extreme level of preoccupation regarding physical exercise (Harrison et al. 2011). Most of ConHD patients result as not satisfying the national recommendations when it comes to the participation in physical exercise (Swan and Hillis 2000), and as a group they have often expressed an interest in it and a desire to have formal advice on what physical exercise they can engage in (Harrison et al. 2011).

Finally, even though the participation to some kind of exercise regime is indicated in the guidelines (Baumgartner et al. 2010; Warnes et al. 2008a), these indications are based more on theoretical rather than scientific knowledge. A little pilot study was conducted which indicated that seven adults with ConHD completed a traditional cardiac rehabilitation program successfully, with an improvement in the capacity for physical exercise at the end of the program (Holloway et al. 2011).

Recent guidelines of cardiology associations (Warnes et al. 2008a; Report of the British Cardiac Society Working Party 2002) indicate the necessity for psychosocial support for adults with congenital heart disease. In the recommendations of the British Cardiac Society Working Party in 2002 (Report of the British Cardiac Society Working Party 2002), it was outlined that specialized consultancies were necessary in the following areas: relationships, contraception, pregnancy, career choice, insurance, psychosocial problems, and risky behaviors when it comes to health and free-time activities.

In 2008, in the guidelines of the American College of Cardiology/American Heart Association Task Force (Warnes et al. 2008b), it was specified how expert nurses, social workers, psychologists, and physician assistants should have a fundamental role in the care of these patients, especially when it comes to their evaluation and the provision of psychosocial assistance. This has been confirmed in other recommendations in which it was specified that it is necessary to offer the availability of specialized psychological support to these patients, which should be integrated in the medical team (Callus and Quadri 2010; Callus et al. 2010; Kovacs et al. 2006). Specific indications about psychosocial care will be given further on in this chapter. In the following paragraphs, the psychological characterization of adults with congenital heart disease will be described.

Psychological Characterization of Adults with Congenital Heart Disease

When it comes to studies assessing the psychological aspects of these patients, there is either a comparison with other healthy groups or an attempt to correlate psychological functioning with other variables, including the ones pertaining to the medical condition.

The majority of the studies in the literature indicate the absence of a relationship between diagnosis, physical functionality, and the presence of residual symptoms and a worse psychological functioning (Cox et al. 2002; Kovacs et al. 2008; Rietveld et al. 2002; Utens et al. 1994, 1998; van Rijen et al. 2003, 2005; Callus et al. 2014). There are only a few studies which suggest a weak link between physical functionality and psychological functioning (Popelova et al. 2001; van Rijen et al. 2004).

There are two literature reviews regarding the psychological aspects of these patients (Callus et al. 2013a; Kovacs et al. 2005). In the review by Kovacs and colleagues (2005), it is indicated that these patients often have to deal with psychosocial difficulties which can influence their emotional functioning, the perception of themselves and their relationships. There patients often have to pay particular attention to their lifestyle as there could be limits to their physical capacity and the possibility of proceeding with pregnancy when it comes to the females with ConHD.

In another more recent review (Callus et al. 2013a), the comparison between the population of these patients and healthy ones and which variables (both related to the cardiac condition and others) are linked to the psychological functioning of these patients is explored.

In some studies, in which a comparison was made between adults with ConHD and the healthy and other populations (Cox et al. 2002; Utens et al. 1994, 1998; van Rijen et al. 2003, 2005), no significant differences were found and in some cases a better psychological functioning was found in these patients. In a more recent study, the only difference found between these patients and the general population was on the subscale of somatic symptoms, which were linked to anxiety and depression symptoms (Eslami et al. 2013).

Some authors have indicated that the possible reasons for these results are linked to the fact that these patients could have a higher "sense of coherence" (Moons and Norekval 2006). Sense of coherence represents the generalized world view of an individual and expresses the extent to which he/she perceives: (1) stimuli as structured and predictable (i.e., comprehensibility), (2) the availability of resources to meet the demands posed by these stimuli (i.e., manageability), and (3) that these demands are challenges in which it is worth to make an investment (i.e., meaningfulness). This theory aims to try to give a description of the processes through which people remain healthy even though they are exposed to ubiquitous stressors. It is hypothesized that sense of coherence exerts its positive influence on health through adaptive health behaviors and coping behavior (Antonovsky 1987).

Other factors which could be influencing these results could be denial and "high-achievement motivation" which could lead to these patients indicating that they are feeling better than they really are in self-report questionnaires (Utens et al. 1994; van Rijen et al. 2003).

Interestingly, in a study in which psychiatric interviews were utilized (Kovacs et al. 2008), it was outlined how an elevated percentage (39 %) of patients who were diagnosed with a mood or anxiety disorder had not received any type of psychological treatment. This was confirmed in two other studies in which similar assessment methodologies were utilized (Bromberg et al. 2003; Horner et al. 2000), where a significant portion of the patients, who were thought being well psychologically, were diagnosed with mood or anxiety disorders (9/29 and 8/22, respectively).

When it comes to the exploration of which variables impact on the psychological functioning of adults with ConHD, the pertinent literature indicates the absence of a relationship between diagnosis, physical functionality, and the presence of residual symptoms and psychopathology (Utens et al. 1998; van Rijen et al. 2005); hostility, neurosis, and a low self-esteem (Utens et al. 1994; van Rijen et al. 2003); anxiety and depression (Cox et al. 2002; Kovacs et al. 2008; Eslami et al. 2013; Bromberg et al. 2003; Horner et al. 2000); and psychological well-being (Callus et al. 2014). Only a few studies suggest a weak link between physical functionality and psychological functioning (Popelova et al. 2001; van Rijen et al. 2004).

A study which does not confirm this trend is the one by Brandhagen (Brandhagen et al. 1991), in which it is specified that adults with congenital heart disease have lower scores when compared to the healthy population. Interestingly, another study on adult patients with ConHD who had to implant an ICD showed high levels of anxiety, and this was also connected to a lower sexual functioning both in males and females (Cook et al. 2013). It was also reported that patients with a high level of trait anxiety were more vulnerable to overperceive symptoms which are connected to the heart (Karsdorp et al. 2009).

In other studies there was an exploration of the variables which are connected to psychological well-being (intended as less anxiety and depression, minor symptoms of psychopathology, and more psychological well-being, on the basis of the different instruments utilized in the various studies) (Kovacs et al. 2008; Rietveld et al. 2002; Callus et al. 2013a, 2014; van Rijen et al. 2004; Eslami et al. 2013), and these resulted as being the following:

- Negative thoughts (Rietveld et al. 2002)
- Solitude (Kovacs et al. 2008)
- Social support (Eslami et al. 2013)
- The fear of negative evaluation (Kovacs et al. 2008)
- The imposition of limits (van Rijen et al. 2004)
- Perceived health status (Kovacs et al. 2008; Callus and Quadri 2008)
- Somatic symptoms (Eslami et al. 2013)
- The perception of an economical difficulty (Eslami et al. 2013)
- Restrictions linked to the surgical scar in females (van Rijen et al. 2004)

As specified previously, being born with a congenital cardiac condition has very different implications when compared to patients who acquire an illness at a much later stage in their life. Complex congenital heart conditions can be assimilated to chronic conditions because of the long-term nature of the condition, the uncertainty of its course and prognosis, the signs and symptoms of the condition, and also the restriction on their everyday lives (Moons et al. 2002).

It is important to take into consideration qualitative studies exploring the life experiences of these patients, so as to improve the medical care provided to them and in order to improve medical adherence.

In the literature it is indicated that adolescents with ConHD struggle with physical limitations and face social exclusion (McMurray et al. 2001; Tong et al. 1998). The severity of the condition influenced the type of the limitations the patients felt. As many as one-fourth of adults with ConHD report their parents as being overprotective during their childhoods and adolescence (Brandhagen et al. 1991; McMurray et al. 2001; Arnett 2000). The tendency for these patients to live longer with their parents could be linked to them being overprotective, and it could be that this also creates difficulty for the patients to become more autonomous (Gersony et al. 1993; Kokkonen and Paavilainen 1992).

When it comes to the life experiences of adults with ConHD, it must be considered that this population is a highly heterogeneous one and this entails very different life experiences; however, some common patterns of experience and perspective seem to have been found in this broad diversity (Verstappen et al. 2006). In fact, in the qualitative studies which have been carried out on this population, it has been outlined how these patients feel different from their healthy peers (Verstappen et al. 2006; Berghammer et al. 2006; Claessens et al. 2005; Gantt 1992, 2002; Callus et al. 2013b). It has been seen for often there is a struggle to feel normal and also to be perceived by others as being normal. This could lead to denial of the conditions and also efforts to exceed their physical boundaries imposed by their condition (Berghammer et al. 2006).

Particular issues which could be present in the female population are concerns regarding fertility, contraception, pregnancy, and their surgical scar. It seems that scarring and cyanosis could bear a more negative influence in females and that for men the difficulties related to their body image are more present during adolescence, probably due to the involvement in sports activities (Claessens et al. 2005; Gantt 1992; Callus et al. 2013b).

Since many of the patients have to spend a lot of time in hospital, these experiences are often referred to in the qualitative studies. In one particular study, it was observed how different expectations about the management of the patients' conditions from the patients, their families, and the nurses were associated with interpersonal conflict, distrust, anxiety, and dissatisfaction with the healthcare provided (Kools et al. 2002), outlining the importance of a transparent communication in these settings.

In a very interesting article (Verstappen et al. 2006), quotations from patients are reported from the Adult Congenital Heart Association in an attempt to address the patients' perspectives in order to outline the implications for care.

There was often an ambiguity regarding their condition and their prognosis, also because of language-based misperception in understanding if the condition is completely cured or not. Many patients reported difficulties when having to go to the "regular" medical system, where the sanitary personnel is not specialized in ConHD. They also reported that the people who are close to them sometimes had difficulties to understand the entity of their restrictions. Other patients have described that information about their condition was withheld from them and they got to know about their real condition at the onset of new problems, causing psychological distress and trust issues.

Interestingly, having this condition does not only have negative consequences, but it can also be linked to having some benefits. Some patients report receiving special attention, gaining an increased resilience and maturity, and also gaining a clearer sense about the meaning of life. There can be an increased appreciation of life, more clarity of purpose, and better decision-making when one has to deal with an ongoing awareness of one's mortality due to specific health conditions (Mathieu 2005).

The Role of Psychologists in the Care for Adults with Congenital Heart Disease

Three main domains in which clinical health psychologists can contribute in the handling of adults with ConHD were identified. Kovacs and colleagues (Kovacs et al. 2006) identified: provision of clinical services, multidisciplinary research, and professional education.

Provision of Clinical Services

It is possible that ConHD patients tend to be more sensitive to heart-focused anxiety and bodily sensations due to their condition (Utens et al. 1998; Eifert et al. 2000; Rietveld et al. 2004). Psychologists can help in the reduction of excessive self-monitoring and reduction of cardiac anxiety by utilizing psychoeducation and behavioral strategies. Patients can also be helped to deal with family and peer concerns through social skills training and guidance in communication strategies (Kovacs et al. 2006).

Clinical strategies in order to maximize psychosocial care in ConHD patients have been previously identified in the literature (Kovacs et al. 2005). In particular, the necessity to demonstrate increased psychosocial awareness in settings which work with these populations was outlined. It was also suggested to initiate proactive discussions as trying to avoid important topics will harm the patient in the long run, and initiating discussions allows them to feel they can ask questions and that what

they are going through is common. Finally, when it comes to screening, the following four A's have been suggested to detect and manage psychosocial issues:

(a) Ask the patient about specific challenges.
(b) Advise the patient on common challenges and how to manage them.
(c) Assist the patient through psychological interventions such as support and brief problem solving.
(d) Arrange referral when the patient is evaluated as needing a mental health specialist.

Patients going through different phases of the illness could benefit from psychological support, in particular:

- **When coping with becoming aware of the condition or changes in cardiac status**: Adults with ConHD often require lifelong medical follow-up (Warnes 2005) and they might have to manage situations where they suddenly get worse after many years of relative stability (Horner et al. 2000). Some patients also learn about their condition in adulthood and could have a hard time adjusting to this (Kovacs et al. 2006).
- **The transition from pediatric to adult care** results to be very difficult for many of these patients, and it has been reported that there is a significant number of adolescents who do not manage to successfully transition to adult care (Reid et al. 2004). Psychologists can provide support and individual consultation to those patients experiencing a difficult transition through strategies such as empowerment (Kovacs et al. 2006).
- **Adjustment to cardiac devices and surgical preparation**: As specified previously, it is possible that some patients have difficulty with the implantation of cardiac devices such as the ICD (Cook et al. 2013), especially if they are young (Sears et al. 1999), and cognitive behavioral strategies have been shown to be useful to enhance the confidence and QoL of ICD recipients (Sears et al. 2004). Psychologists can provide preparation techniques which improve the reduction of anxiety in cardiac patients which have to undergo a surgical procedure (Seskevich et al. 2004).
- **Maximization of adherence and behavioral modification**: It is especially important for cardiac disease patients to take care of their diet, to exercise appropriately, and not to indulge in risky health behaviors which can compromise their health. As indicated previously, physical exercise is especially important also in this population. Psychoeducation seems to be helpful when it comes to lifestyle behaviors in patients with coronary heart disease (Dusseldorp et al. 1999) although there are no specific studies regarding this in ConHD patients.
- **Dealing with anticipatory grief and mortality**: It is also possible that the patients of this population have an increased awareness of mortality and a psychologist could help by providing support, dealing with anticipatory grief, and working on strategies to communicate effectively with relatives and sanitary personnel.

Referral for psychosocial care can be initiated in a variety of ways and by different professional figures depending on the situation. However, it is important that psychological and psychiatric referrals are made with the patient's knowledge; otherwise the opposite effect could be obtained. Teams caring for these patients should have clear referral indications, which should be established with collaborating psychologists (Kovacs et al. 2006). In particular cases, referral to other specialists such as psychiatrists (Bassett et al. 2005) and experts in substance abuse (especially since it has been linked to unsuccessful transitioning from pediatric to adult care (Reid et al. 2004)) could be necessary.

Multidisciplinary Research

Psychologists can contribute in the conduction of multidisciplinary research in ACHD patients, especially in the following areas (Kovacs et al. 2006):

- **Development of specific measures**: there is a need for the creation of specific psychosocial measures developed for this population as there have been many studies using different instruments in this population (Deanfield et al. 2003). Some attempts in this direction have already been made (Kamphuis et al. 2004), although it would be advisable to develop additional measures in order to address the unique concerns of this population, as the psychosocial measures developed for acquired cardiac disease do not fully capture this population's experience (Kovacs et al. 2006).
- **Longitudinal psychosocial assessment**: there are few of these studies present in the literature and more are required to understand how the population deals with the various issues through time.
- **Evaluation of psychosocial interventions**: no trials yet exist when it comes to psychological interventions for adults with ConHD (Lip et al. 2003), and since there are few specialized centers, it is also feasible to think about how to provide long-distance support and how to evaluate it.
- **Evaluation of medical interventions and the relationship between mental and physical health**: psychologists can provide insights on the effectiveness of medical interventions by exploring how the patients feel before and after, especially in the domains of quality of life and psychological functioning. It is also important to assess how psychological factors could possibly influence physical functioning in this population.

Professional Education: Increasing Psychosocial Awareness

The guidelines mentioned previously specify that in order to be defined as a competent specialist for adults with ConHD, it would be advisable for the professional to be knowledgeable about the psychosocial aspects of adolescence, the transition to adulthood, and experience with lifestyle counseling and advocacy

(Deanfield et al. 2003). A psychologist could be a very useful figure to provide insight and resources when it comes to these areas.

Conclusion

As outlined in this chapter, the psychological implications of ConHD are quite specific to this population. More research on the psychological characteristics of these patients is required, particularly in the area of psychological interventions. It would also be interesting to compare the populations of acquired and congenital heart disease when it comes to psychological variables. Finally, it is important for psychological professionals to be adequately trained on the specificity of this population.

References

Antonovsky, A. (1987). *Unraveling the mystery of health: How people manage stress and stay well*. San Fransisco: Jossey-Bass.

Arnett, J. J. (2000). Emerging adulthood: A theory of development form the late teens through the twenties. *American Psychologist, 55*(5), 469–480.

Bassett, A. S., et al. (2005). Clinical features of 78 adults with 22q11 Deletion syndrome. *American Journal of Medical Genetics Part A, 138*(4), 307–313.

Baumgartner, H., et al. (2010). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *European Heart Journal, 31*(23), 2915–2957.

Berghammer, M., Dellborg, M., & Ekman, I. (2006). Young adults experiences of living with congenital heart disease. *International Journal of Cardiology, 110*(3), 340–347.

Brandhagen, D. J., Feldt, R. H., & Williams, D. E. (1991). Long-term psychologic implications of congenital heart disease: A 25-year follow-up. *Mayo Clinic Proceedings, 66*(5), 474–479.

Bromberg, J. I., et al. (2003). Depression and anxiety in adults with congenital heart disease: A pilot study. *Heart and Lung, 32*(2), 105–110.

Callus, E., & Quadri, E. (2008). Psychological features of patients with congenital heart diseases. *Pediatria Medica e Chirurgica, 30*(5), 265–266.

Callus, E., & Quadri, E. (2010). The necessity for psychological support during critical moments in pediatric cardiology and cardiac surgery. *Pediatria Medica e Chirurgica, 32*(5), 229.

Callus, E., Quadri, E., & Chessa, M. (2010). Elements of psychocardiology in the psychosocial handling of adults with congenital heart disease. *Frontiers in Psychology, 1*, 34.

Callus, E., Utens, E. M., Quadri, E., Ricci, C., Carminati, M., Giamberti, A., & Chessa, M. (2014). The impact of actual and perceived disease severity on pre-operative psychological well-being and illness behaviour in adult congenital heart disease patients. *Cardiol Young, 24*(2), 275–282. doi: 10.1017/S1047951113000218.

Callus, E., et al. (2013a). Update on psychological functioning in adults with congenital heart disease: A systematic review. *Expert Review of Cardiovascular Therapy, 11*(6), 785–791.

Callus, E., et al. (2013b). Life experiences and coping strategies in adults with congenital heart disease. *Pediatria Medica e Chirurgica, 35*(5), 231–240.

Claessens, P., et al. (2005). What does it mean to live with a congenital heart disease? A qualitative study on the lived experiences of adult patients. *European Journal of Cardiovascular Nursing, 4*(1), 3–10.

Cook, S. C., et al. (2013). Shock-related anxiety and sexual function in adults with congenital heart disease and implantable cardioverter-defibrillators. *Heart Rhythm, 10*(6), 805–810.
Cox, D., et al. (2002). A cross-sectional study of the prevalence of psychopathology in adults with congenital heart disease. *Journal of Psychosomatic Research, 52*(2), 65–68.
Deanfield, J., et al. (2003). Management of grown up congenital heart disease. *European Heart Journal, 24*(11), 1035–1084.
Diller, G. P., et al. (2005). Exercise intolerance in adult congenital heart disease: Comparative severity, correlates, and prognostic implication. *Circulation, 112*(6), 828–835.
Dusseldorp, E., et al. (1999). A meta-analysis of psychoeduational programs for coronary heart disease patients. *Health Psychology, 18*(5), 506–519.
Eifert, G. H., Zvolensky, M. J., & Lejuez, C. W. (2000). Heart-focused anxiety and chest pain: A conceptual and clinical review. *Clinical Psychology: Science and Practice, 7*, 403–417.
Eslami, B., et al. (2013). Anxiety, depressive and somatic symptoms in adults with congenital heart disease. *Journal of Psychosomatic Research, 74*(1), 49–56.
Gantt, L. T. (1992). Growing up heartsick: The experiences of young women with congenital heart disease. *Health Care for Women International, 13*(3), 241–248.
Gantt, L. (2002). As normal a life as possible: Mothers and their daughters with congenital heart disease. *Health Care for Women International, 23*(5), 481–491.
Gatzoulis, M. A., et al. (2005). *Adult congenital heart disease: A practical guide*. Blackwell. http://www.amazon.com/Adult-Congenital-Heart-Disease-Practical/dp/0727916688#reader_0727916688
Gersony, W. M., et al. (1993). Second natural history study of congenital heart defects. Quality of life of patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation, 87*(2 Suppl), I52–I65.
Giannakoulas, G., & Dimopoulos, K. (2010). Exercise training in congenital heart disease: Should we follow the heart failure paradigm? *International Journal of Cardiology, 138*(2), 109–111.
Harrison, J. L., et al. (2011). Healthcare needs of adults with congenital heart disease: Study of the patient perspective. *Journal of Cardiovascular Nursing, 26*(6), 497–503.
Holloway, T. M., et al. (2011). A call for adult congenital heart disease patient participation in cardiac rehabilitation. *International Journal of Cardiology, 150*(3), 345–346.
Horner, T., Liberthson, R., & Jellinek, M. S. (2000). Psychosocial profile of adults with complex congenital heart disease. *Mayo Clinic Proceedings, 75*(1), 31–36.
Kamphuis, M., et al. (2004). A cardiac-specific health-related quality of life module for young adults with congenital heart disease: Development and validation. *Quality of Life Research, 13*(4), 735–745.
Karsdorp, P. A., et al. (2009). False heart rate feedback and the perception of heart symptoms in patients with congenital heart disease and anxiety. *International Journal of Behavioral Medicine, 16*(1), 81–88.
Kokkonen, J., & Paavilainen, T. (1992). Social adaptation of young adults with congenital heart disease. *International Journal of Cardiology, 36*(1), 23–29.
Kools, S., et al. (2002). Hospital experiences of young adults with congenital heart disease: Divergence in expectations and dissonance in care. *American Journal of Critical Care, 11*(2), 115–125. quiz 126-7.
Kovacs, A. H., Sears, S. F., & Saidi, A. S. (2005). Biopsychosocial experiences of adults with congenital heart disease: Review of the literature. *American Heart Journal, 150*(2), 193–201.
Kovacs, A. H., et al. (2006). The role of the psychologist in adult congenital heart disease. *Cardiology Clinics, 24*(4), 607–618, vi.
Kovacs, A.H., et al. (2008). Depression and anxiety in adult congenital heart disease: Predictors and prevalence. *International Journal of Cardiology, 150*, 193–201
Lip, G. Y., et al. (2003). Psychological interventions for depression in adolescent and adult congenital heart disease. *Cochrane Database of Systematic Reviews, 3*, CD004394.
Mampuya, W. M. (2012). Cardiac rehabilitation past, present and future: An overview. *Cardiovascular Diagnosis and Therapy, 2*(1), 38–49.

Marelli, A. J., et al. (2007). Congenital heart disease in the general population: Changing prevalence and age distribution. *Circulation, 115*(2), 163–172.
Marelli, A. J., et al. (2014). Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation, 130*(9), 749–756.
Marino, B. S., Bird, G. L., & Wernovsky, G. (2001). Diagnosis and management of the newborn with suspected congenital heart disease. *Clinics in Perinatology, 28*(1), 91–136.
Mathieu, P. (2005). *What's your expiry date?* Ontario: Patrick Mathieu Unlimited.
McMurray, R., et al. (2001). A life less ordinary: Growing up and coping with congenital heart disease. *Coronary Health Care, 5*, 51–57.
Moons, P., & Norekval, T. M. (2006). Is sense of coherence a pathway for improving the quality of life of patients who grow up with chronic diseases? A hypothesis. *European Journal of Cardiovascular Nursing, 5*(1), 16–20.
Moons, P., De Geest, S., & Budts, W. (2002). Comprehensive care for adults with congenital heart disease: Expanding roles for nurses. *European Journal of Cardiovascular Nursing, 1*(1), 23–28.
Moons, P., et al. (2010). Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. *Circulation, 122*(22), 2264–2272.
Popelova, J., Slavik, Z., & Skovranek, J. (2001). Are cyanosed adults with congenital cardiac malformations depressed? *Cardiology in the Young, 11*(4), 379–384.
Reid, G. J., et al. (2004). Prevalence and correlates of successful transfer from pediatric to adult health care among a cohort of young adults with complex congenital heart defects. *Pediatrics, 113*(3 Pt 1), e197–e205.
Report of the British Cardiac Society Working Party. (2002). Grown-up congenital heart (GUCH) disease: Current needs and provision of service for adolescents and adults with congenital heart disease in the UK. *Heart, 88*(Suppl 1), i1–i4.
Rietveld, S., et al. (2002). Negative thoughts in adults with congenital heart disease. *International Journal of Cardiology, 86*(1), 19–26.
Rietveld, S., Karsdorp, P. A., & Mulder, B. J. (2004). Heartbeat sensitivity in adults with congenital heart disease. *International Journal of Behavioral Medicine, 11*(4), 203–211.
Samanek, M. (2000). Congenital heart malformations: Prevalence, severity, survival, and quality of life. *Cardiology in the Young, 10*(3), 179–185.
Sears, S. F., Jr., et al. (1999). Examining the psychosocial impact of implantable cardioverter defibrillators: A literature review. *Clinical Cardiology, 22*(7), 481–489.
Sears, S. F., et al. (2004). Innovations in health psychology: The psychosocial care of adults with implantable cardioverter defibrillators. *Professional Psychology Research and Practice, 35*(5), 520–526.
Seskevich, J. E., et al. (2004). Beneficial effects of noetic therapies on mood before percutaneous intervention for unstable coronary syndromes. *Nursing Research, 53*(2), 116–121.
Swan, L., & Hillis, W. S. (2000). Exercise prescription in adults with congenital heart disease: A long way to go. *Heart, 83*(6), 685–687.
Tong, E. M., et al. (1998). Growing up with congenital heart disease: The dilemmas of adolescents and young adults [see comment]. *Cardiology in the Young, 8*(3), 303–309.
Utens, E. M., et al. (1994). Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: A follow-up study. *Journal of Psychosomatic Research, 38*(7), 745–758.
Utens, E. M., et al. (1998). Psychopathology in young adults with congenital heart disease. Follow-up results. *European Heart Journal, 19*(4), 647–651.
van der Linde, D., et al. (2011). Birth prevalence of congenital heart disease worldwide: A systematic review and meta-analysis. *Journal of the American College of Cardiology, 58*(21), 2241–2247.
van Rijen, E. H., et al. (2003). Psychosocial functioning of the adult with congenital heart disease: A 20–33 years follow-up. *European Heart Journal, 24*(7), 673–683.

van Rijen, E. H., et al. (2004). Medical predictors for psychopathology in adults with operated congenital heart disease. *European Heart Journal, 25*(18), 1605–1613.

van Rijen, E. H., et al. (2005). Longitudinal development of psychopathology in an adult congenital heart disease cohort. *International Journal of Cardiology, 99*(2), 315–323.

Verstappen, A., Pearson, D., & Kovacs, A. H. (2006). Adult congenital heart disease: The patient's perspective. *Cardiology Clinics, 24*(4), 515–529. v.

Warnes, C. A. (2005). The adult with congenital heart disease: Born to be bad? *Journal of the American College of Cardiology, 46*(1), 1–8.

Warnes, C. A., et al. (2008a). ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation, 118*(23), e714–e833.

Warnes, C. A., et al. (2008b). ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: Executive Summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease). *Circulation, 118*(23), 2395–2451.

The Interaction Between Psychological Health and Valvular Heart Disease: Pathogenesis, Clinical Course, and Treatment

Robert Gooley, Ian Meredith, and James Cameron

Contents

R. Gooley (✉) • J. Cameron
MonashHeart, Monash Medical Centre, Monash Health, Clayton, VIC, Australia

Monash Cardiovascular Research Centre, Southern Clinical School, Monash University, Melbourne, VIC, Australia
e-mail: robert.gooley@monashhealth.org; robertgooley@hotmail.com; james.cameron@monash.edu

I. Meredith
MonashHeart, Monash Medical Centre, Clayton, VIC, Australia

Southern Clinical School, Monash Cardiovascular Research Centre, Monash University, Melbourne, VIC, Australia
e-mail: ian.meredith@monash.edu; ian.meredith@myheart.id.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_24

Abstract

Valvular heart disease is an increasing health concern in most developed countries due to aging populations resulting in increased prevalence. While there is significant focus on ensuring timely medical care and developing less-invasive procedures to treat the functional valve lesions, there is often little attention given to the psychological impact of valvular heart disease.

Indeed while the impact of ischemic heart disease on psychological health and even the potential causative association between psychological illness and ischemic heart disease have been widely acknowledged, such a link is often not recognized in valvular heart disease. However among this unique population who are often older and frailer, assessment of psychological health may be even more important.

Keywords

Valvular heart disease • Aortic stenosis • Mitral regurgitation • Transcatheter aortic valve implantation • Percutaneous mitral valve repair • Surgical valve replacement

Introduction

Valvular heart disease encompasses numerous conditions that are united by dysfunction of one or more of the four cardiac valves: tricuspid, pulmonary, mitral, or aortic. In the majority of conditions, this is manifested as either obstruction to normal blood flow across the valve or regurgitation of blood in a retrograde direction. The clinical sequelae of a specific valve lesion are highly variable, from complete lack of symptoms to resultant heart failure and potentially death. The etiology of valvular dysfunction varies depending on the type of valve lesion, with the prevalence varying based on geographical location and age of the individual.

The aging population of most developed nations has resulted in an increased prevalence of valvular heart disease and resulted in a new health epidemic. In addition, treatment options are continually expanding, with the development of minimally invasive surgical and percutaneous valve repair and replacement techniques, leading to treatment of a cohort previously deemed inoperable due to age, frailty, or other comorbidities.

Like most chronic illnesses, patients with valvular heart disease experience a higher prevalence of psychological conditions including depression, anxiety, and personality disturbance. The significant impact these conditions have on patients' perceptions of their disease, treatment, and prognosis is often under-recognized.

This chapter will explore the interaction between psychological factors and valvular heart disease from etiology to treatment and to prognosis. We will also

explore the psychological impact of new valvular heart disease treatment modalities compared to traditional approaches of care. The psychological aspects of valvular heart disease overlap with those of other chronic cardiac conditions such as ischemic heart disease, heart failure, and cardiac transplantation. Where relevant the interaction and comparison with these conditions will be emphasized.

Valvular Heart Disease

Definition

The human heart contains four cardiac valves, composed of either two or three connective tissue leaflets. The valves separate the four cardiac chambers; the tricuspid valve is positioned between the right atrium and right ventricle, the pulmonary valve between the right ventricle and pulmonary artery, the mitral valve between the left atrium and left ventricle, and the aortic valve between the left ventricle and aorta (Fig. 1). In health, the valves facilitate unidirectional, antegrade flow of blood through the heart when a forward pressure differential forms and close to prevent regurgitation of blood when a negative forward pressure differential forms.

Valvular heart disease collectively refers to conditions that result in either obstruction to antegrade flow or regurgitation of blood through one or more of the cardiac valves. Valvular heart disease, therefore, encompasses a diverse number of conditions covering more than 25 International Classification of Disease (ICD-10) categories (World Health Organization 2010).

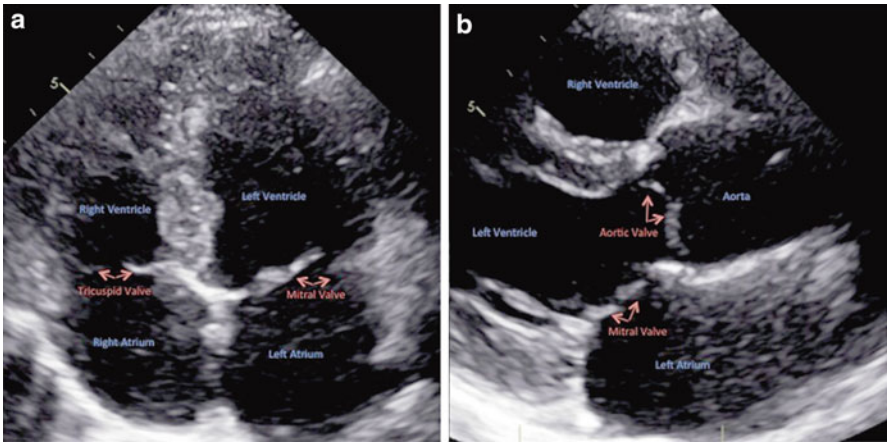


Fig. 1 Normal transthoracic echocardiographic images. (**a**) Apical four-chamber image demonstrating the mitral valve separating the left atrium and left ventricle and the tricuspid valve separating the right atrium and right ventricle. (**b**) Parasternal long-axis image demonstrating the mitral valve separating the left atrium and left ventricle and the aortic valve separating the left ventricle and aorta

Prevalence

Valvular heart disease prevalence increases with age, affecting approximately 2.5 % of the population with prevalence increasing from <1 % among people aged less than 45 years to over 12 % in people aged over 75 years (Nkomo et al. 2006). The Australian population is aging with the proportion of people aged over 65 years projected to rise from 14 % in 2012 to approximately 20 % in 2031 and 25 % in 2061 (Australian Bureau of Statistics 2013). Valvular heart disease is therefore set to become a major health epidemic in Australia with similar patterns in most developing countries, associated with substantial costs to the health service and significant impact on patients' quality of life.

Etiology

The etiology of each valve condition differs; however common causes of regurgitation include rheumatic valve disease, ischemic heart disease, connective tissue conditions, congenitally abnormal valves, and endocarditis, while causes of valve stenosis include age-related calcific degeneration, rheumatic valve disease, and congenitally abnormal valve architecture. A more detailed list of potential etiologies for common valve lesions is presented in Table 1.

Even within a single country, there is variability in the rates of valvular heart disease and also the predominant etiology. While rheumatic heart disease is now an uncommon cause of valvular dysfunction in most western countries, within Australia there remains a significantly higher incidence among the indigenous Aboriginal population. Within Australia's Northern Territory, 93 % of patients with rheumatic heart disease are indigenous with prevalence among indigenous women of 3.2 % and indigenous men of 1.7 % compared to 0.2 % and 0.1 % for their respective nonindigenous contemporaries (Australian Institute of Health and Welfare 2011).

Treatment and Prognosis

The majority of people with mild or moderate valve dysfunction remain in a latent phase without any subjective or objective symptoms. This asymptomatic period has a variable duration but generally lasts decades before disease severity progresses and symptoms are identified. Often no specific treatment is required in this phase of valvular heart disease.

Guidelines recommend that patients identified with valvular heart disease be monitored for development of symptoms and with transthoracic echocardiography to allow early identification of negative compensatory cardiac changes such as chamber dilatation (Nishimura et al. 2014). This watchful waiting approach may lead to a prolonged latent period with no symptom burden but significant

Table 1 Common etiologies of valvular defects

Aortic stenosis	**Aortic regurgitation**
Calcific degeneration	Acute
Bicuspid aortic valve	Infective endocarditis
Rheumatic heart disease	Trauma
	Aortic dissection
	Chronic
	Aortic root dilatation
	Idiopathic
	Hypertension
	Osteogenesis imperfecta
	Syphilitic aortitis
	Rheumatic heart disease
	Bicuspid aortic valve
	Connective tissue disease
Mitral stenosis	**Mitral regurgitation**
Rheumatic heart disease	Acute
Calcific degeneration	Infective endocarditis
	Ruptured papillary muscle
	Chronic
	Mitral valve prolapse
	Myxomatous degeneration
	Left ventricular remodeling
	Ischemic
	Dilated cardiomyopathy
	Rheumatic heart disease
	Marfan's syndrome
Pulmonary stenosis	**Pulmonary regurgitation**
Congenital heart disease	Pulmonary hypertension
Rheumatic heart disease	Congenital heart disease
Carcinoid tumor	
Tricuspid stenosis	**Tricuspid regurgitation**
Rheumatic heart disease	Acute
Right atrial myxoma	Infective endocarditis
Carcinoid syndrome	Chronic
Connective tissue disease	Right ventricular dilatation
Congenital heart disease	LV dysfunction
	RV ischemia
	Cor pulmonale
	Ebstein's anomaly
	Carcinoid
	Myxomatous degeneration

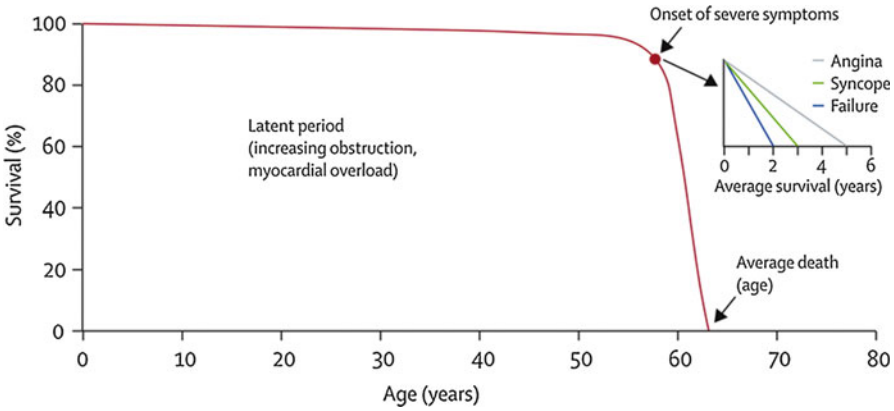


Fig. 2 The natural history of aortic stenosis includes a long latent period prior to the development of symptoms. After symptom development there is a rapid decline in survival

anticipation driven by awareness of the underlying condition and the need for regular surveillance investigations. Some people will never move beyond this latent period due either to lack of disease progression or because other medical illnesses intervene first. Such anticipation may, however, be associated with psychological impact such as development of anxiety or depression in susceptible patients.

While the asymptomatic disease phase may last for a number of years or even decades, progression to severe dysfunction generally heralds the development of heart failure symptoms and associated morbidity and mortality (Fig. 2). Mild symptoms such as dyspnea or fatigue may be countered by commencement of medication, particularly diuretic therapy. The onset of symptoms together with identification of severe valvular dysfunction on echocardiography, however, warrants consideration of definitive treatment. This has traditionally centered on open-heart surgery with repair or replacement of the affected valve. Given the older demographic, up to 30 % of patients with symptomatic severe valvular heart disease have previously been denied or refused surgery (Iung et al. 2005). This has lead to the development of newer, less-invasive catheter-based treatments that have proven, in appropriate patients, to be as efficacious as open surgery. The advent of these catheter-based therapies has opened treatment to a group of patients previously denied operative management due to real or perceived risks by the patient or physician.

Prevalence of Depression and Anxiety in Patients with Valvular Heart Disease

It is generally acknowledged that patients with valvular heart disease, like other chronic illnesses, have a high rate of psychological conditions such as depression and anxiety. The actual prevalence of depression and anxiety, however, has not

been widely studied. The rate of depression in patients with cardiovascular disease, a condition that shares some symptoms and treatment modalities with valvular heart disease, approaches 15 % (Colquhoun et al. 2013), while rates of 20–30 % (Rumsfeld et al. 2003; Rutledge et al. 2006; Sullivan et al. 2004) have been reported among patients with chronic heart failure, a condition that is a common sequelae of valvular heart disease. Among the limited published data, the reported rate of depression in patients with valvular heart disease has reached 80 % (Carney et al. 1990).

The significant variability in reported prevalence of psychological disturbance in valvular heart disease is likely multifactorial. Existing studies are generally small and potentially underpowered to give a true prevalence rate in the general valvular heart disease population. Populations studied can also vary significantly, from relatively asymptomatic patients in the community to hospitalized patients with end-stage heart failure. Perhaps one of the greatest limitations to determining true prevalence of psychological disturbance among people with valvular heart disease is the lack of consistent definitions of depression, anxiety, and personality disorder together with variable tools employed for disease detection. While the *Diagnostic and Statistical Manual of Mental Disorders* is used to formally diagnose these conditions in clinical practice, most research studies rely on simpler and potentially less accurate means of detection. Some studies rely on self-diagnosis and reporting of symptoms; others use various standardized questionnaires or scoring symptoms, while only a few utilize formal psychological assessment by a trained professional.

The significant degree of variability in detection was eloquently demonstrated in a study examining a cohort of elderly women with mitral stenosis. When the cohort was assessed using the Hospital Anxiety and Depression Scale (HADS), both anxiety and depression were significantly higher than age-matched controls. However, administration of the Short Form (36) Health Survey in the same population did not elicit any difference between the groups in mental health scores (Shuldham et al. 2001). This suggests that while individual studies may be able to show an increased rate of psychological disturbance between cohorts, results are often not comparable between studies.

Despite high prevalence of psychological disturbance among people with valvular heart disease, the issue receives little to no attention in published guidelines (Nishimura et al. 2014; Vahanian et al. 2012). While national guidelines rely heavily on a sufficient evidence base prior to making formal recommendations, the omission of the significant psychological/cardiac interplay fails to address this important aspect of holistic care. The European Society of Cardiology guidelines, in only one paragraph regarding assessment of comorbidities, lists frequently encountered physical conditions but no psychological conditions. It briefly states that "validated scores enable the assessment of cognitive and functional capacities which have important prognostic implications in the elderly" (Vahanian et al. 2012). The guidelines do not state which validated scores should be used, and indeed it is unclear if they are instead focused more on the detection of cognitive impairment in the elderly rather than psychological illness in the entire

cohort. Unfortunately, this lack of guidance regarding the need for screening for psychological symptoms, the optimal screening tool, and the best treatment of psychological disorders when present is likely to contribute further to lack of detection, lack of understanding, and suboptimal care within both the research and clinical environments.

The Etiology of Psychological Conditions in Patients with Valvular Heart Disease

While the association between psychological conditions and valvular heart disease is generally accepted, a causal relationship is far more difficult to establish and prove. Valvular heart disease is a chronic illness that is associated with significant morbidity and mortality, and there is an extensive evidence pool that depressive and anxiety disorders are more common in patients with chronic illnesses (Katon et al. 2007). The health impact of a chronic illness often leads to reactive depressive disorders with an increasing prevalence as the severity of the underlying medical illness worsens (Cassem 1995). If the patient is unable to employ appropriate adaptive responses, these reactive disorders can develop into major depressive or anxiety disorders.

Further pathophysiological mechanisms to explain the development of psychological conditions in the setting of valvular heart disease have been postulated. Left-sided annular and valvular calcification is associated with increased subclinical cerebral infarcts identified on magnetic resonance imaging (Rodriguez et al. 2011). It has been demonstrated that up to half of presenile major depression may be associated with similar silent cerebral infarction (Fujikawa et al. 1993). While this offers a potential mechanistic association between valvular heart disease and higher rates of psychological disturbance, reactive psychological disturbance remains a more feasible explanation in the majority of cases.

The Role of Psychological Disturbance in the Etiology of Valvular Heart Disease

While it is generally accepted that the presence of a chronic illness can lead to reactive psychological conditions, a number of hypotheses exist regarding a pathobiological role for psychological conditions exacerbating or contributing to the development of cardiac disease. The majority of these theories were developed in populations with chronic ischemic heart disease but may also hold in association with valvular heart disease.

Major depressive disorder has been shown to result in alteration of the neurohormonal milieu including up-titration of a number of pro-inflammatory cytokines including TNF-alpha, IL-10, IFN-gamma, BNP, and ADMA (Anisman and Merali 2002; Zorrilla et al. 2001). This has led to the suggestion that depression may be considered a low-grade chronic inflammatory condition.

These inflammatory cytokines through direct pro-inflammatory action on the endothelium and by downregulation of anti-inflammatory/vasodilatory nitric oxide (NO) may result in vascular inflammation, attraction of inflammatory cells, and hence accelerated atherosclerosis (Empana et al. 2005). While a similar relationship has not been proven in the setting of valvular heart disease, histopathological studies of aortic stenosis have found an increase in inflammatory cell infiltrate suggesting that there may be at least an inflammatory component to this disease (Wallby et al. 2013). It could, therefore, be hypothesized that these same pro-inflammatory cytokines that are upregulated in the setting of major depressive disorder could result in valve leaflet inflammation and calcific degeneration.

An association has been demonstrated between recurrent major depression in middle-aged women and development of coronary and aortic calcification. One study looking at calcification in 200 healthy middle-aged women found that a history of recurrent major depression was associated with an odds ratio of 3.39 (95 % confidence interval 1.34–8.63) for high aortic calcification compared to those with no history of depression or only an isolated episode (Agatisa et al. 2005). While age-related valvular degeneration often involves calcification of the valvular apparatus, this study did not extend to investigation of valvular calcification. Other studies have, however, shown that the presence of coronary and/or aortic calcification correlates with the presence of aortic valve and mitral annular calcification (Jeon et al. 2001). Further work is required to directly assess the role of depression and other psychological conditions, in the pathogenesis of valvular calcification and dysfunction and whether the previously described inflammatory-mediated hypothesis is the causative process.

Even if depression and anxiety are proven not to be causative in the development of valvular heart disease, it is highly likely that their presence alters patients' perceptions of their valvular disease and symptom burden and potentially alters outcome. Psychological conditions may result in increased awareness of symptoms compared to age-matched controls when corrected for objective means of disease severity assessment (Katon et al. 2001). Depression and anxiety may also be associated with upregulation of the autonomic nervous system resulting in a fight or flight response with somatic symptoms such as increased muscle tension, palpitations, perspiration, and dyspnea.

The Impact of Psychological Illness on Valvular Heart Disease and Its Treatment

The presence of psychological stressors negatively impact on the clinical outcomes of patients with most chronic illnesses and valvular heart disease is no exception. Conditions such as depression, anxiety, and personality disorder can affect compliance with recommended therapy, physician's judgment in offering treatment, and potentially the efficacy of treatment.

Testing and Costs

The presence of a psychological condition can result in increased awareness of symptoms and potentially over-reporting of disease severity. This may result in patients being subjected to an increased number of tests or at an increased frequency resulting in costs of treatment in some cases 50 % higher than matched patients without comorbid psychological illness (Katon 2003). Cardiac societies in a number of countries have established screening guidelines for patients with documented valvular heart disease. These guidelines are designed to identify changes in disease severity or unfavorable compensatory changes early yet not overburden the patient or health system with unnecessarily frequent testing.

The finding of increased health costs in the setting of comorbid depression and chronic illness has been demonstrated in a number of illnesses. In a population of patients with diabetes mellitus in the United States of America, the presence of major depression, as assessed by the nine-item PHQ survey, was associated with a 70 % increase in healthcare costs (Simon et al. 2005). While the presence of depression can increase the costs of chronic illness care provision, there is also evidence that appropriate recognition and treatment of depression can reduce costs. One randomized study, also in a diabetic cohort with depression, found that implementation of case-managed depression intervention resulted in a net cost saving over 2 years despite an initial additional cost for the mental health treatment (Katon et al. 2006). Given the significant health costs encountered in a valvular heart disease cohort during all phases of screening, surveillance, and treatment, potential cost savings are significant.

Heart Failure

Progression in the severity of valvular heart disease can result in complications such as heart failure, arrhythmia, and stroke, each of which has psychological implications for patients. Heart failure is the most common clinical sequelae of valvular heart disease and occurs when the cardiac output is not sufficient to meet the metabolic demands of the organs despite normal filling pressures. The symptoms of heart failure include dyspnea, fatigue, lethargy, and peripheral edema. The presence of heart failure is associated with increased rates of depression with reported prevalence of 11–58 % (Koenig 1998; Havranek et al. 1999; Turvey et al. 2002) and anxiety with reported prevalence ranging from 29 % to 45 % (Friedmann et al. 2006; Jiang et al. 2004). Despite the high rate of comorbid psychological disturbance in the heart failure population, there is evidence that early intervention can ameliorate this. The presence of strong social supports and family relationships may, however, counter the onset of depression (Friedmann et al. 2006; Scherer et al. 2007).

There is evidence that as heart failure severity worsens, as measured by the New York Heart Association class, the incidence of depression increases (Scherer et al. 2007). The New York Heart Association classification grades heart failure

Table 2 The New York Heart Association (NYHA) classification of heart failure symptoms

NHYA class	Definition
I	Documented cardiac disease **without symptoms** or physical limitation. Ordinary physical activity does not cause fatigue, palpitation, dyspnea, or angina
II	Documented cardiac disease resulting in **slight limitation** of physical activity. Ordinary physical activity results in fatigue, dyspnea, palpitation, or angina. No symptoms are present at rest
III	Documented cardiac disease resulting in **marked limitation** of physical activity. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina. No symptoms are present at rest
IV	Documented cardiac disease resulting in inability to perform physical activity without symptoms. Symptoms may also be **present at rest**

severity based on the degree of functional limitation due to heart failure symptoms (Table 2). However such results may be confounded by over-reporting of symptoms in patients with depression. Although not consistently demonstrated, the majority of evidence suggests that the presence of a depressive disorder adversely affects heart failure prognosis, independent of other measures of disease severity (Faris et al. 2002; Jiang et al. 2001; Murberg et al. 1999). One such study, a retrospective analysis of 396 patients hospitalized with nonischemic heart failure, identified those with a documented history of depression. When adjusted for conflicting variables, a history of depression predicted mortality with a hazard ratio of 3.0 (CI 1.4–6.6, $p = 0.004$) (Faris et al. 2002). A similar association has been demonstrated in patients with stable heart failure symptoms not necessitating admission. A population of 119 stable Norwegian outpatients attending a cardiology clinic were enrolled. These patients were assessed for depressive symptoms using the Zung Depression Scale (Zung 1965). Depressed mood was found to inversely predict 2-year survival with an almost doubling of the hazard ratio (HR $= 1.9$, $p = 0.002$) (Murberg et al. 1999).

Pharmacological Treatment

Medical management remains the mainstay of treatment for patients with valvular heart disease during most phases of care as opposed to surgical or percutaneous intervention, which are generally only required in symptomatic severe dysfunction. In the setting of valvular dysfunction, medication may be used to prevent the development of, or mitigate the clinical effect of, valvular heart disease symptoms. In patients who have undergone percutaneous or operative intervention, medication is even more important in preventing complications such as prosthesis thrombosis or systemic thromboembolism.

Comorbid depression has been shown to correlate with reduced medication compliance in a number of chronic illness settings. A meta-analysis looking at this issue analyzed 31 studies with chronic illnesses including heart failure,

coronary artery disease, hypertension, dyslipidemia, and diabetes. The presence of depression in these populations was associated with 1.76 times the odds of medication noncompliance. The means of measuring noncompliance in the included studies varied from self-reporting to analysis of pharmacy records and electronic medication container measurements (Grenard et al. 2011). Another meta-analysis looked for association between not only depression but also anxiety and medication noncompliance. Again depression was associated with increased noncompliance (OR 3.03, CI 1.95–4.89). The combined results of 13 studies assessing anxiety, however, did not demonstrate a significant increase in noncompliance (DiMatteo et al. 2000). Medication noncompliance may lead to worsening of symptoms which, given that symptom burden has been shown to correlate with depression, may further exacerbate underlying psychological conditions creating a vicious circle of deteriorating physical and mental health.

Once depression is diagnosed, patients may be commenced on antidepressant medication. While no large-scale trials have assessed the safety and efficacy of antidepressants in a valvular heart disease population, they have been widely used without significant issue. Despite some concern regarding a possible link between the use of serotonin selective reuptake inhibitors (SSRIs) and valvular heart disease, this has not been proven in clinical or research use. Such concerns stemmed from previously used weight loss agents, particularly fenfluramine, which substantially raised plasma levels of serotonin as well as possessing agonistic properties at the 5-HT_{2B} receptor resulting in fibrotic valvulopathy. SSRI agents do not result in such significant serotonin levels and lack the direct receptor activity that was the likely predominant mechanism of fenfluramine-induced valvulopathy. While no firm recommendation can be made regarding the optimal class of antidepressant for use in valvular heart disease, small studies have suggested that SSRIs have a lower side effect profile than tricyclic antidepressants in other cardiac conditions such as ischemic heart disease and heart failure.

Surgical Valve Repair or Replacement

Up to 30 % of elderly patients with severe aortic stenosis are denied surgical treatment due to physician or patient preference (Iung et al. 2005). The rationale for physician refusal in this population has been studied and in most cases is multifactorial although comorbidities such as depression contribute to each individual's global perceived risk. Denial of definitive operative or percutaneous treatment leaves patients at the mercy of the natural history of the underlying valvular condition (Fig. 2), which includes worsening physical health and hence often worsening psychological health. In the case of aortic stenosis, the natural disease history includes a 50 % mortality rate of over 2 years in patients with severe stenosis and symptoms. Failure to identify underlying psychological conditions and treat them appropriately may, therefore, lead to denial of lifesaving treatments.

While some patients with existing depressive illness may be unfairly denied definitive treatment, the presence of depression adversely affects patients who do undergo surgery. One study comparing patients with baseline depression to those without prior to coronary artery bypass grafting found that it was independently associated with increased mortality with an adjusted hazard ratio of 2.4 (Blumenthal et al. 2003).

The Impact of Valvular Heart Disease Treatment on Psychological Illness and Quality of Life

While the presence of psychological illness may affect treatment offered or the efficacy of treatment for valvular heart disease, the effect of valvular heart disease interventions on patients' psychological health must also be considered. Treatment of advanced valvular heart disease often involves invasive surgical or complex percutaneous interventions. Even among patients without pre-existing psychological illness, such major events may result in new onset depression or anxiety. In patients with existing depression or anxiety, the effect of invasive treatment on the underlying psychological illness is variable. The advent of percutaneous valve interventions has led to treatment of an older, frailer, and generally more physically unwell cohort whose psychological response to valvular treatment may differ from patients undergoing traditional operative valve replacement and from reported community cohorts with valvular heart disease.

Pharmacological Treatment

Inhibition of beta-adrenoreceptor activation with the use of beta-blockers is commonly used in the treatment of valvular heart disease conditions. Beta-blockers have traditionally been thought to increase the incidence of depression, along with other side effects including fatigue and sexual dysfunction. A recently published meta-analysis of 15 randomized trials, however, found no significant difference in the incidence of depression in patients on beta-blockers compared to placebo and only a small increase in the rate of fatigue and sexual dysfunction (Ko et al. 2002).

Angiotensin-converting enzyme inhibitors (ACEIs) are similarly used in valvular heart disease for their beneficial effect in reducing cardiac afterload and reducing negative ventricular remodeling. One study using a prescription sequence symmetry analysis suggested that ACEI may increase the incidence of depression with a hazard ratio of 1.29 (1.08–1.56) (Hallas 1996). This form of analysis compares the rate of people commencing an ACEI prior to an antidepressant with those who commence an antidepressant prior to an ACEI. Of course such an analysis has many intrinsic flaws so it should be seen only as hypothesis generation with a need for formal studies.

Surgical Valve Repair or Replacement

Definitive management of valvular heart disease by surgical intervention is often required once disease severity worsens and symptoms develop. Surgical procedures can vary from minimally invasive thoracoscopic-guided intervention to open sternotomy and from repair of native valves to replacement with bioprosthetic or mechanical devices.

The incidence of anxiety and depression as assessed by the HADS score is high following cardiac surgery with reported rates of 16 % and 20 %, respectively (Okamoto et al. 2013). These high rates of psychological illness are important as the presence of psychological ill health (Zipfel et al. 2002) or significant social isolation (Oxman et al. 1995) may lead to a worse surgical outcome and recovery. Patients who develop worsening depressive symptoms within 2 months of cardiac surgery have a lower reported quality of life at 6 months postoperation (Goyal et al. 2005).

Despite high rates of depression and anxiety following cardiac surgery, among a more select patient population undergoing cardiac transplantation, it has been demonstrated that psychological preparation leads to an increased use of more productive, active problem-focused coping mechanisms rather than emotion-focused coping mechanisms (Pfeifer et al. 2013). The use of such preemptive strategies may reduce the rates of depression seen and hence improve postoperative recovery and survival. It is likely that similar psychological preparation would be beneficial prior to other cardiothoracic surgical procedures and potentially newer transcatheter procedures.

While it remains important to identify and treat new onset depression and anxiety following cardiac surgery and transplantation, the majority of patients note an improved quality of life (Rimington et al. 2010). In one such study, the overall improvement in mental health outcomes was actually greater than self-reported improvement in physical quality of life. This same study identified baseline depression and mental health illness as predictors of poor mental health quality of life at 1 year while advanced age appeared to be protective (Rimington et al. 2010).

Transcatheter Aortic Valve Intervention

Transcatheter aortic valve implantation (TAVI) or transcatheter aortic valve replacement (TAVR) was developed as a minimally invasive method of replacing the aortic valve in high-surgical-risk patients. The first case was performed in 2002 (Cribier et al. 2002) with subsequent rapid adoption of the technology. It is now estimated that more than 100,000 procedures have been performed globally with a number of competing devices now available. The replacement valve is inserted in a constrained form via a delivery catheter through either the femoral artery, alternate peripheral vessel, or in some cases a minimal surgical approach allowing access to the ventricular apex or the ascending aorta. The constrained valve is positioned

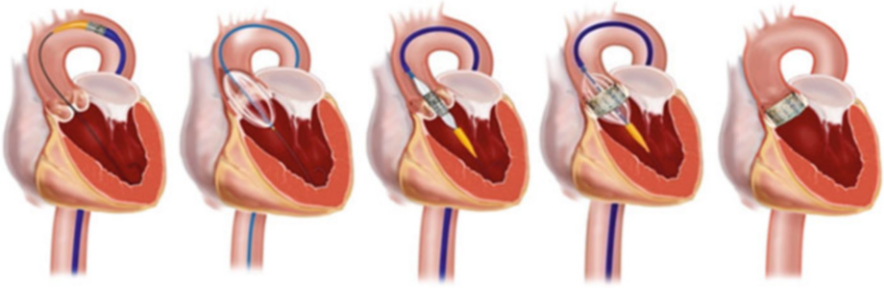


Fig. 3 Transcatheter aortic valves are delivered in a constrained form to the native aortic valve. The valve frame is then expanded by balloon, self-expansion, or mechanical expansion, exposing the new tissue leaflets within the frame and displacing the native leaflets into the sinuses of Valsalva

across the native valve and expanded. This displaces the native valve leaflets between the valve frame and the sinuses of Valsalva while new tissue leaflets sutured to the valve frame begin to function (Fig. 3). This percutaneous approach negates the need for a midline sternotomy, reduces risk, and hence hastens recovery.

TAVI, while less invasive than open surgery, has modest yet significant complication rates that may directly or indirectly impact on patients' psychological well-being. The TAVI procedure often involves a balloon valvuloplasty followed by passage of a delivery catheter across the aortic arch to the native aortic valve. Manipulating the native aortic valve and maneuvering the delivery catheter through an often-diseased aorta may result in embolization of atherosclerotic and/or calcific debris. This has been demonstrated in clinical trials where the rate of clinically detected stroke has been reported to be between 2 % and 5 %. The rate of magnetic resonance (MR) detected cerebral lesions, however, is much higher at 60–100 % (Ghanem et al. 2010, 2013; Kahlert et al. 2010). The majority of MR-detected lesions are randomly distributed throughout the subcortex. While this has led to the assertion that the majority of new cerebral lesions do not result in clinical sequelae, it is highly likely that the means of symptom detection used in published trials as well as in clinical practice are flawed and inadequate. Commonly used assessments vary but may include patient reports of symptoms, non-neurologist physical assessments, or global assessment tools such as the Modified Rankin or NIH Stroke Scale. Subtle neurocognitive and behavioral changes are likely to be missed in such global cognitive assessments (Barber et al. 2008). Nonspecialist review in such situations is likely to focus on the presence of new gross sensory or motor deficits rather than mild psychological disturbance, which may also be a clinical consequence of stroke.

While the rate of new onset psychological disturbance due to procedural complications may be under-recognized, the majority of studies have shown that patients undergoing TAVI have an improvement in quality of life, including mental health scores (Ussia et al. 2009; Kala et al. 2013). In some studies the improvement in self-reported quality of mental health was greater than that in physical quality of

life. These improvements in mental health correlate with functional improvement and reduction in cardiovascular symptoms as measured by the New York Heart Association score. Unfortunately, the majority of these studies have relied on participants completing self-assessment forms such as the Medical Outcomes Trust Short Form 12 (Ware et al. 1996), Medical Outcomes Trust Short Form 36 (Ware et al. 1993), or EuroQol EQ-5D (Rabin and de Charro 2001). With reported response rates of 73–77 %, this opens such means of detection to responder bias and hence may under-detect psychological and mental health disturbance.

Percutaneous Mitral Valve Repair

Similar to the advent of TAVI, the need for percutaneous mitral valve repair has been identified as a preferable treatment modality among a cohort of patients who are highly symptomatic due to severe mitral regurgitation yet are at high or extreme operative risk. The MitraClip (Abbott Vascular, IL, USA) device functions by clipping the leading edge of the anterior and posterior mitral leaflets together to form a double-orifice valve (Fig. 4). Approximating the two leaflets in this manner reduces the degree of mitral regurgitation in a similar mechanism to the surgical Alfieri (or edge-to-edge) repair.

The MitraClip device is inserted via the femoral vein with a transseptal puncture performed to gain access to the left atrium. The MitraClip entered clinical practice after TAVI and as such the body of evidence regarding its effect on psychological health is limited. In one large reported cohort of 127 patients, however, it was demonstrated that the SF36 quality of life scores improved significantly post procedure. This improvement was seen in both the physical and mental component SF36 summary scores (Lim et al. 2013). To date no published studies have looked at the rate of subclinical stroke by routine cerebral imaging.

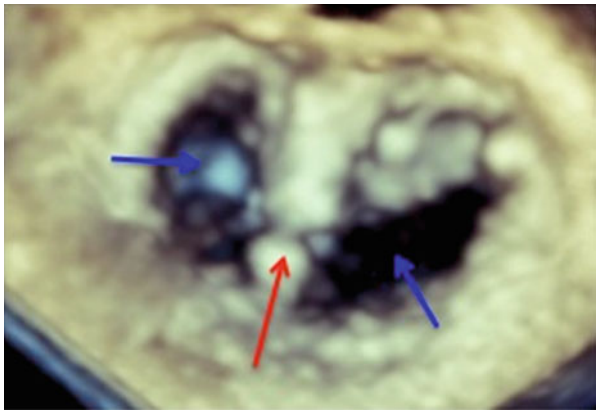


Fig. 4 Three-dimensional echocardiographic image of the mitral valve following deployment of a MitraClip. The MitraClip (*red arrow*) approximates the edge of the two mitral valve leaflets leaving a double-orifice mitral valve (*blue arrows*)

Practical Implications of Psychological Conditions and Valvular Heart Disease

With the increasing burden of valvular heart disease on the health service and on patients' quality of life, most clinicians, not only cardiologists but also other medical professions including psychologists, psychiatrists, and allied health providers, will encounter affected patients. The role of psychological conditions that patients experience during all stages of valvular heart disease is probably grossly under-recognized. Prompt diagnosis and treatment of depression, anxiety, and/or personality disorders may result in reduction of somatic symptom burden, increased efficacy of treatment, and improved rapid recovery following intervention. With the advent of new technologies opening treatment to a new, potentially more high-risk cohort, the importance of multidisciplinary care is imperative and now well recognized. Within most jurisdictions the "Heart Team" has been adopted for the care of patients in whom TAVI has been considered and, however, is often limited in its composition to include only cardiologists, cardiothoracic surgeons, anesthetists, and primary care physicians. While limited in the diversity of healthcare providers, such Heart Teams are in line with current societal guidelines with the current 2014 American Heart Association/American College of Cardiology guidelines stating the importance of the Heart Team, in particular to decisions regarding TAVI, but mention only the need to include professionals with expertise in valvular heart disease, cardiac imaging, interventional cardiology, cardiac anesthesia, and cardiac surgery (Nishimura et al. 2014). Given the importance of psychological health and early detection of depression or anxiety, thought should be given to expanding this team to include psychologists and/or psychiatrists while ensuring that the "Heart Team" is involved in most patients with valvular heart disease, not just those undergoing transcatheter procedures (Fig. 5). The current European Society of Cardiology guidelines fail to mention the importance of a more diverse Heart Team, stating only that the Heart Team should include cardiologists and cardiac surgeons and other specialists if necessary (Vahanian et al. 2012). It could be argued that recognizing when other specialists "are necessary" is unlikely to occur if appropriate specialists are not routinely involved to detect the patient need.

Conclusion

There is no doubt that valvular heart disease is a health epidemic predominantly due to the aging population of most western societies. At the same time, treatment options are growing, leading to a larger population of treated patients. Psychological disturbance occurs in a valvular heart disease cohort at a higher rate than age-matched controls and can occur at all phases of the disease process. Depression and anxiety remain under-reported, underdiagnosed, and undertreated. Failure to diagnose and treat conditions such as depression, anxiety, and personality disorders may lead to increased morbidity, inappropriate denial of access to treatment,

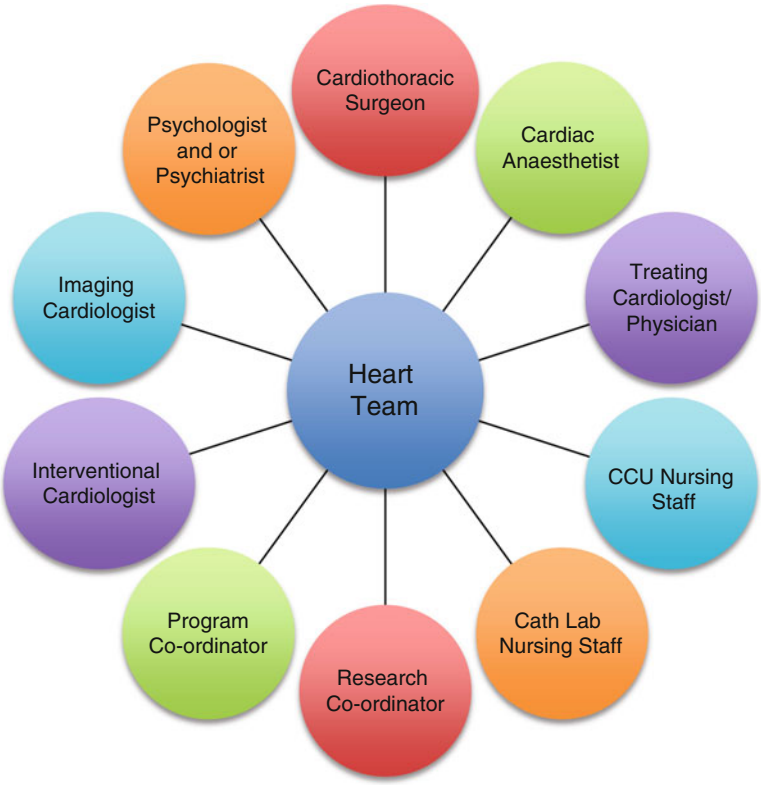


Fig. 5 The Heart Team concept was formally introduced with the advent of TAVI though used prior to this in many institutions. The inclusion of a trained psychologist or psychiatrist is, however, not currently mandated in European or United States guidelines

and poorer patient outcomes following treatment. Engagement of a multidisciplinary team including psychologists and psychiatrists during all aspects of valvular heart disease treatment is imperative to provide early recognition of psychological disturbance, provide necessary psychological treatment, and support and guide appropriate patient-centered valvular heart disease care.

References

Agatisa, P. K., Matthews, K. A., Bromberger, J. T., Edmundowicz, D., Chang, Y. F., & Sutton-Tyrrell, K. (2005). Coronary and aortic calcification in women with a history of major depression. *Archives of Internal Medicine, 165*, 1229–1236.

Anisman, H., & Merali, Z. (2002). Cytokines, stress, and depressive illness. *Brain, Behavior, and Immunity, 16*, 513–524.

Australian Bureau of Statistics. (2013). *Population projections, Australia, 2012 (base) to 2101*. Belconnen: Australian Bureau of Statistics.

Australian Institute of Health and Welfare. (2011). *Aboriginal and Torres Strait Islander health performance framework 2010: Detailed analyses*. Canberra: Australian Institute of Health and Welfare.

Barber, P. A., Hach, S., Tippett, L. J., Ross, L., Merry, A. F., & Milsom, P. (2008). Cerebral ischemic lesions on diffusion-weighted imaging are associated with neurocognitive decline after cardiac surgery. *Stroke; A Journal of Cerebral Circulation, 39*, 1427–1433.

Blumenthal, J. A., Lett, H. S., Babyak, M. A., et al. (2003). Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet, 362*, 604–609.

Carney, R. M., Freedland, K. E., Ludbrook, P. A., Saunders, R. D., & Jaffe, A. S. (1990). Major depression, panic disorder, and mitral valve prolapse in patients who complain of chest pain. *American Journal of Medicine, 89*, 757–760.

Cassem, E. H. (1995). Depressive disorders in the medically ill. An overview. *Psychosomatics, 36*, S2–S10.

Colquhoun, D. M., Bunker, S. J., Clarke, D. M., et al. (2013). Screening, referral and treatment for depression in patients with coronary heart disease. *Medical Journal of Australia, 198*, 483–484.

Cribier, A., Eltchaninoff, H., Bash, A., et al. (2002). Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: First human case description. *Circulation, 106*, 3006–3008.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine, 160*, 2101–2107.

Empana, J. P., Sykes, D. H., Luc, G., et al. (2005). Contributions of depressive mood and circulating inflammatory markers to coronary heart disease in healthy European men: The prospective epidemiological study of myocardial infarction (PRIME). *Circulation, 111*, 2299–2305.

Faris, R., Purcell, H., Henein, M. Y., & Coats, A. J. (2002). Clinical depression is common and significantly associated with reduced survival in patients with non-ischaemic heart failure. *European Journal of Heart Failure, 4*, 541–551.

Friedmann, E., Thomas, S. A., Liu, F., Morton, P. G., Chapa, D., & Gottlieb, S. S. (2006). Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. *American Heart Journal, 152*, 940 e1–940 e8.

Fujikawa, T., Yamawaki, S., & Touhouda, Y. (1993). Incidence of silent cerebral infarction in patients with major depression. *Stroke; A Journal of Cerebral Circulation, 24*, 1631–1634.

Ghanem, A., Muller, A., Nahle, C. P., et al. (2010). Risk and fate of cerebral embolism after transfemoral aortic valve implantation: A prospective pilot study with diffusion-weighted magnetic resonance imaging. *Journal of the American College of Cardiology, 55*, 1427–1432.

Ghanem, A., Kocurek, J., Sinning, J. M., et al. (2013). Cognitive trajectory after transcatheter aortic valve implantation. *Circulation Cardiovascular Interventions, 6*, 615–624.

Goyal, T. M., Idler, E. L., Krause, T. J., & Contrada, R. J. (2005). Quality of life following cardiac surgery: Impact of the severity and course of depressive symptoms. *Psychosomatic Medicine, 67*, 759–765.

Grenard, J. L., Munjas, B. A., Adams, J. L., et al. (2011). Depression and medication adherence in the treatment of chronic diseases in the United States: A meta-analysis. *Journal of General Internal Medicine, 26*, 1175–1182.

Hallas, J. (1996). Evidence of depression provoked by cardiovascular medication: A prescription sequence symmetry analysis. *Epidemiology, 7*, 478–484.

Havranek, E. P., Ware, M. G., & Lowes, B. D. (1999). Prevalence of depression in congestive heart failure. *American Journal of Cardiology, 84*, 348–350. A9.

Iung, B., Cachier, A., Baron, G., et al. (2005). Decision-making in elderly patients with severe aortic stenosis: Why are so many denied surgery? *European Heart Journal, 26*, 2714–2720.

Jeon, D. S., Atar, S., Brasch, A. V., et al. (2001). Association of mitral annulus calcification, aortic valve sclerosis and aortic root calcification with abnormal myocardial perfusion single photon

emission tomography in subjects age < or =65 years old. *Journal of the American College of Cardiology, 38*, 1988–1993.

Jiang, W., Alexander, J., Christopher, E., et al. (2001). Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Archives of Internal Medicine, 161*, 1849–1856.

Jiang, W., Kuchibhatla, M., Cuffe, M. S., et al. (2004). Prognostic value of anxiety and depression in patients with chronic heart failure. *Circulation, 110*, 3452–3456.

Kahlert, P., Knipp, S. C., Schlamann, M., et al. (2010). Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: A diffusion-weighted magnetic resonance imaging study. *Circulation, 121*, 870–878.

Kala, P., Tretina, M., Poloczek, M., et al. (2013). Quality of life after transcatheter aortic valve implantation and surgical replacement in high-risk elderly patients. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia, 157*, 75–80.

Katon, W. J. (2003). Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biological Psychiatry, 54*, 216–226.

Katon, W., Sullivan, M., & Walker, E. (2001). Medical symptoms without identified pathology: Relationship to psychiatric disorders, childhood and adult trauma, and personality traits. *Annals of Internal Medicine, 134*, 917–925.

Katon, W., Unutzer, J., Fan, M. Y., et al. (2006). Cost-effectiveness and net benefit of enhanced treatment of depression for older adults with diabetes and depression. *Diabetes Care, 29*, 265–270.

Katon, W., Lin, E. H., & Kroenke, K. (2007). The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *General Hospital Psychiatry, 29*, 147–155.

Ko, D. T., Hebert, P. R., Coffey, C. S., Sedrakyan, A., Curtis, J. P., & Krumholz, H. M. (2002). Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA, 288*, 351–357.

Koenig, H. G. (1998). Depression in hospitalized older patients with congestive heart failure. *General Hospital Psychiatry, 20*, 29–43.

Lim, D. S., Reynolds, M. R., Feldman, T., et al. (2013). Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation following transcatheter mitral valve repair with the MitraClip(R) system. *Journal of the American College of Cardiology*. J Am Coll Cardiol. 2014 Jul 15;*64*(2):182–92.

Murberg, T. A., Bru, E., Svebak, S., Tveteras, R., & Aarsland, T. (1999). Depressed mood and subjective health symptoms as predictors of mortality in patients with congestive heart failure: A two-years follow-up study. *International Journal of Psychiatry in Medicine, 29*, 311–326.

Nishimura, R. A., Otto, C. M., Bonow, R. O., et al. (2014). AHA/ACC guideline for the management of patients with valvular heart disease: Executive summary: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol *63*(22):2438–2488.

Nkomo, V. T., Gardin, J. M., Skelton, T. N., Gottdiener, J. S., Scott, C. G., & Enriquez-Sarano, M. (2006). Burden of valvular heart diseases: A population-based study. *Lancet, 368*, 1005–1011.

Okamoto, Y., Motomura, N., Murashima, S., & Takamoto, S. (2013). Anxiety and depression after thoracic aortic surgery or coronary artery bypass. *Asian Cardiovascular & Thoracic Annals, 21*, 22–30.

Oxman, T. E., Freeman, D. H., Jr., & Manheimer, E. D. (1995). Lack of social participation or religious strength and comfort as risk factors for death after cardiac surgery in the elderly. *Psychosomatic Medicine, 57*, 5–15.

Pfeifer, P. M., Ruschel, P. P., & Bordignon, S. (2013). Coping strategies after heart transplantation: Psychological implications. *Revista Brasileira de Cirurgia Cardiovascular: Orgao Oficial da Sociedade Brasileira de Cirurgia Cardiovascular, 28*, 61–68.

Rabin, R., & de Charro, F. (2001). EQ-5D: A measure of health status from the EuroQol group. *Annals of Medicine, 33*, 337–343.

Rimington, H., Weinman, J., & Chambers, J. B. (2010). Predicting outcome after valve replacement. *Heart, 96*, 118–123.

Rodriguez, C. J., Bartz, T. M., Longstreth, W. T., Jr., et al. (2011). Association of annular calcification and aortic valve sclerosis with brain findings on magnetic resonance imaging in community dwelling older adults: The cardiovascular health study. *Journal of the American College of Cardiology, 57*, 2172–2180.

Rumsfeld, J. S., Havranek, E., Masoudi, F. A., et al. (2003). Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. *Journal of the American College of Cardiology, 42*, 1811–1817.

Rutledge, T., Reis, V. A., Linke, S. E., Greenberg, B. H., & Mills, P. J. (2006). Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology, 48*, 1527–1537.

Scherer, M., Himmel, W., Stanske, B., et al. (2007). Psychological distress in primary care patients with heart failure: A longitudinal study. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners, 57*, 801–807.

Shuldham, C., Goodman, H., Fleming, S., Tattersall, K., & Pryse-Hawkins, H. (2001). Anxiety, depression and functional capacity in older women with mitral valve stenosis. *International Journal of Nursing Practice, 7*, 322–328.

Simon, G. E., Katon, W. J., Lin, E. H., et al. (2005). Diabetes complications and depression as predictors of health service costs. *General Hospital Psychiatry, 27*, 344–351.

Sullivan, M., Levy, W. C., Russo, J. E., & Spertus, J. A. (2004). Depression and health status in patients with advanced heart failure: A prospective study in tertiary care. *Journal of Cardiac Failure, 10*, 390–396.

Turvey, C. L., Schultz, K., Arndt, S., Wallace, R. B., & Herzog, R. (2002). Prevalence and correlates of depressive symptoms in a community sample of people suffering from heart failure. *Journal of American Geriatrics Society, 50*, 2003–2008.

Ussia, G. P., Mule, M., Barbanti, M., et al. (2009). Quality of life assessment after percutaneous aortic valve implantation. *European Heart Journal, 30*, 1790–1796.

Vahanian, A., Alfieri, O., Andreotti, F., et al. (2012). Guidelines on the management of valvular heart disease (version 2012). *European Heart Journal, 33*, 2451–2496.

Wallby, L., Steffensen, T., Jonasson, L., Broqvist, M. (2013). Inflammatory characteristics of stenotic aortic valves: A comparison between rheumatic and nonrheumatic aortic stenosis. *Cardiology Research and Practice,* 895215.

Ware, J., Snow, K. K., & Kosinski, M. (1993). *SF-36 health survey*. Boston: New England Medical Center, The Health Institute.

Ware, J., Jr., Kosinski, M., & Keller, S. D. (1996). A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. *Medical Care, 34*, 220–233.

World Health Organization. (2010). *International statistical classification of diseases and related health problems: 10th revision*. Geneva: World Health Organization.

Zipfel, S., Schneider, A., Wild, B., et al. (2002). Effect of depressive symptoms on survival after heart transplantation. *Psychosomatic Medicine, 64*, 740–747.

Zorrilla, E. P., Luborsky, L., McKay, J. R., et al. (2001). The relationship of depression and stressors to immunological assays: A meta-analytic review. *Brain, Behavior, and Immunity, 15*, 199–226.

Zung, W. W. (1965). A self-rating depression scale. *Archives of General Psychiatry, 12*, 63–70.

The Psychosocial Impact of Syncope

Gautam Vaddadi and Marlies E. Alvarenga

Contents

Abstract

Syncope is a transient and abrupt loss of consciousness and postural tone due to a transient reduction in cerebral blood flow, typically due to a fall in blood pressure. There are many causes of syncope, and some people may suffer from recurrent and unexplained episodes. Recurrent t syncope can be challenging to diagnose and treat with the potential for severe psychosocial morbidity.

Keywords

Neurocardiogenic syncope. *See* vasovagal syncope (VVS) • Noradrenaline transporter (NET) dysfunction • Postural orthostatic tachycardia syndrome (POTS) • Psychogenic pseudosyncope (PPS) • Syncope • Causes • Prevalence • Transient loss of consciousness (TLOC) • Vasovagal syncope (VVS)

G. Vaddadi (✉)
Department of Cardiology, The Alfred Hospital, Melbourne, VIC, Australia
e-mail: drgvaddadi@gmail.com; admin@mitchamrdconsulting.com.au

M.E. Alvarenga
MonashHEART, Monash Cardiovascular Research Centre, Monash Health and Department of Medicine (SCS at Monash), Monash University, Melbourne, VIC, Australia
e-mail: marlies.alvarenga@monash.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_66

Introduction

Syncope is a transient and abrupt loss of consciousness and postural tone that is generally followed by rapid recovery without the need for major intervention (Vaddadi et al. 2007). It is due to a transient reduction in cerebral blood flow and is perhaps the most common cause of syncope in the general population. Syncope has a lifetime cumulative incidence of 35 % (Ganzeboom et al. 2006) and accounts for 1–2 % of all emergency department visits (Mathias et al. 2001). The morbidity from syncope can be profound and often underappreciated in the health-care sector, with 70 % of people with recurrent syncope suffering from impairments to their activities of daily living, 6 % have fractures, 64 % restrict driving, and 39 % may change employment (Vaddadi et al. 2007). Some studies also suggest that recurrent syncope can have the same impact on psychosocial quality of life as other major chronic illnesses.

The common causes of syncope include but are not limited to:

1. Vasovagal syncope (fainting)
2. Postural orthostatic tachycardia syndrome (POTS)
3. Heart disease such as rhythm disturbances (arrhythmias), severe valvular disease, etc.
4. Low supine systolic blood pressure
5. Medication (e.g., drugs that lower blood pressure)
6. Dehydration

Thus, it can be appreciated that causes of syncope are varied and range in risk of morbidity and mortality. Psychiatric illnesses have been touted as a possible cause of syncope. The still limited research in this area proposes that psychiatric diseases account for 1–7 % of all causes of syncope and that in psychiatric patients with medically undetermined syncope, the figures can be as high as 26 % (Gomes-Andrghetto et al. 1999). For the purpose of this chapter, we will focus on vasovagal syncope and postural tachycardia syndrome (POTS) which commonly cause recurrent syncope and result in significant psychosocial morbidity.

Vasovagal Syncope

Vasovagal syncope (VVS) or neurocardiogenic syncope is the medical term that is frequently used to describe the “common faint.” Other terms that are used and mean the same thing include neurally mediated syncope and neurally mediated hypotension. This type of syncope is physiologically manifested as an abrupt drop in blood pressure (BP) and/or heart rate (Vaddadi et al. 2010). This drop in BP causes reduced blood flow into the brain (cerebral hypoperfusion) and is the cause of the transient loss of consciousness that ensues. The underlying mechanism is controversial. All humans have the ability to faint and we appear to be unique in the animal kingdom in this regard. It is thought to be a “hard wired” neural reflex that

can be triggered, either spontaneously or more commonly by some external factor. Someone who faints at the sight of blood has had an episode of vasovagal syncope triggered by an external factor – the sight of blood, a common problem during blood donation. Other external factors include dehydration, alcohol, heat, pain, emotional stress, and fear.

Common symptoms of a vasovagal event include nausea, rising heat, palpitations, cold and clammy skin, diaphoresis, visual clouding or closing in, and the sensation of light-headedness. A brief convulsion due to cerebral hypoperfusion is common, and in fact, video EEG studies have demonstrated that these convulsive episodes can mimic epilepsy. It has been estimated that 20 % of patients being followed up in long-term hospital epilepsy clinics are misdiagnosed – many have transient loss of consciousness due to syncope and not epilepsy (Vaddadi et al. 2010).

VVS may occur as an isolated episode in an individual; many of us have fainted at least once. The challenge lies in caring for patients in whom VVS occurs repeatedly, either due to certain triggers or, worse, in a random manner without an avoidable trigger. Patients like this often struggle to get a diagnosis with recurrent VVS being poorly recognized and understood in the medical community, particularly at a primary care level. It is not uncommon for a patient to seek the input of multiple doctors over many years, and a diverse range of medical tests may be employed, some of which are probably inappropriate. This situation itself can be psychologically detrimental.

VVS is also a challenge to treat. There are limited effective therapies with no simple "magic bullet" that can be applied to every patient. Each clinical situation is unique, and a tailored approach to both diagnostic assessment and treatment is needed. Patients with recurrent VVS may have regular episodes, but it is also common for syncope to occur in a more unpredictable manner with months or even years between episodes. VVS episodes may cluster together, resulting in multiple episodes even within the same day. This can be terrifying for the patient, family, and friends alike.

Psychosocial and Quality-of-Life Impact of VVS

VVS is increasingly recognized as a chronic illness. In 1991, Linzer et al. published a valuable insight into the impairment of physical and psychosocial function in recurrent syncope (Linzer et al. 1991), utilizing the Symptom Impact Profile (SIP) and the Symptom Checklist-90-R (SCL-90-R) scales. The SIP was markedly elevated in syncope suggesting a level of impairment similar to rheumatoid arthritis or chronic low back pain. SCL-90-R scores were high – similar to those with chronic psychiatric illness. Neither age nor number of comorbid diseases correlated with measures of psychosocial function, leading the authors to suggest that syncope itself leads to psychosocial dysfunction.

These results were confirmed by Rose et al. in 2000 in a study of 136 patients, with a median number of 7.5 episodes of syncope. They found the frequency of

spells to be correlated with quality of life (QoL) in patients who had experienced more than or equal to six episodes.

In 2006 van Dijk published a much larger study of the QoL of patients with transient loss of consciousness in a population of patients that is more reflective of what is seen in routine clinical practice (van Dijk et al. 2006). It is the most comprehensive evaluation of QoL to date and provides valuable and detailed insight into the heavy burden VVS and other causes of transient loss of consciousness (TLOC) can have on our patients. The two studies referred to earlier were in a population of patients with more severe syncope. A disease-specific scale assessing QoL was employed, consisting of 11 yes/no questions, assessing the degree to which syncope interferes with a patient's daily life and three 8-point Likert-scale questions that assess a patient's fear and worry about syncope. A syncope dysfunction score (SDS) was calculated, which is a mean of the composite of the impairment score and the fear-worry score.

In this study transient loss of consciousness (TLOC) (syncope being a very common cause) had a serious effect on the QoL of patients. Patients had significantly lower scores on all scales compared to the reference population, with moderate to large effect sizes. Disease-specific QoL was seriously affected, with an average impairment in 33 % of applicable areas. The QoL of patients presenting with TLOC is comparable to that of patients with chronic arthritis or recurrent moderate depressive disorder.

Gender, higher level of comorbidity, and the presence of presyncopal episodes (feeling like one may faint but not actually losing consciousness) were associated with poorer physical functioning. Presyncopal episodes predict worse mental functioning and disease-specific QoL. Patients with a longer period of complaints show better mental functioning and disease-specific QoL than those with a recent onset of symptoms in this study. This suggests that patients with new-onset syncope should be more aggressively supported and counseled in the hope of having a positive impact on QoL. The presence of more than one episode of syncope in the year before presentation is associated with worse disease-specific QoL. QoL scores, as would be expected, correlate well with presyncope and syncope frequency.

Patients with recurrent syncope, even though they should be quite "normal" between episodes, experience significant physical limitations comparable to that of chronic illnesses. This is probably due to a range of factors such as fear of a recurrence, perceived risk of injury, and legal restrictions, for instance, on driving, that may limit the patient in performing daily physical activities and embarrassment should syncope occur in a public setting. Patients with syncope and their family members often worry that syncope may occur when the patient is alone and help may not be accessible. It is not uncommon for doctors to be dismissive of VVS because it is not lethal. The psychosocial burden of disease may be underrecognized or dismissed which is usually to the detriment of the patients' long-term health.

Psychological triggers such as anxiety and emotional stress are well-recognized precipitants for VVS. Anxiety and depression may be caused by syncope and can

also act as a trigger for syncope. It is therefore essential to engage in this space effectively, utilizing standard treatment techniques.

Postural Orthostatic Tachycardia Syndrome (POTS)

POTS is a diverse and challenging condition that has only become more widely recognized over the last 20 years (Vaddadi et al. 2007; Raj 2006). It is characterized by a marked and sustained increase in heart rate when going from lying to standing (>30 beats per minute increase over supine heart rate). In addition to the marked tachycardia, presyncope, and syncope, patients with POTS often complain of lightheadedness, fatigue, and difficulty in concentrating. It affects women substantially more commonly than men and typically presents in those aged 15–50 years. The mechanism driving presyncope and syncope in this patient group is not understood because blood pressure is usually normal or high during the episodes which should in theory result in "normal" cerebral perfusion. Some studies suggest abnormalities in the sympathetic nervous system (Lambert and Lambert 2014; Lambert et al. 2008) and with cerebral blood flow (Ocon et al. 2009; Del Pozzi et al. 2014a, b; Stewart et al. 2015), but no study has conclusively identified the mechanism which remains speculative at best. Some researchers have endeavored to "subtype" POTS. This has been controversial and challenging, but the most reasonable two subtypes from a clinical perspective are "neuropathic" POTS which is characterized by reduced adrenergic vasoconstriction and may have an overlap with various connective tissue disorders that reduce the ability of the peripheral vessels to constrict, promoting venous pooling when standing, and the "hyperadrenergic" POTS characterized by enhanced arterial vasoconstriction (Ross et al. 2014).

POTS patients often struggle with chronic fatigue, difficulty concentrating that is often worse during orthostatic stress (Ross et al. 2013) (upright posture), brain fog, and anxiety, and there is generally a significant impact on activities of daily living, educational prospects, and employment. Again, the mechanisms driving this are unknown. Cognitive impairment is commonly reported as one of the top complaints of young patients with POTS and is often referred to as "brain fog" by patients (Ross et al. 2013). Brain fog is an imprecise term and is thought to be similar in meaning to mental fatigue. It is characterized by being forgetful and cloudy with difficulties in focusing, thinking, and attention. Although brain fog is often worse when standing, lying down does not consistently ameliorate the symptom sufficiently to normalize performance on tasks a patient with POTS wishes to achieve. Over 80 % of patients believe that their brain fog is brought on by prolonged or intense concentration, while almost 70 % of patients feel this can trigger brain fog even when lying down (Ross et al. 2013). The top triggers for brain fog are fatigue and sleep deprivation. Sleep disorders appear to be common in patients with POTS, affecting at least 30 % of subjects. Common diagnoses include insomnia, sleep apnea, and restless leg syndrome. Sleep disturbance itself is well recognized to

impair various cognitive functions which may exacerbate the neurocognitive impairment in POTS. Dehydration appears to worsen brain fog and therapy with intravenous saline improves it. Caffeine is reported by patients with POTS to worsen and improve brain fog equally, and in our experience, the use of caffeine to treat their brain fog becomes the choice of the patient. Theoretically caffeine may make POTS worse by inducing a diuresis (causing dehydration) and elevating heart rate.

A small but comprehensive study of patients with POTS has shown that commonly POTS patients present with depressive symptoms, elevated anxiety, and increased anxiety sensitivity (Anderson et al. 2014). They also have a poorer subjective health-related quality of life in both the physical and mental health domains. In this study patients with POTS performed worse in tests of current intellectual functioning (verbal and nonverbal IQ), and in measures of focused attention (digits forward) and short-term memory (digits back), test results were influenced largely by years of education and the underlying level of depression and anxiety rather than the categorical diagnosis of POTS. Acute changes in cognitive performance in response to head-up tilt were evident in the POTS patients (Anderson et al. 2014).

Patients with POTS experienced markedly diminished health-related quality of life across both physical and mental health domains. It is recognized that the prevalence of depression is elevated in patients with chronic, physical illnesses such as heart disease, stroke, cancer, and diabetes mellitus (Clarke and Currie 2009). POTS patients also frequently suffer from major depression, while McGrady et al. found that subjects who had a positive tilt table test for autonomic dysfunction (autonomic dysfunction may cause syncope) had higher depression scores (McGrady et al. 2001). Depressive symptoms have been associated with distractibility and impaired cognitive processing, particularly in the context of higher cognitive abilities such as executive processing, organization, and recall of information. Raj et al. have shown that patients with POTS scored worse than controls on Conners' adult attention deficit hyperactivity disorder (ADHD) inattention/memory problem subscale (Raj et al. 2009). It is likely that the association between depression and cognitive performance reflects the underlying neurobiology of depression, with alterations in brain monoamines influencing both depression and cognition (Lambert et al. 2000; Austin et al. 2001; Schmitt et al. 2006; Chalermpalanupap et al. 2013; Barton et al. 2008; Brown et al. 2009). Noradrenaline transporter (NET) dysfunction is evident in patients with POTS (Lambert et al. 2008; Robertson et al. 2000; Shannon et al. 2000) and in untreated patients with major depressive disorder (Barton et al. 2007). Interestingly, genetic variation in the NET gene has been associated with deficits in memory and attention in patients with ADHD (Sengupta et al. 2012; Thakur et al. 2012). Although coding mutations in the NET gene in POTS are rare, epigenetic modification of the NET gene may impact NET expression in POTS (Bayles et al. 2012).

Given the distinctive feature of POTS, namely, the marked elevation in heart rate on standing and increased anxiety sensitivity, particularly in relation to cardiac features, is perhaps not surprising and is consistent with some (Benrud-Larson

et al. 2002, 2003; Thieben et al. 2007) but not all previously reported data (Raj et al. 2009). Individuals with disorders of postural syncope may be more likely to focus attention on the negative consequences of fainting, a preoccupation which subsequently contributes to reduction in perceived health-related quality of life (McGrady et al. 2001). Hypervigilance to somatic sensations has been associated with greater limitations on day-to-day activities and increased perception of disability (Benrud-Larson et al. 2003).

Reduction in cognitive performance is significantly associated with the magnitude of the change in heart rate during head-up tilt, and patients with POTS display significantly elevated anxiety sensitivity in relation to cardiac symptoms; it is possible that, in the context of increased vigilance to somatic sensations, attention is diverted and impaired cognitive performance follows (Anderson et al. 2014); indeed, fear of arousal may amplify the physiological signs associated with syncope and lead to an increase in the fear associated with syncope (Rapee et al. 1992).

Treatment of POTS involves the implementation of a disease management plan encompassing education, pharmacotherapy, and exercise. Remaining hydrated; avoidance of excessive heat; wearing compression tights in order to reduce venous pooling; administration of fluid retaining agents, low-dose propranolol, midodrine, and acetylcholinesterase inhibitors; and exercise are all important elements of the POTS treatment arsenal (Vaddadi et al. 2007; Ross et al. 2014; Anderson et al. 2014; Fu and Levine 2015; Mallien et al. 2014; Figueroa et al. 2014). Psychological interventions aimed at facilitating stress reduction such as relaxation techniques and cognitive behavior therapy, with an emphasis on identifying and restructuring unhelpful beliefs, primarily those catastrophizing consequences of physical symptoms from standing, may aid in recovery and facilitate uptake and adherence of other treatment modalities (Anderson et al. 2014). Indeed, helping patients with syncope to identify and restructure unhelpful beliefs, address maladaptive somatic attention, and reduce avoidance of certain situations has been shown to be helpful (Gracie et al. 2004).

Psychogenic Pseudosyncope

In psychiatric illnesses such as somatization disorders and panic disorders, dizziness, vertigo, or syncope is usually included as a clinical finding. Anxiety over the feeling or experience of syncope leads patients to see a range of specialists including primary care physicians, cardiologists, and neurologists. Psychogenic pseudosyncope (PPS) differs from syncope in that it appears that there is a loss of consciousness (LOC) when in fact there is no true LOC. Thus, the patient might demonstrate orthostatic intolerance during a tilt table test but with no significant concomitant hemodynamic abnormalities. The illness spectrum also encompasses non-epileptic seizures or pseudoseizures, indicating that PPS might be unrepresented as a syndrome. There is limited literature describing PPS (van Dijk and Wieling 2013), and the reported incidence is low (0–8 %). This is in contrast to pseudoseizures which are well recognized and thought to account for up to 30 % of

assessments for epilepsy (Raj et al. 2014). In our clinical experience, PPS is most commonly seen in adolescent females although it can affect all age groups and is not gender exclusive. It is likely that most cases of PPS represent conversion disorder (Raj et al. 2014).

Traditionally, it has been a clinical challenge to recognize functional neurological symptom disorders such as conversion disorder. In assessing syncope the measurement of psychological constructs is narrow and with a focus on simply identifying the presence or absence of distress (Gracie et al. 2004). Measures such as the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI) provide a measure of the depth of depression and anxiety those affected with the syncope presentation might be experiencing, but they do not provide an understanding of the reasons why someone might be depressed or anxious and how this impacts on their syncope presentation. Therefore, a psychiatric interview of the patient is recommended to ascertain whether the presentation of syncope is part of a psychosomatic manifestation, such as conversion disorder. Although the precise cause of a conversion disorder is unknown, it seems that the part of the brain that controls muscles and senses may be involved, and it may be the brain's way of reacting immediately to something that seems like a threat in what might be an extreme manifestation of the "fight/flight response" (Coversion Disorder). Indeed, conversion disorders typically follow a traumatic event or occur in the context of psychological conflict (Raj et al. 2014).

Raj et al. (2014) published a leading text on the diagnosis and management of PPS and reported a high prevalence of comorbidity between syncope and psychopathology. Research into the quality of distress in patients experiencing nonorganic syncope proposed that anxiety and characteristics associated with anxiety (avoidance, concern about people and situations, high personal standards, and overall sensitivity to self and environment) appeared to be more prominent than depression in this patient cohort (Shafffer et al. 2001). Anxiety disorders such as somatoform disorders distinguish themselves by a high level of interoceptive acuity on the part of the patient. Indeed, it has been suggested that interpretive cognitive bias for ambiguous interoceptive stimuli may be a risk factor for the development of these sorts of anxiety presentations (Richards et al. 2001). Therefore, there is further scope in the research literature to more carefully assess constructs of anxiety sensitivity and the experience of syncope. Such analysis would be particularly significant in better understanding the nature of PPS and guiding more effective treatment interventions.

Treatment guidelines for PPS proposed by Raj et al. (2014) outline the importance of psychoeducation and the inclusion of psychotherapy as the treatment of choice in these patients. Cognitive behavioral therapy (CBT), which addresses the patient's thoughts, feelings, and associated behaviors, is particularly identified as an effective form of intervention (LaFrance et al. 2013). It is in the context of CBT that patients can also learn stress management and relaxation techniques as well as address avoidance behaviors, insomnia, as well as fear of anticipation to faint. The use of pharmacotherapy in PPS has been inconsistent in its success, although Linzer et al. (1992) stated that clonazepam and fluoxetine reduced the symptoms of

syncope in most patients (Linzer et al. 1992). In perhaps the same way as with somatoform disorders, pharmacotherapy might be best seen as an adjunct to psychotherapy in bringing about successful outcomes in PPS patients. An analysis of the literature points to additional studies required in exploring PPS phenomena.

Conclusions

Syncope is a common and challenging problem to diagnose and treat. This is compounded by serious adverse psychosocial effects and comorbid psychiatric illness. In order to effectively treat a patient with syncope, significant clinical effort needs to be made in applying comprehensive diagnostic and therapeutic strategies that fully encompass all aspects of mental health care. In this regard cardiologists can benefit from collaborating with mental health professionals. Failure to do so will for many patients result in inadequate treatment that can have a major impact on long-term quality of life.

References

Anderson, J. W., et al. (2014). Cognitive function, health-related quality of life, and symptoms of depression and anxiety sensitivity are impaired in patients with the postural orthostatic tachycardia syndrome (POTS). *Frontiers in Physiology, 5*, 230.

Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression: Possible implications for functional neuropathology. *British Journal of Psychiatry, 178*, 200–206.

Barton, D. A., et al. (2007). Sympathetic activity in major depressive disorder: Identifying those at increased cardiac risk? *Journal of Hypertension, 25*(10), 2117–2124.

Barton, D. A., et al. (2008). Elevated brain serotonin turnover in patients with depression: Effect of genotype and therapy. *Archives of General Psychiatry, 65*(1), 38–46.

Bayles, R., et al. (2012). Epigenetic modification of the norepinephrine transporter gene in postural tachycardia syndrome. *Arteriosclerosis, Thrombosis, and Vascular Biology, 32*(8), 1910–1916.

Benrud-Larson, L. M., et al. (2002). Quality of life in patients with postural tachycardia syndrome. *Mayo Clinic Proceedings, 77*(6), 531–537.

Benrud-Larson, L. M., et al. (2003). Correlates of functional disability in patients with postural tachycardia syndrome: Preliminary cross-sectional findings. *Health Psychology, 22*(6), 643–648.

Brown, A. D., Barton, D. A., & Lambert, G. W. (2009). Cardiovascular abnormalities in patients with major depressive disorder: Autonomic mechanisms and implications for treatment. *CNS Drugs, 23*(7), 583–602.

Chalermpalanupap, T., et al. (2013). Targeting norepinephrine in mild cognitive impairment and Alzheimer's disease. *Alzheimer's Research & Therapy, 5*(2), 21.

Clarke, D. M., & Currie, K. C. (2009). Depression, anxiety and their relationship with chronic diseases: A review of the epidemiology, risk and treatment evidence. *Medical Journal of Australia, 190*(7 Suppl), S54–S60.

Coversion Disorder. http://www.mayoclinic.org/diseases-conditions/conversion-disorder/basics/causes/con-20029533. Accessed Apr 2015.

Del Pozzi, A. T., et al. (2014a). Blunted cerebral blood flow velocity in response to a nitric oxide donor in postural tachycardia syndrome. *American Journal of Physiology Heart and Circulatory Physiology, 307*(3), H397–H404.

Del Pozzi, A. T., et al. (2014b). Reduced cerebral blood flow with orthostasis precedes hypocapnic hyperpnea, sympathetic activation, and postural tachycardia syndrome. *Hypertension, 63*(6), 1302–1308.

Figueroa, R. A., et al. (2014). Acute volume loading and exercise capacity in postural tachycardia syndrome. *Journal of Applied Physiology (1985), 117*(6), 663–668.

Fu, Q., & Levine, B. D. (2015). Exercise in the postural orthostatic tachycardia syndrome. *Autonomic Neuroscience, 188*, 86–89.

Ganzeboom, K. S., et al. (2006). Lifetime cumulative incidence of syncope in the general population: A study of 549 Dutch subjects aged 35–60 years. *Journal of Cardiovascular Electrophysiology, 17*(11), 1172–1176.

Gomes-Andrghetto, A., John, A. B., Neuhaus-Barbisan, J., Vernet, & Taborda, J. G. (1999). Medically unexplained syncope and its relationship to psychiatric disorders. *Arquivos Brasileiros de Cardiologia, 72*(6), 756–760.

Gracie, J., Baker, C., Freeston, M. H., & Newton, J. L. (2004). The role of psychological factors in the aetiology and treatment of vasovagal syncope. *Indian Pacific and Electrophysiology, 4*(2), 79–84.

LaFrance, W. C., Jr., Reuber, M., & Goldstein, L. H. (2013). Management of psychogenic nonepileptic seizures. *Epilepsia, 54*(1), 53–67.

Lambert, E., & Lambert, G. W. (2014). Sympathetic dysfunction in vasovagal syncope and the postural orthostatic tachycardia syndrome. *Frontiers in Physiology, 5*, 280.

Lambert, G., et al. (2000). Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: Evidence in support of the catecholamine hypothesis of mood disorders. *Archives of General Psychiatry, 57*(8), 787–793.

Lambert, E., et al. (2008). Altered sympathetic nervous reactivity and norepinephrine transporter expression in patients with postural tachycardia syndrome. *Circulation. Arrhythmia and Electrophysiology, 1*(2), 103–109.

Linzer, M., et al. (1991). Impairment of physical and psychosocial function in recurrent syncope. *Journal of Clinical Epidemiology, 44*(10), 1037–1043.

Linzer, Pontinen, M., Divine, G. W., & Estes, N. A. M. (1992). Medically unexplained syncope: Relationship to psychiatric illness. *American Journal of Medicine, 92*(1A), 1A–18S.

Mallien, J., et al. (2014). Sleep disturbances and autonomic dysfunction in patients with postural orthostatic tachycardia syndrome. *Frontiers in Neurology, 5*, 118.

Mathias, C. J., Deguchi, K., & Schatz, I. (2001). Observations on recurrent syncope and presyncope in 641 patients. *Lancet, 357*(9253), 348–353.

McGrady, A., et al. (2001). Psychological and physiological factors associated with tilt table testing for neurally mediated syncopal syndromes. *Pacing and Clinical Electrophysiology, 24*(3), 296–301.

Ocon, A. J., et al. (2009). Decreased upright cerebral blood flow and cerebral autoregulation in normocapnic postural tachycardia syndrome. *American Journal of Physiology Heart and Circulatory Physiology, 297*(2), H664–H673.

Raj, S. R. (2006). The postural tachycardia syndrome (POTS): Pathophysiology, diagnosis & management. *Indian Pacing Electrophysiology Journal, 6*(2), 84–99.

Raj, V., et al. (2009). Psychiatric profile and attention deficits in postural tachycardia syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry, 80*(3), 339–344.

Raj, V., et al. (2014). Psychogenic pseudosyncope: Diagnosis and management. *Autonomic Neuroscience, 184*, 66–72.

Rapee, R. M., Sandeson, W. C., McCauley, P. A., et al. (1992). Differences in reported symptom profile between panic disorder and other DSM-III anxiety disorders. *Behaviour Research and Therapy, 30*, 45–52.

Richards, J. C., Austin, D., & Alvarenga, M. E. (2001). Interpretation of ambiguous interceptive stimuli in panic disorder and non-clinical panic. *Cognitive Therapy and Research, 25*(3), 235–246.

Robertson, D., et al. (2000). Orthostatic intolerance and the postural tachycardia syndrome: Genetic and environment pathophysiologies. Neurolab autonomic team. *Pflügers Archiv, 441* (2–3 Suppl), R48–R51.

Ross, A. J., et al. (2013). What is brain fog? An evaluation of the symptom in postural tachycardia syndrome. *Clinical Autonomic Research, 23*(6), 305–311.

Ross, A. J., et al. (2014). A double-blind placebo-controlled cross-over study of the vascular effects of midodrine in neuropathic compared with hyperadrenergic postural tachycardia syndrome. *Clinical Science (London), 126*(4), 289–296.

Schmitt, J. A., et al. (2006). Serotonin and human cognitive performance. *Current Pharmaceutical Design, 12*(20), 2473–2486.

Sengupta, S. M., et al. (2012). Differential association between the norepinephrine transporter gene and ADHD: Role of sex and subtype. *Journal of Psychiatry and Neuroscience, 37*(2), 129–137.

Shafffer, C., Jackson, L., Larecki, S., et al. (2001). Characteristics, perceived stressors and coping strategies of patients who experience neurally medicated syncope. *The American Journal Acute and Critical Care, 30*, 244–249.

Shannon, J. R., et al. (2000). Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. *New England Journal of Medicine, 342*(8), 541–549.

Stewart, J. M., et al. (2015). Oscillatory cerebral blood flow is associated with impaired neurocognition and functional hyperemia in postural tachycardia syndrome during graded tilt. *Hypertension, 65*(3), 636–643.

Thakur, G. A., et al. (2012). Comprehensive phenotype/genotype analyses of the norepinephrine transporter gene (SLC6A2) in ADHD: Relation to maternal smoking during pregnancy. *PloS One, 7*(11), e49616.

Thieben, M. J., et al. (2007). Postural orthostatic tachycardia syndrome: The Mayo clinic experience. *Mayo Clinic Proceedings, 82*(3), 308–313.

Vaddadi, G., et al. (2007). Postural syncope: Mechanisms and management. *Medical Journal of Australia, 187*(5), 299–304.

Vaddadi, G., Corcoran, S. J., & Esler, M. (2010). Management strategies for recurrent vasovagal syncope. *Internal Medicine Journal, 40*(8), 554–560.

van Dijk, J. G., & Wieling, W. (2013). Pathophysiological basis of syncope and neurological conditions that mimic syncope. *Progress in Cardiovascular Diseases, 55*(4), 345–356.

van Dijk, N., et al. (2006). Clinical factors associated with quality of life in patients with transient loss of consciousness. *Journal of Cardiovascular Electrophysiology, 17*(9), 998–1003.

Psychological Responses to Acute Coronary Syndrome

Alyna Turner and Adrienne O'Neil

Contents

A. Turner (✉)
IMPACT SRC, School of Medicine, Deakin University, Geelong, VIC, Australia

School of Medicine and Public Health, The University of Newcastle, Callaghan, NSW, Australia

Department of Psychiatry, University of Melbourne, Parkville, VIC, Australia
e-mail: alyna.turner@newcastle.edu.au

A. O'Neil
Melbourne School of Population and Global Health, The University of Melbourne, Parkville VIC, USA

School of Public Health and Preventive Medicine, Monash University, Clayton, VIC, USA

IMPACT Strategic Research Centre, Deakin University, Geelong, VIC, USA
e-mail: a.oneil@deakin.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_21

Abstract

Psychological reactions to a cardiac event differ among patients, impacting upon individual presentation and recovery. Cognitive response to symptoms and resulting coping mechanisms will impact on how quickly a patient will seek help, comprehend, and adjust to their condition and engage in interpersonal relationships. Negative cognitive responses can result in, or be a product of, common mental health issues often seen following acute coronary syndrome including adjustment disorder, depression, anxiety, stress, trauma, anger, or hostility. The increasing recognition of the link between these negative emotions and cardiac disease has increased the focus on whether treatment can mitigate negative outcomes. Findings highlight the importance of elucidating beliefs and understanding around illness and targeting interventions appropriately to modify any maladaptive beliefs. This includes implementing routine screening processes that identify patients at risk of persistent mental health problems.

Keywords

Acute coronary syndrome • Acute myocardial infarction • Illness perceptions • Coping • Adjustment • Depression • Anxiety • Anger • Post-traumatic stress • Interpersonal relationships

Introduction

Acute coronary syndrome (ACS; acute myocardial infarction [AMI] or unstable angina) may be the first indication that a person is living with coronary heart disease (CHD). For others, it will be a new presentation of a known chronic condition. Physical recovery from ACS will depend on a number of factors: the extent of myocardial damage and complications, course of treatment including (non)invasive interventions such as coronary artery bypass graft surgery or PCI, and other factors such as age, overall health, and coexisting conditions. Similarly, the cognitive, emotional, and behavioral reactions to ACS vary between individuals. In 1966, Rosen and Bibring wrote that "Fifty male patients. . .hospitalized because of heart attack, showed striking differences in their overt psychological responses to their illness. Responses ranged from frank depression to cheerfulness, from extreme anxiety to casualness, and from scrupulous cooperation with the medical regimen to active defiance" (Rosen and Bibring 1966).

Qualitative and quantitative studies over the last five decades have expanded on these early findings (Barnason et al. 2012). Psychological responses influence presentation and recovery from the point of onset of cardiac symptoms. The cognitive response to symptoms and resulting coping mechanisms will impact on help-seeking behaviors. Any delay in seeking treatment will potentially affect the degree of damage and resulting recovery. During recovery and beyond, ACS is considered by many to be life changing (Groleau et al. 2010). The initial post-event

period can be marked by emotional shock, particularly at the speed of the event (Astin et al. 2009), feeling overwhelmed and powerless, and finding the situation chaotic and dealing with a loss of independence (Kerr and Fothergill-Bourbonnais 2002). Initially, many have difficulty making sense of their condition, lack knowledge and understanding, and perceive their condition as acute and curable (Astin et al. 2009). For many, developing an understanding of the condition may lead to positive transitions, including adoption of recommended treatments and lifestyle changes, and shifts in values, responsibilities, and identity (Groleau et al. 2010; Gulanick et al. 1998).

Concurrently, patients often experience ongoing physical symptoms, particularly in the ensuing 3–4 months, including persistent chest pain, dyspnea or shortness of breath, palpitations, dizziness, and swelling in the lower extremities (Barnason et al. 2012). Other less anticipated symptoms include fatigue, exhaustion or tiredness, sleep disturbance, gastrointestinal distress, and appetite problems, all of which impact day-to-day functioning. For example, people with fatigue following ACS have more limited physical activity and impaired physical functioning, as well as greater interference of usual routines and activities (Barnason et al. 2012). Unsurprisingly, fatigue is also associated with reduced quality of life (Brink et al. 2012).

ACS survivors with persistent depression symptoms have reported that living with physical limitations contribute to low mood (Grace et al. 2005). Other factors exacerbating depressive symptoms include uncertainty around the future, knowledge of their cardiac condition, rehospitalization, and living with the prescribed treatments for coronary heart disease (adverse effects of medication, quitting smoking, and dietary changes) (Grace et al. 2005). Participants in the UPBEAT-UK study also identified a range of interpersonal, health, and control losses that they believed linked CHD and depression (see Fig. 1) (Simmonds et al. 2013). While some patients experience persistent depression post-ACS, for most, symptoms will either be sufficiently mild to result in little or no impact on an individual's day-to-day life or will be transitory, resolving spontaneously over the first 4 months (Barnason et al. 2012). In addition to depression, people recovering from ACS also report feelings of anxiety, uncertainty, apprehensiveness, ambiguity, and insecurity; apprehension and fearfulness, particularly of a recurrence or deterioration in health; or of boredom and inertia. Dependency and feelings of overprotection, discouragement, tearfulness, and powerlessness are common, as are anger and frustration (Barnason et al. 2012). Normal day-to-day activities may be attached to new fears and uncertainties, for example, avoiding sexual activity for fear of having another AMI or uncertainty about safe levels of physical activity. As with depression, for a small proportion of people, symptoms of anxiety- or adjustment-related emotional distress may be more severe or pervasive, or the trauma of the event may trigger a more severe post-traumatic stress response. An acute cardiac event can also impact on an individual's social network which can influence the survivor's recovery and quality of life. This chapter will review each of these important issues.

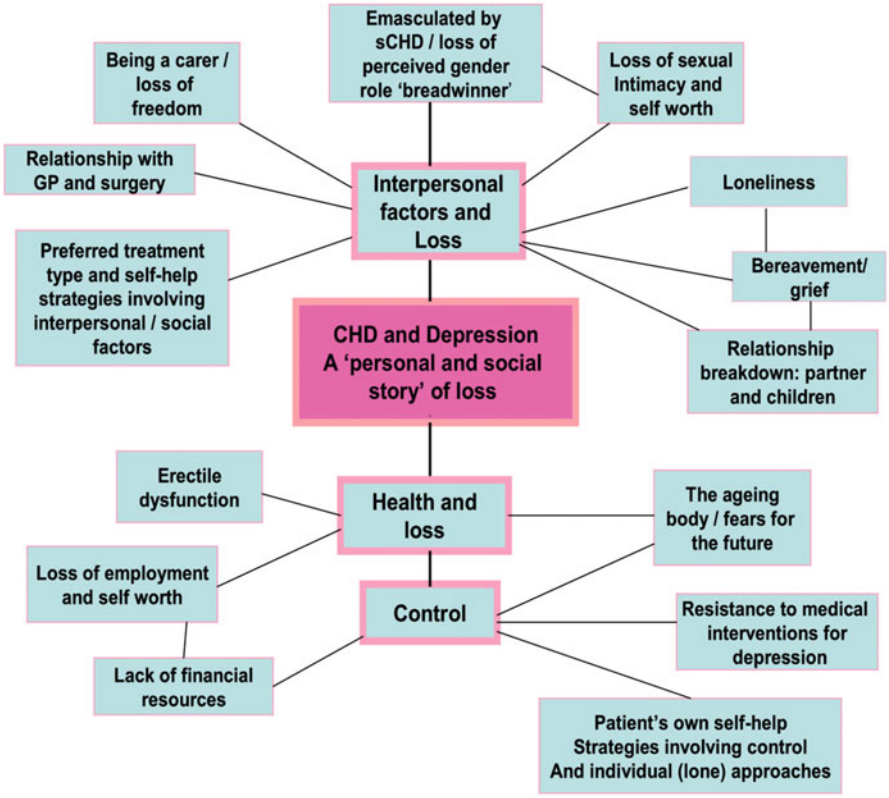


Fig. 1 A model of participants' perceptions of links between coronary heart disease and depression (Originally published by BioMed Central in Simmonds et al. (2013))

Seeking Treatment for an ACS

"Decision delay" refers to the delay between the time of onset of cardiac symptoms until the decision is made to seek professional care. A range of factors have been associated with decision delay time. Female gender and increased age are associated with increased delay time (Khraim and Carey 2009). Gender differences may be due to the perception of heart disease as being a "male" problem (Higginson 2008), the onset of heart disease at an older age in women than men, and also their difference in symptom presentation which may affect symptom recognition and interpretation. Women are less likely to experience chest pain at all during AMI, while symptoms that are more intense, continual, and have a fast onset are associated with shorter delay (Khraim and Carey 2009). Preexisting mental health conditions and traits have been associated with increased delay, including depression (Bunde and Martin 2006), PTSD (Newman et al. 2011), neuroticism (Rosenfeld 2004), and alexithymia (Preti et al. 2013). Physical health conditions

may affect decision-making, with some studies finding past AMI associated with reduced delay (potentially due to knowledge and experience), while a history of angina and diabetes was associated with longer delay (Khraim and Carey 2009).

Other factors associated with delay include context (onset while at home or alone), cognitive factors (symptom expectations, perceived control over symptoms, knowledge, and perceived threat), affective factors (fear of consequences or troubling others, denial, embarrassment), and behavioral factors (contacting emergency services vs. primary healthcare provider vs. others; choosing to wait it out or trying to relax) (Khraim and Carey 2009). Feelings of anxiety and vulnerability have been reported acting as both triggers and barriers to seeking treatment (Johansson et al. 2007). People may delay seeking treatment as they believe they could never have an AMI (Harralson 2007), or symptoms are minimized, denied, or misattributed to other conditions (Hwang and Jeong 2012), and/or they prefer to self medicate (Higginson 2008). Treatment-seeking decisions may further be influenced by healthcare factors, including access to, or knowledge about, emergency services and treatment and past experience with services (Kaur et al. 2006). Other sociocultural factors such as the family situation, social support, cultural beliefs, and practices may also impact on decision-making.

Psychosocial support and guidance from the environment are often fundamental to the patient's management of the situation (Johansson et al. 2007). Often, relatives will act as the decision-maker to seek care, even providing transportation to hospital to expedite admission (Henriksson et al. 2007). One study found that if the patient's partner understands the severity of the situation, has knowledge, and was rational and consulted with others as needed, prehospital time is reduced. Conversely, delay can occur when a partner restrained their own emotions and sought agreement from the partner as a result of established roles and experiences (Johansson et al. 2008).

Understanding ACS

During recovery from ACS, survivors will seek to understand what happened and why, to make sense of the event and their condition, the cause, and the personal significance of the illness and to answer the question "Why me?" (Baldacchino 2010). Cognitive representations of an illness constructed by the patient, including beliefs about symptom constellation (identity), cause of the condition (cause), condition duration (timeline), lifetime consequences of the condition (consequences), and the extent to which it can be cured or controlled (control/cure), are collectively known as illness perceptions (Cameron and Leventhal 2003). Additionally, the extent to which the patient's illness makes sense (illness coherence) has been found to be important, particularly if self-management ideas differ from those of their healthcare provider (Gardner et al. 2003). Illness perceptions can be transient depending on the stage of illness, diagnosis, and information given and are thus amendable to intervention (Broadbent et al. 2009).

A meta-analysis by Foxwell and colleagues (2013) found that illness perceptions in people with CHD were associated with physical, social, and emotional aspects of

quality of life (QOL) and depression and anxiety. Physical and emotional QOL were positively associated with identity, consequences, coherence, perceived personal and treatment control, chronicity, and a belief that stress caused the illness. Social QOL was associated with perceived consequences, coherence, and a cyclical timeline. Elevated depression and anxiety were associated with lower illness coherence, lower perceived personal control, and increased perception of chronicity; the former also contributed to perceived negative illness consequences and a belief that stress or personality caused the cardiac condition. Anxious patients attributed more symptoms to their condition. Another study of AMI survivors found that higher perceived risk of future AMI was associated with illness perceptions including worse consequences of the AMI and lower beliefs in the benefits of treatment, as well as higher levels of anxiety (Broadbent et al. 2006). Perceived risk was not associated with demographics (age or sex), history of previous AMI, or risk factors (family history of CHD, diabetes, current smokers).

Coping with an ACS

Coping refers to the use of an array of dispositions and cognitive, emotional, and behavioral strategies that people draw on to maintain well-being and avoid harm in the face of significant internal and external demands and stressors such as those precipitated by physical illness. ACS survivors will draw on a range of coping strategies throughout their recovery period. Coping strategies and behaviors are flexible and situational, influenced by duration, severity, and nature of the crisis, trauma, or loss (Lazarus and Folkman 1984). Early taxonomies of coping included problem-solving coping (active efforts to address the stressor) and emotion-focused coping (focusing on managing the resulting emotions due to the assumption that the problem faced cannot be modified) (Lazarus and Folkman 1984). Additional coping styles have since been proposed; however, many still fit broadly into the problem-focused or emotion-focused styles. Denial, a form of avoidance coping (fitting into the emotion focused style), is often mentioned with regard to people with a new diagnosis of a chronic illness. Interestingly, denial has been associated with positive emotional outcomes in the short term following a cardiac event, possibly due to protecting the person from taking on too much new information at once (Bennett and Boothby 2007). In the longer term, avoidant- and emotion-focused coping have been associated with poorer physical and emotional outcomes (Chiavarino et al. 2012; De Fazio et al. 2012). Patients who feel powerless as a result of the illness, and those who have expectations that healthcare providers are responsible for their care, tend to display poorer coping strategies. These patients are less likely to make significant lifestyle modifications following ACS (Bonsaksen et al. 2012).

ACS patients most commonly use adaptive, problem-solving style coping strategies, such as optimistic coping, active coping, active problem solving,

positive reappraisal, and seeking social support (Bennett and Boothby 2007), and these coping strategies are associated with positive outcomes. For example, social support has been found to be associated with lower levels of anxiety, while people with more coping strategies were more likely to attend cardiac rehabilitation (French et al. 2006). Women have been shown to more often use supportive coping and more coping strategies overall, while men more heavily rely on their spouses and use more informational and instrumental support (Bennett and Boothby 2007).

Spirituality (existential and religious coping) may play a role in coping (Baldacchino et al. 2012). Walton reported that AMI survivors in a predominantly Christian region of the United States described going through five spiritual phases during recovery: facing mortality, relinquishing fear and turmoil, identifying and enacting lifestyle changes, seeking God's purpose, and finding meaning in everyday life (Walton 2002). Positive associations have been shown between religious coping and spirituality and outcomes in people with chronic illness, such as more effective coping and greater health-related QOL (Mueller et al. 2001). Cardiac patients specifically have identified religion as a source of strength and comfort following the event (Kamm-Steigelman et al. 2006). However, another US study found that measures of religiosity and religious coping were not associated with quality of life or self-esteem, while discontent coping (a sense of anger or distance from God) was associated with lower levels of physical self-efficacy at the end of cardiac rehabilitation (Miller et al. 2007). Park et al. found that positive and negative forms of religious coping were associated with increased depression symptoms in hospital and at 1 month follow-up and argued that active coping strategies be promoted in the recovery period (Park and Dornelas 2012). Illness perceptions, specifically helplessness and illness acceptance, can mediate the relationship between intrinsic religiousness and subjective health in chronic cardiac patients (Karademas 2010). A recent meta-analysis of the effects of spiritual interventions within cardiac rehabilitation programs reported encouraging findings; however, more studies are required (Nadarajah et al. 2013).

A qualitative study found a sense of control is central to coping for ACS patients (Salminen-Tuomaala et al. 2012). Other factors promoting coping include personal coping resources, sense of coherence, acceptance of the situation, spiritual conviction and prayer, a safe care environment and rapid alleviation of symptoms, keeping up to date via information and counseling and test results, support from and sharing with fellow patients, encouraging the patient room atmosphere, and emotional support from family. Factors that interfere with coping include experiencing acute, serious illness and difficult symptoms, different fears, denial of the situation, sense of losing control over the situation, depression and powerlessness, strange hospital environment and culture, constant waiting and state of readiness, lack of emotional support from healthcare staff, lack of open communication between the patient and family, hiding the seriousness of the situation from family, and difficulties speaking about the illness with the family.

Adjustment to an ACS

Grief and Loss

Illness perceptions and coping strategies impact on the process of adjustment following ACS and vice versa. The process of adjustment considers the illness itself, treatments and lifestyle changes, and impact on lifestyle, family, work, finances, and other aspects of day-to-day life. A majority of ACS patients will adjust positively, displaying a capacity to cope with illness and adapt their lifestyle to imposed limitations using strategies including acceptance, appreciation, or changing their lifestyle to adapt to their limitations. Those reacting more negatively express loss of identity, physical limitations, and other disease symptoms (Silverman et al. 2009).

ACS patients and their family are faced with multiple losses including independence, control, financial security, relationships patterns, roles, and sense of worth (Simmonds et al. 2013). Further, there can be loss of optimism and freedom. Current and perceived future losses may precipitate grieving as part of the adjustment process. Worden (2008) identified four tasks of grieving: accepting the reality of loss (i.e., reality of the diagnosis and its consequences and impact), processing the pain of grief (commonly manifesting as emotional distress in ACS survivors, such as fear, anxiety, sadness, depression, anger), adjusting to the world without the deceased, and finding an enduring connection with the deceased (or in the case of illness, accommodation of the illness into the larger self rather than a sole focus on the illness) (Worden 2008). In chronic illness those tasks may be revisited over the lifetime in response to changes to the illness, treatment, prognosis, impact and consequences, comorbidities, and effects of aging.

Adjusting to Treatments and Lifestyle Recommendations

Adjustment to new medical treatments is often not recognized by health professionals. A group of new-onset AMI patients reported attributed bodily sensations to new medications not the AMI (Attebring et al. 2005). These patients reported that while medication use felt intrusive, it provided security. Confusion following communication with health professionals was common, particularly around their treatment and severity of their condition, highlighting the need for clear communication (Attebring et al. 2005). Condon and McCarthy (2006) investigated adjustment to lifestyle changes by interviewing ten AMI patients (6-week post-discharge), from which a number of themes emerged. Firstly, there was a belief that warning signs (e.g., chest pain) would make the patient aware of any potentially negative effects of lifestyle habits, prior to an event such as AMI. Post-AMI, survival became a central issue and a major factor in empowering and motivating lifestyle change in the recovery period. Patients became motivated to take

responsibility for lifestyle changes following acceptance of the diagnosis, although had mixed experiences when undertaking changes due to underestimation of the difficulty. Participants also reported that information, care, and easy and efficient access to acute healthcare were a source of satisfaction, importance, and security, and they were keen to get "back to normal" as soon as possible and leave the event behind them.

Self-Efficacy

Self-efficacy refers to the way in which an individual's belief in their capacity to perform a task in a desired manner affects their level of engagement and likelihood of completing a task (Bandura 1977). Self-efficacy has been shown to be associated with health-related behaviors and outcomes in a range of disease populations (Sarkar et al. 2009) as well as their commitment and ability to undertake lifestyle changes and thus adhere to a management plan (Sharp and Salyer 2012). Indeed, cardiac patients who demonstrate confidence to self-manage are more likely to show beneficial changes (Tsay and Chao 2002), and conversely patients with low self-efficacy report worse health outcomes (Maeda et al. 2012). O'Neil and colleagues (2013) demonstrated that higher cardiac self-efficacy scores at baseline (3-month post-discharge) significantly predicted better cardiac functioning and self-rated mental and physical health at 6- and 9-month post-discharge. However, when taking into account potential psychosocial confounders, depression was shown to account for much of the association. Other studies of heart failure (HF) patients have shown that those with low self-efficacy report greater physical limitation, symptom burden, and impairments in quality of life (Sarkar et al. 2007, 2009) as well as greater risk of mood disturbances (Blanchard et al. 2002; Tsay and Chao 2002).

Adjustment Disorder

While adjustment following AMI is straightforward for some, for others, the process incites significant symptoms of emotional distress that impinge day-to-day life. The diagnostic term "adjustment disorder", first appearing in the Diagnostic and Statistical Manual III (DSM-III), is used when the "emotional or behavioral symptoms" in response to an identifiable stressor, such as ACS, "cause distress that is out of proportion to the severity or intensity of the stressor and/or significant impairment in social, occupational, or other important areas of functioning." Symptoms start within 3 months of the stressor and resolve within 6 months following its termination. Adjustment disorder diagnosis is applied only in the absence of fulfillment of criteria for another disorder (e.g., depression or anxiety), and symptoms are not due to normal bereavement (American Psychiatric Association 2013).

ACS and Depression

Depression and related symptoms are commonly experienced by people with cardiovascular disease. Symptoms include feeling down; loss of pleasure; sleep and/or appetite disturbance; lack of energy; difficulty concentrating and/or making decisions; psychomotor slowing or agitation; feelings of guilt, worthlessness, hopelessness, helplessness, and/or pessimism; irritability; thoughts that they would be better off dead; and/or suicidal ideation. Around 30–50 % of people in the early post-ACS period score above threshold on a self-report depression measures (e.g., Beck Depression Inventory) indicating clinically significant depression symptoms, while approximately 15–20 % meet diagnostic criteria for a clinical depression in hospital (Lichtman et al. 2014). Even more experience subclinical symptoms. The presence of depression symptoms, at all levels of severity, negatively impacts patient mortality and morbidity in a dose-dependent fashion (Lichtman et al. 2014).

With regard to the pattern of depression symptoms over time post-event, an integrative review by Barnanson et al. (2012) reported that depression was commonly present in the ensuing days post-discharge, dissipating over the following 4 months. Other cohort studies show depression symptoms spontaneously remit over 6 months (Grace et al. 2005), independent of disease severity or cardiac rehabilitation participation. This study also demonstrated that those with higher levels of depressive symptoms are less likely to participate in cardiac rehabilitation, while younger participants, those with unstable angina, and lower family income are more likely to be depressed. Murphy and colleagues investigated trajectories of depression in female AMI and CABGS patients and found that most change occurred in the first 2 months (Murphy et al. 2008). While most had relatively low levels of depression that improved over the first year, the remaining 11 % had relatively high levels of symptoms that worsened over time. Similarly, Doyle et al. found that among their group of 375 ACS patients, 15 % demonstrated persistent depression symptoms and 37 % demonstrated subthreshold symptoms, while 48 % were never depressed (Doyle et al. 2011). Kaptein et al. (2006) reported a more complex pattern of change of depression symptoms over 12 months in 475 people admitted for AMI. Five change trajectories were described: 56 % reported no or minimal depression symptoms at all time points, 26 % reported persistent mild depression symptoms, 9 % reported moderate and increasing depression symptoms, 5 % reported significant and decreasing depression symptoms, and 4 % reported significant and increasing depression symptoms. One study however suggests that initial symptoms may be more robust and stable over the longer term. In 287 AMI patients, a stable course of depressive symptoms was observed, with 40 % nondepressed, 42 % mildly depressed, 14 % moderately depressed, and 4 % severely depressed (Martens et al. 2008). Overall, trajectory studies suggest that the majority of ACS patients exhibit either minimal symptoms of depression or mild symptoms that improve over time, while a smaller proportion have more severe symptoms that persist.

Risk factors for persistent depression identified from these studies include a first language other than English, comorbid diabetes, cardiac history, prior depression, and Type D personality (Martens et al. 2008; Murphy et al. 2008). The Type D personality construct was developed by Denollet (Denollet and Brutsaert 1998), triggered by observations of cardiac patients, and refers to a "distressed" personality type characterized by a high level of negative affectivity and high level of social inhibition. Doyle found that selected theoretical depression vulnerabilities (stressful life events; reduced reinforcing events; cognitive distortions; and Type D personality) predicted depression trajectories (Doyle et al. 2011).

The differential effects of more depression subtypes on key clinical outcomes of ACS patients have also been documented. Of note is the predictive role of cognitive subtypes such as anhedonia (Leroy et al. 2010), helplessness and hopelessness (Pedersen et al. 2007), and pessimism (Tindle et al. 2009). Somatic subtypes of depression have been shown to predict CV prognosis and mortality (Rumsfeld and Ho 2005). It is plausible that routine depression screening at the granular level following ACS may facilitate long-term functioning and recovery (Clarke 2003). Studies examining the prognostic role of latent classes of depression and anxiety symptoms in ACS patients are currently underway (Oldroyd et al. 2013).

Suicide Risk Following ACS

While often a symptom of depression, suicidal ideation can occur in the absence of clinical depression. Physical illness is a risk factor for suicidal ideation and attempts in higher- and lower-income countries; a positive relationship has been observed between suicide risk and number of physical illnesses (Scott et al. 2010). Several studies have confirmed an association between coronary heart disease and AMI and suicidal ideation (Kim et al. 2006; Kishi et al. 2001; Larsen et al. 2010). A population-based, case-control study conducted in Denmark found that AMI was associated with an increased risk of suicide for up to 5 years post-AMI (Larsen et al. 2010). Risk was more pronounced in the first month following discharge for AMI. Perhaps most notably, suicide risk was 64 times greater for those with a recorded history of psychiatric illness (compared with those without). The risk tended to decrease with age, with no gender difference found despite males being at greater risk of completed suicide in the general population. Clinicians should be aware of the increase risk of suicide and suicidal ideation at any time post-AMI, particularly in the early post-discharge period and in those with a psychiatric history.

ACS and Anxiety

Anxiety is a normal and common emotion that occurs in response to a real or perceived threat. Depending on severity, anxious symptoms can include feelings of uneasiness, fear, and panic; cognitive symptoms such as worrying and rumination;

and physical symptoms such as racing heart, hot and cold flushes, tightening chest, agitation, dry mouth, nausea, numbness, and tingling in hands or feet. A reaction that is designed to help deal with danger, anxiety can be adaptive when a situation calls for a "flight or fight" response or when activating active coping strategies such as gathering further information to address concerns or following health recommendations. It can also be maladaptive when it persists or worsens to the point where it impedes a person's day-to-day functioning.

Anxiety following a significant health event such as ACS is extremely common, precipitated by a range of factors such as pain; fear of recurrence, disability or death, and uncertainty around prognosis; dealing with new and complex treatment regimens including lifestyle changes; and wider life stressors such as financial concerns and restrictions to usual work and social activities. Approximately half of ACS patients experience significant anxiety symptoms in the early post-event period (De Jong et al. 2004), and (as with depression) symptoms can persist into the longer term for some. There are a range of clinical anxiety disorders that are diagnosed when anxiety levels are pathological, with two particularly relevant disorders to ACS being panic disorder and generalized anxiety.

Panic disorder is an anxiety condition that involves recurrent panic attacks. Panic attacks are common in the general community, with around 35 % experiencing one at some time in their life, although recurrent panic attacks are less common. A challenge for a person living with panic disorder, their family, and clinician is the overlap between ACS symptoms and panic attack, such as chest tightness or discomfort, shortness of breath, sweating, palpitations, light-headedness, nausea, and vomiting. Panic attacks also involve feelings of dread, danger or foreboding, fear of going mad, losing control, and dying. Over one-third of patients who present with noncardiac chest pain have panic disorder (Soh and Lee 2010). However, panic disorder has also been found to be common in people with established CHD, compared with the general population, with rates between 11–27 % (Soh and Lee 2010) and 2–3 %, respectively (Kessler et al. 2005).

Generalized anxiety disorder (GAD) is characterized by at least 6 months of feeling very worried to the extent that it is difficult to stop, impacting on everyday activities. In addition, people experiencing GAD may feel restless or on edge, easily tired, difficulty concentrating, irritable, muscle pain, and sleep disturbance. A meta-analysis of studies investigating GAD in cardiac populations revealed a prevalence of 11–14 % in people with existing CHD, while lifetime prevalence was found to be 26 % (Tully and Cosh 2013). This compares with a yearly prevalence of 3 % and lifetime prevalence of 5 % in the general population (Weisberg 2009). While some have found GAD to be associated with increased mortality (Roest et al. 2012), Parker and colleagues (2011) found that both a current and a lifetime diagnosis of GAD was associated with a superior 5-year outcome, particularly in those with no other anxiety disorder. This suggests that there may be an element of "constructive worrying" precipitating help seeking and adherence to treatment recommendations (Parker et al. 2011). In the general community, high rates of comorbidity have been found for GAD and major depressive disorder (MDD), with the two conditions sharing a number of symptoms and features (e.g., concentration and sleep

disturbance, fatigue, restlessness and psychomotor agitation, rumination, and worry). Substantial overlap in MDD and GAD has also been shown in cardiac patients, with both associated with recurrent events (Frasure-Smith and Lesperance 2008). It is interesting to note that this comorbidity occurs at lower rates in people with CHD, suggesting that these conditions are inextricably linked but their effects may be unique/independent on outcome (Tully and Cosh 2013).

Indeed, the presence of different anxious subtypes has been shown to lead to different prognoses. For example, somatic subtypes of anxiety disorder may predict coronary heart disease (independent of depression) (Nabi et al. 2010), while cognitive subtypes can predict in-hospital arrhythmic and ischemic complications following ACS (Huffman et al. 2008).

Stress and ACS

Stress refers to both an external event, or "stressor," and the physical and psychological reactions to the stressor, or the "stress response." Stress has long been linked with heart problems in the public view, with some ACS survivors perceiving stress as being a more likely and greater cause of their heart problems than known risk factors such as smoking and diet (Clark 2003). Stress following an ACS can be multifactorial, consisting of different and interrelated elements. In addition to the health event itself and directly related stressors (seeking understanding, dealing with medical treatments and lifestyle changes), external stressors such as job stress, adverse life events, and financial problems may also result, be exacerbated, or be harder to deal with due to compromised resources.

The stress response varies between individuals but consists of cognitive symptoms (e.g., memory and concentration problems, poor judgment, worrying, anxious, or racing thoughts), emotional symptoms (e.g., feeling down, depressed or unhappy, feeling overwhelmed, agitated, irritable, or moody, and a sense of isolation and loneliness), physical symptoms (e.g., rapid heartbeat or chest pain, nausea, dizziness, diarrhea or constipation, aches and pains, loss of libido, frequent colds), and behavioral symptoms (change in appetite and sleeping patterns, isolating self, procrastination, substance use, nervous habits). In addition to triggering symptoms of emotional distress, stress can also be a risk factor for the onset or exacerbation of many mental health conditions.

Qualitative studies reveal personal experiences of stress post-ACS. A study of female ACS survivors reported that while their life pre-AMI was stressful due to multiple roles, they needed and wanted support in the post-discharge period and were fearful about returning home. Patients and their relatives were uncertain about their capacity (Sjostrom-Strand and Fridlund 2007). Upon investigating lifestyle factors, Condon and McCarthy (2006) identified stress as a major concern for participants who reported overwork, poverty, addictions, and managing multiple roles (homemaker, breadwinner, parent, partner, etc.) as key sources. However, despite believing that stress contributed to their AMI, patients were unsure about everyday stress management (Condon and McCarthy 2006).

Post-trauma Responses

In some cases, the response to the stress and trauma of an ACS can trigger a psychological disorder. Acute stress disorder and post-traumatic stress disorder (PTSD) are significant post-traumatic syndromes precipitated by traumatic events, for example, a natural disaster, combat, or sexual assault. Symptoms include reexperiencing the event, avoidance of reminders of the event, negative changes to mood and cognitions, and physiological hyperarousal. The DSM-IV specified that the triggering events could also include life-threatening illness such as ACS, stroke, and cancer; however, its successor, the DSM-V, is less clear, stating medical triggers must involve sudden, catastrophic events such as anaphylactic shock and waking during surgery. The primary difference between acute stress disorder and PTSD is the timing of symptom presentation and persistence, with acute stress disorder more immediate and PTSD a longer-term disorder. To fulfill criteria of acute stress disorder, symptoms are required to be present within 2 days and 4 weeks of the event, while PTSD is diagnosed at least 1 month post-event. Acute stress disorder is often a precursor to PTSD.

A number of studies have demonstrated that a cardiovascular event, such as AMI, can trigger a post-trauma disorder in some survivors. Prevalence of acute stress disorder in ACS survivors has been reported as 4–18 % (Roberge et al. 2008), while the prevalence of ACS-induced PTSD has been found to be 12 % (95 % CI 9–15 %) (Edmondson et al. 2012). Some studies have identified potential risk factors for PTSD following ACS including acute stress disorder, as well as a history of other psychiatric disorders and symptoms or traits (including a history of psychiatric disorder before ACS, depression symptoms during hospitalization, alexithymia, and neuroticism), responses during the event (including intense fear, perceived life threat, helplessness, dissociation, and lack of control), chest pain during the event, and demographic variables (younger age, female gender, ethnic minority, and low socioeconomic status) (Edmondson et al. 2012). Wilkman and colleagues (2008) found that PTSD symptoms persisted in a group of ACS patients for at least 3 years post-event. This suggests a chronic and persistent course and highlights the importance of early detection and intervention.

While some experience deleterious trauma reactions, others not only recover but experience positive change, termed "post-traumatic growth." A review of the qualitative post-traumatic growth literature in those with life-threatening physical illness suggests change occurs over four domains – reappraisal of life and priorities, trauma equaling development of self, existential reevaluation, and a new awareness of the body (Hefferon et al. 2009). In ACS patients, reappraisal of life and priorities was demonstrated by a new appreciation of life and time and being alive, prioritizing friends, an increased importance of and improved relationship with family, and prioritizing health. ACS patients also report increased empathy as a form of self-development, as well as an existential reevaluation, with recognition of mortality and the brevity of life. Finally, a new awareness of the body occurs for some post-ACS, characterized by an increased awareness, importance and sense of responsibility for their own health, and engagement in preventative health behaviors such as diet, exercise, reduced stress, and reduced substance use.

ACS and Anger

Feelings of anger, irritability, and frustration are common after a life-changing event such as ACS. These emotions may emerge as part of normal adjustment, grief and loss reactions, a stress response, or a symptom of a depression, anxiety, or trauma disorder. Anger may be the emotional expression or an enduring hostile personality or disposition, where hostility is defined as a resentful, suspicious, and cynical attitude toward others. An early hypothesis that Type A personality (a behavior pattern with personality characteristics including impatience, hostility, intolerance as well as being rushed, ambitious, and competitive) is risk factor for CHD and outcomes has since been rejected based on overwhelming evidence (Bunker et al. 2003). However, there is evidence that anger and hostility are associated with increased CHD risk in both healthy and CHD populations (Chida and Steptoe 2009), and acute anger (as well as other strong negative emotions) may act as a trigger for ACS in a proportion of people with established CHD (Steptoe and Brydon 2009).

There have been fewer studies investigating the prevalence of anger post-ACS than depression or anxiety presentations. One study of elderly cardiac patients 3-month post-hospitalization found higher rates of hostility (as well as anxiety and depression) than in a comparison group of healthy elders (Moser et al. 2010). A study evaluating the association of anger and sleep found that anger suppression was associated with poor sleep quality in CHD patients, after adjusting for established poor sleep risk factors such as age and socioeconomic factors, medical comorbidities, lifestyle factors, and depressive symptoms (Caska et al. 2009). In turn, poor sleep quality and short sleep duration are associated with increased CVD risk (Cappuccio et al. 2011; Chandola et al. 2010).

ACS and Interpersonal Relationships

ACS can have a significant impact on a patient's friends and family, as well as their relationships and interactions. Partners of AMI survivors are at increased risk of depression and suicide with male partners at higher risk of depression than female partners (Fosbol et al. 2013). Female partners report suffering a major loss, missing their "former" partner sexually and emotionally, while also feeling their partner is controlling them or limiting their life (Arenhall et al. 2011). A systematic review on the impact of cardiac disease on the partner relationship revealed five themes: overprotection, communication deficiency, sexual concerns, changes in domestic roles, and adjustment to illness (Dalteg et al. 2011).

Reports of overprotective behavior by the patient were often around carrying out "allowable" activities and lifestyle changes. Partners often worried about recurrent AMI or angina attack when the patient was alone. While patients needed and valued family support and often recognized the good intentions of their partner and children, resistance and residual tension in the household could occur (Condon and McCarthy 2006). Overprotectiveness led to feelings of resentment and

frustration in the patient as they felt controlled or "on probation" and compelled to report back to their partner, resulting to conflict and arguments (Dalteg et al. 2011). Overprotectiveness could also encourage dependency, which contrasted with the patient's desire to "get back to normal" as soon as possible and to regain and maintain independence (Condon and McCarthy 2006).

Communication challenges were reported, particularly with regard to inhibition of emotions (Dalteg et al. 2011). Patients did not want to provoke anxiety in their partner or be perceived as whining. In turn, partners did not want to upset the patient. Often couples did not discuss the disease or handle its implications together and were sometimes uncertain how to talk about the experience and potential of death with the other. Partners found it stressful dealing with the patient's emotional distress. However, if partners disengaged this could lead to further anxiety in the patient. So and La Guardia found that greater inhibition of feelings about an AMI leads to poorer psychological and relational functioning, while closeness to their partner was associated with greater disclosure (So and La Guardia 2011).

Another common concern for patients and partners centered on sexual relationships. Frequency of sexual activity is known to decline following AMI, with sexual dysfunction seen as a direct consequence of cardiac disease and medication (Mosack and Steinke 2009). One study found that fewer than half of patients interviewed had resumed sexual activity 12 weeks post-discharge. Resumption was significantly more likely in those completing cardiac rehabilitation (Eyada and Atwa 2007). Another longer-term study found sexual concerns and dysfunction were present 6 months post-AMI (Mosack and Steinke 2009). For many, there is a fear that resuming sexual activities will trigger another ACS event, while other factors delaying return to sexual activity include continued health problems, medication, sexual dysfunction, lack of information or partner concerns, health problems, or decline in sexual interest (Mosack and Steinke 2009). For some people, there is a belief that no one would be interested in a relationship with them because of their health problems (Mosack and Steinke 2009). Furthermore, most patients were either unsatisfied or mostly dissatisfied with their sexual activity (Eyada and Atwa 2007). Those who participate may experience overall dissatisfaction with their sex life due to decreased frequency of activity or decreased sexual desire and ability to satisfy their partner (Mosack and Steinke 2009). Another study found that higher anxiety was associated with lower sexual satisfaction (Steinke and Wright 2006).

A shift in domestic roles and responsibilities during recovery (and potentially in the longer term) can occur for AMI patients cohabitating with a partner (Dalteg et al. 2011). An increase in partner workload occurring as a result of patient incapacitation may cause frustration and anxiety, or guilt if the patient performed physically stressful chores. The extra workload compromising other enjoyable activities can be perceived as limiting a partner's life.

Finally, in addition to their individual adjustment to the heart condition, the dyad team also undergoes an adjustment process (Dalteg et al. 2011). Adaption and

adjustment issues include incorporation of new diets, routines, and healthy lifestyle practices into both the patient and partners life, resulting in feelings of stress for the partner but also solidarity with the patient; a diminishing of joint activities, particularly those that were more physically demanding; and attempts to lead a normal life and regaining balance while being hopeful for improvement in the future. While the experience of an ACS can result in great distress for the couple, it can synergize some couples through reconnection and new meaning. However, partner anxiety or depression has been found to negatively impact on the adjustment of the patient; some couples withdraw from each other or avoid discussing or making future plans, goals, or hopes.

Clinical Implications

This chapter has highlighted the importance of illness perceptions, in particular those around control, coherence, and timeline for people who experience an AMI. Those who lack confidence in their ability to control symptoms of the illness, lack understanding of the illness, and see CHD as chronic may experience greater emotional distress and poorer QOL. This may subsequently impact on their risk-factor behaviors known to be important in recovery and secondary prevention (e.g., changing diet and physical activity and attending cardiac rehabilitation). However, while it is putative that negative emotions following ACS produce negative outcomes, there is also some evidence that certain symptoms can produce positive outcomes, likely driven by hypervigilance around self-management and lifestyle modification. Screening ACS patients in order to identify the combination of symptoms that may allow patients to harness their negative emotions may lead to superior patient outcomes. Elucidating beliefs and understanding around illness and targeting interventions appropriately to modify any maladaptive beliefs are also likely to be useful.

Conclusions

Psychological reactions to a cardiac event vary and impact upon individual presentation and recovery. The processes of help seeking, understanding, and adjusting to the event can be impacted by, and impact on, cognitive responses to symptoms, coping mechanisms, and interpersonal relationships. Emotional distress is common and may present as adjustment disorders, depression, anxiety, stress, trauma, anger, or hostility. Conversely, many individuals report positive or post-traumatic growth responses. The increasing recognition of the link between these emotional responses and health outcomes has increased the focus on whether treatment can mitigate negative outcomes.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington: American Psychiatric Publishing.

Arenhall, E., Kristofferzon, M. L., Fridlund, B., & Nilsson, U. (2011). The female partners' experiences of intimate relationship after a first myocardial infarction. *Journal of Clinical Nursing, 20*(11–12), 1677–1684. doi:10.1111/j.1365-2702.2010.03312.x.

Astin, F., Closs, S. J., McLenachan, J., Hunter, S., & Priestley, C. (2009). Primary angioplasty for heart attack: Mismatch between expectations and reality? *Journal of Advanced Nursing, 65*(1), 72–83. doi:10.1111/j.1365-2648.2008.04836.x.

Attebring, M. F., Herlitz, J., & Ekman, I. (2005). Intrusion and confusion – The impact of medication and health professionals after acute myocardial infarction. *European Journal of Cardiovascular Nursing, 4*(2), 153–159. doi:10.1016/j.ejcnurse.2005.02.001.

Baldacchino, D. (2010). Long-term causal meaning of myocardial infarction. *British Journal of Nursing, 19*(12), 774–781. doi:10.12968/bjon.2010.19.12.48656.

Baldacchino, D. R., Borg, J., Muscat, C., & Sturgeon, C. (2012). Psychology and theology meet: Illness appraisal and spiritual coping. *Western Journal of Nursing Research, 34*(6), 818–847. doi:10.1177/0193945912441265.

Bandura, A. (1977). Self-efficacy: Toward a unifying theory of behavioral change. *Psychological Review, 84*(2), 191–215. doi:10.1016/0146-6402(78)90002-4.

Barnason, S., Zimmerman, L., Nieveen, J., Schulz, P., & Young, L. (2012). Patient recovery and transitions after hospitalization for acute cardiac events: An integrative review. *Journal of Cardiovascular Nursing, 27*(2), 175–191. doi:10.1097/JCN.0b013e318239f5f5.

Bennett, K. K., & Boothby, J. L. (2007). Coping and heart disease: Implications for prevention and treatment. In E. Martz & H. Livneh (Eds.), *Coping with chronic illness and disability: Theoretical, empirical and clinical aspects*. New York: Springer.

Blanchard, C. M., Rodgers, W. M., Courneya, K. S., Daub, B., & Black, B. (2002). Self-efficacy and mood in cardiac rehabilitation: Should gender be considered? *Behavioral Medicine, 27*(4), 149–160. doi:10.1080/08964280209596040.

Bonsaksen, T., Lerdal, A., & Fagermoen, M. S. (2012). Factors associated with self-efficacy in persons with chronic illness. *Scandinavian Journal of Psychology, 53*(4), 333–339. doi:10.1111/j.1467-9450.2012.00959.x.

Brink, E., Alsen, P., Herlitz, J., Kjellgren, K., & Cliffordson, C. (2012). General self-efficacy and health-related quality of life after myocardial infarction. *Psychology, Health & Medicine, 17*(3), 346–355. doi:10.1080/13548506.2011.608807.

Broadbent, E., Petrie, K. J., Ellis, C. J., Anderson, J., Gamble, G., Anderson, D., & Benjamin, W. (2006). Patients with acute myocardial infarction have an inaccurate understanding of their risk of a future cardiac event. *Internal Medicine Journal, 36*(10), 643–647. doi:10.1111/j.1445-5994.2006.01150.x.

Broadbent, E., Ellis, C. J., Thomas, J., Gamble, G., & Petrie, K. J. (2009). Further development of an illness perception intervention for myocardial infarction patients: A randomized controlled trial. *Journal of Psychosomatic Research, 67*(1), 17–23. doi:10.1016/j.jpsychores.2008.12.001.

Bunde, J., & Martin, R. (2006). Depression and prehospital delay in the context of myocardial infarction. *Psychosomatic Medicine, 68*(1), 51–57. doi:10.1097/01.psy.0000195724.58085.f0.

Bunker, S. J., Colquhoun, D. M., Esler, M. D., Hickie, I. B., Hunt, D., Jelinek, V. M., . . . Tonkin, A. M. (2003). "Stress" and coronary heart disease: Psychosocial risk factors. *Medical Journal of Australia, 178*(6), 272–276.

Cameron, L. D., & Leventhal, H. (2003). *The self-regulation of health and illness behaviour*. London: Routledge.

Cappuccio, F. P., Cooper, D., D'Elia, L., Strazzullo, P., & Miller, M. A. (2011). Sleep duration predicts cardiovascular outcomes: A systematic review and meta-analysis of prospective studies. *European Heart Journal, 32*(12), 1484–1492. doi:10.1093/eurheartj/ehr007.

Caska, C. M., Hendrickson, B. E., Wong, M. H., Ali, S., Neylan, T., & Whooley, M. A. (2009). Anger expression and sleep quality in patients with coronary heart disease: Findings from the Heart and Soul Study. *Psychosomatic Medicine, 71*(3), 280–285. doi:10.1097/PSY.0b013e31819b6a08.

Chandola, T., Ferrie, J. E., Perski, A., Akbaraly, T., & Marmot, M. G. (2010). The effect of short sleep duration on coronary heart disease risk is greatest among those with sleep disturbance: A prospective study from the Whitehall II cohort. *Sleep, 33*(6), 739.

Chiavarino, C., Rabellino, D., Ardito, R. B., Cavallero, E., Palumbo, L., Bergerone, S., . . . Bara, B. G. (2012). Emotional coping is a better predictor of cardiac prognosis than depression and anxiety. *Journal of Psychosomatic Research, 73*(6), 473–475. doi:10.1016/j.jpsychores.2012.10.002.

Chida, Y., & Steptoe, A. (2009). The association of anger and hostility with future coronary heart disease: A meta-analytic review of prospective evidence. *Journal of the American College of Cardiology, 53*(11), 936–946. doi:10.1016/j.jacc.2008.11.044.

Clark, A. M. (2003). "It's like an explosion in your life. . .": Lay perspectives on stress and myocardial infarction. *Journal of Clinical Nursing, 12*(4), 544–553. doi:10.1046/j.1365-2702.2003.00740.

Clarke, D. M. (2003). An empirically derived taxonomy of common distress syndromes in the medically ill. *Journal of Psychosomatic Research, 54*, 323–330. doi:10.1016/S0022-3999(02)00410-5.

Condon, C., & McCarthy, G. (2006). Lifestyle changes following acute myocardial infarction: Patients perspectives. *European Journal of Cardiovascular Nursing, 5*(1), 37–44. doi:10.1016/j.ejcnurse.2005.06.005.

Dalteg, T., Benzein, E., Fridlund, B., & Malm, D. (2011). Cardiac disease and its consequences on the partner relationship: A systematic review. *European Journal of Cardiovascular Nursing, 10*(3), 140–149. doi:10.1016/j.ejcnurse.2011.01.006.

De Fazio, P., Caroleo, M., Rizza, P., Cerminara, G., De Serio, D., Indolfi, C., & Segura-Garcia, C. (2012). Specific personality traits and coping styles predict affective symptoms in early post acute coronary syndrome inpatients. *International Journal of Psychiatry in Medicine, 44*(2), 119–132. doi:10.2190/PM.44.2.c.

De Jong, M. J., Chung, M. L., Roser, L. P., Jensen, L. A., Kelso, L. A., Dracup, K., . . . Moser, D. K. (2004). A five-country comparison of anxiety early after acute myocardial infarction. *European Journal of Cardiovascular Nursing, 3*(2), 129–134. doi:10.1016/j.ejcnurse.2004.01.004.

Denollet, J., & Brutsaert, D. L. (1998). Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. *Circulation, 97*(2), 167–173. doi:10.1161/01.CIR.97.2.167.

Doyle, F., McGee, H., Delaney, M., Motterlini, N., & Conroy, R. (2011). Depressive vulnerabilities predict depression status and trajectories of depression over 1 year in persons with acute coronary syndrome. *General Hospital Psychiatry, 33*(3), 224–231. doi:10.1016/j.genhosppsych.2011.03.008.

Edmondson, D., Richardson, S., Falzon, L., Davidson, K. W., Mills, M. A., & Neria, Y. (2012). Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: A meta-analytic review. *PLoS One, 7*(6), e38915. doi:10.1371/journal.pone.0038915.

Eyada, M., & Atwa, M. (2007). Sexual function in female patients with unstable angina or non-ST-elevation myocardial infarction. *Journal of Sexual Medicine, 4*(5), 1373–1380. doi:10.1111/j.1743-6109.2007.00473.x.

Fosbol, E. L., Peterson, E. D., Weeke, P., Wang, T. Y., Mathews, R., Kober, L., . . . Torp-Pedersen, C. (2013). Spousal depression, anxiety, and suicide after myocardial infarction. *European Heart Journal, 34*(9), 649–656. doi:10.1093/eurheartj/ehs242.

Foxwell, R., Morley, C., & Frizelle, D. (2013). Illness perceptions, mood and quality of life: A systematic review of coronary heart disease patients. *Journal of Psychosomatic Research, 75*(3), 211–222. doi:10.1016/j.jpsychores.2013.05.003.

Frasure-Smith, N., & Lesperance, F. (2008). Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Archives of General Psychiatry, 65*(1), 62–71. doi:10.1001/archgenpsychiatry.2007.4.

French, D. P., Cooper, A., & Weinman, J. (2006). Illness perceptions predict attendance at cardiac rehabilitation following acute myocardial infarction: A systematic review with meta-analysis. *Journal of Psychosomatic Research, 61*(6), 757–767. doi:10.1016/j.jpsychores.2006.07.029.

Gardner, J. K., McConnell, T. R., Klinger, T. A., Herman, C. P., Hauck, C. A., & Laubach, C. A., Jr. (2003). Quality of life and self-efficacy: Gender and diagnoses considerations for management during cardiac rehabilitation. *Journal of Cardiopulmonary Rehabilitation, 23*(4), 299–306. doi:10.1097/00008483-200307000-00007.

Grace, S. L., Abbey, S. E., Pinto, R., Shnek, Z. M., Irvine, J., & Stewart, D. E. (2005). Longitudinal course of depressive symptomatology after a cardiac event: Effects of gender and cardiac rehabilitation. *Psychosomatic Medicine, 67*(1), 52–58. doi:10.1097/01.psy.0000151486.28349.70.

Groleau, D., Whitley, R., Lesperance, F., & Kirmayer, L. J. (2010). Spiritual reconfigurations of self after a myocardial infarction: Influence of culture and place. *Health & Place, 16*(5), 853–860. doi:10.1016/j.healthplace.2010.04.010.

Gulanick, M., Bliley, A., Perino, B., & Keough, V. (1998). Recovery patterns and lifestyle changes after coronary angioplasty: The patient's perspective. *Heart & Lung, 27*(4), 253–262. doi:10.1016/S0147-9563(98)90037-1.

Harralson, T. L. (2007). Factors influencing delay in seeking treatment for acute ischemic symptoms among lower income, urban women. *Heart & Lung, 36*(2), 96–104. doi:10.1016/j.hrtlng.2006.08.002.

Hefferon, K., Grealy, M., & Mutrie, N. (2009). Post-traumatic growth and life threatening physical illness: A systematic review of the qualitative literature. *British Journal of Health Psychology, 14*(Pt 2), 343–378. doi:10.1348/135910708X332936.

Henriksson, C., Lindahl, B., & Larsson, M. (2007). Patients' and relatives' thoughts and actions during and after symptom presentation for an acute myocardial infarction. *European Journal of Cardiovascular Nursing, 6*(4), 280–286. doi:10.1016/j.ejcnurse.2007.02.001.

Higginson, R. (2008). Women's help-seeking behaviour at the onset of myocardial infarction. *British Journal of Nursing, 17*(1), 10–14. doi:10.12968/bjon.2008.17.1.28054.

Huffman, J. C., Smith, F. A., Blais, M. A., Januzzi, J. L., & Fricchione, G. L. (2008). Anxiety, independent of depressive symptoms, is associated with in-hospital cardiac complications after acute myocardial infarction. *Journal of Psychosomatic Research, 65*(6), 557–563. doi:10.1016/j.jpsychores.2008.08.001.

Hwang, S. Y., & Jeong, M. H. (2012). Cognitive factors that influence delayed decision to seek treatment among older patients with acute myocardial infarction in Korea. *European Journal of Cardiovascular Nursing, 11*(2), 154-159. doi: 10.1016/j.ejcnurse.2010.11.002.

Johansson, I., Swahn, E., & Stromberg, A. (2007). Manageability, vulnerability and interaction: A qualitative analysis of acute myocardial infarction patients' conceptions of the event. *European Journal of Cardiovascular Nursing, 6*(3), 184–191. doi:10.1016/j.ejcnurse.2006.08.003.

Johansson, I., Swahn, E., & Stromberg, A. (2008). Spouses' conceptions of the pre-hospital phase when their partners suffered an acute myocardial infarction – A qualitative analysis. *European Journal of Cardiovascular Nursing, 7*(3), 182–188. doi:10.1016/j.ejcnurse.2007.11.002.

Kamm-Steigelman, L., Kimble, L. P., Dunbar, S., Sowell, R. L., & Bairan, A. (2006). Religion, relationships and mental health in midlife women following acute myocardial infarction. *Issues in Mental Health Nursing, 27*(2), 141–159. doi:10.1080/01612840500436925.

Kaptein, K. I., de Jonge, P., van den Brink, R. H., & Korf, J. (2006). Course of depressive symptoms after myocardial infarction and cardiac prognosis: A latent class analysis. *Psychosomatic Medicine, 68*(5), 662–668. doi:10.1097/01.psy.0000233237.79085.57.

Karademas, E. C. (2010). Illness cognitions as a pathway between religiousness and subjective health in chronic cardiac patients. *Journal of Health Psychology, 15*(2), 239–247. doi:10.1177/1359105309347585.

Kaur, R., Lopez, V., & Thompson, D. R. (2006). Factors influencing Hong Kong Chinese patients' decision-making in seeking early treatment for acute myocardial infarction. *Research in Nursing & Health, 29*(6), 636–646. doi:10.1002/nur.20171.

Kerr, E. E., & Fothergill-Bourbonnais, F. (2002). The recovery mosaic: Older women's lived experiences after a myocardial infarction. *Heart & Lung, 31*(5), 355–367. doi:10.1067/mhl.2002.127939.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 617–627. doi:10.1001/archpsyc.62.6.617.

Khraim, F. M., & Carey, M. G. (2009). Predictors of pre-hospital delay among patients with acute myocardial infarction. *Patient Education and Counseling, 75*(2), 155–161. doi:10.1016/j.pec.2008.09.019.

Kim, Y. A., Bogner, H. R., Brown, G. K., & Gallo, J. J. (2006). Chronic medical conditions and wishes to die among older primary care patients. *International Journal of Psychiatry in Medicine, 36*(2), 183–198. doi:10.2190/3QXD-UR0H-K8FH-2CU8.

Kishi, Y., Robinson, R. G., & Kosier, J. T. (2001). Suicidal ideation among patients with acute life-threatening physical illness: Patients with stroke, traumatic brain injury, myocardial infarction, and spinal cord injury. *Psychosomatics, 42*(5), 382–390. doi:10.1176/appi.psy.42.5.382.

Larsen, K. K., Agerbo, E., Christensen, B., Sondergaard, J., & Vestergaard, M. (2010). Myocardial infarction and risk of suicide: A population-based case-control study. *Circulation, 122*(23), 2388–2393. doi:10.1161/CIRCULATIONAHA.110.956136.

Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and coping*. New York: Springer.

Leroy, M., Loas, G., & Perez-Diaz, F. (2010). Anhedonia as predictor of clinical events after acute coronary syndromes: A 3-year prospective study. *Comprehensive Psychiatry, 51*(1), 8–14. doi:10.1016/j.comppsych.2009.01.011.

Lichtman, J. H., Froelicher, E. S., Blumenthal, J. A., Carney, R. M., Doering, L. V., Frasure-Smith, N., ... Stroke Nursing. (2014). Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: Systematic review and recommendations: A scientific statement from the American Heart Association. *Circulation, 129*(12), 1350–1369. doi:10.1161/CIR.0000000000000019.

Maeda, U., Shen, B. J., Schwarz, E. R., Farrell, K. A., & Mallon, S. (2012). Self-efficacy mediates the associations of social support and depression with treatment adherence in heart failure patients. *International Journal of Behavioral Medicine*. doi:10.1007/s12529-011-9215-0.

Martens, E. J., Smith, O. R., Winter, J., Denollet, J., & Pedersen, S. S. (2008). Cardiac history, prior depression and personality predict course of depressive symptoms after myocardial infarction. *Psychological Medicine, 38*(2), 257–264. doi:10.1017/S0033291707001377.

Miller, J. F., McConnell, T. R., & Klinger, T. A. (2007). Religiosity and spirituality: Influence on quality of life and perceived patient self-efficacy among cardiac patients and their spouses. *Journal of Religion and Health, 46*(2), 299–313. doi:10.1007/s10943-006-9070-5.

Mosack, V., & Steinke, E. E. (2009). Trends in sexual concerns after myocardial infarction. *Journal of Cardiovascular Nursing, 24*(2), 162–170. doi:10.1097/JCN.0b013e318197aaa1.

Moser, D. K., Dracup, K., Evangelista, L. S., Zambroski, C. H., Lennie, T. A., Chung, M. L., ... Heo, S. (2010). Comparison of prevalence of symptoms of depression, anxiety, and hostility in elderly patients with heart failure, myocardial infarction, and a coronary artery bypass graft. *Heart & Lung, 39*(5), 378–385. doi:10.1016/j.hrtlng.2009.10.017.

Mueller, P. S., Plevak, D. J., & Rummans, T. A. (2001). Religious involvement, spirituality, and medicine: Implications for clinical practice. *Mayo Clinical Proceedings, 76*(12), 1225–1235. doi:10.4065/76.12.1225.

Murphy, B. M., Elliott, P. C., Worcester, M. U., Higgins, R. O., Le Grande, M. R., Roberts, S. B., & Goble, A. J. (2008). Trajectories and predictors of anxiety and depression in women during the 12 months following an acute cardiac event. *British Journal of Health Psychology, 13* (Pt 1), 135–153. doi:10.1348/135910707X173312.

Nabi, H., Hall, M., Koskenvuo, M., Singh-Manoux, A., Oksanen, T., Suomimen, S., ... Vahtera, J. (2010). Psychological and somatic symptoms of anxiety and risk of coronary heart disease: The health and social support prospective cohort study. *Biological Psychiatry, 67*, 378–385. doi:10.1016/j.biopsych.2009.07.040.

Nadarajah, S., Berger, A. M., & Thomas, S. A. (2013). Current status of spirituality in cardiac rehabilitation programs: A review of literature. *Journal of Cardiopulmonary Rehabilitation & Prevention, 33*(3), 135–143. doi:10.1097/HCR.0b013e318291381e.

Newman, J. D., Muntner, P., Shimbo, D., Davidson, K. W., Shaffer, J. A., & Edmondson, D. (2011). Post-traumatic stress disorder (PTSD) symptoms predict delay to hospital in patients with acute coronary syndrome. *PLoS ONE [Electronic Resource], 6*(11), e27640. doi:10.1371/journal.pone.0027640.

O'Neil, A., Berk, M., Davis, J., & Stafford, L. (2013). Cardiac-self efficacy as a predictor of adverse outcomes in recently hospitalized Coronary Artery Disease (CAD) patients. *Health Psychology, 5*, 6–14. doi:10.4236/health.2013.57A3002.

Oldroyd, J. C., Cyril, S., Wijayatilaka, B. S., O'Neil, A., McKenzie, D. P., Zavarsek, S., ... Oldenburg, B. (2013). Evaluating the impact of depression, anxiety & autonomic function on health related quality of life, vocational functioning and health care utilisation in acute coronary syndrome patients: The ADVENT study protocol. *BMC Cardiovascular Disorders, 13*, 103. doi:10.1186/1471-2261-13-103.

Park, C. L., & Dornelas, E. (2012). Is religious coping related to better quality of life following acute myocardial infarction? *Journal of Religion & Health, 51*(4), 1337–1346. doi:10.1007/s10943-010-9446-4.

Parker, G., Hyett, M., Hadzi-Pavlovic, D., Brotchie, H., & Walsh, W. (2011). GAD is good? Generalized anxiety disorder predicts a superior five-year outcome following an acute coronary syndrome. *Psychiatry Research, 188*(3), 383–389. doi:10.1016/j.psychres.2011.05.018.

Pedersen, S. S., Denollet, J., Daemen, J., van de Sande, M., de Jaegere, P. T., Serruys, P. W., ... van Domburg, R. T. (2007). Fatigue, depressive symptoms, and hopelessness as predictors of adverse clinical events following percutaneous coronary intervention with paclitaxel-eluting stents. *Journal of Psychosomatic Research, 62*(4), 455–461. doi:10.1016/j.jpsychores.2006.12.018.

Preti, A., Sancassiani, F., Cadoni, F., & Carta, M. G. (2013). Alexithymia affects pre-hospital delay of patients with acute myocardial infarction: Meta-analysis of existing studies. *Clinical Practice and Epidemiology in Mental Health, 9*, 69–73. doi:10.2174/1745017901309010069.

Roberge, M. A., Dupuis, G., & Marchand, A. (2008). Acute stress disorder after myocardial infarction: Prevalence and associated factors. *Psychosomatic Medicine, 70*(9), 1028–1034. doi:10.1097/PSY.0b013e318189a920.

Roest, A. M., Zuidersma, M., & de Jonge, P. (2012). Myocardial infarction and generalised anxiety disorder: 10-year follow-up. *British Journal of Psychiatry, 200*(4), 324–329. doi:10.1192/bjp.bp.111.103549.

Rosen, J. L., & Bibring, G. L. (1966). Psychological reactions of hospitalized male patients to a heart attack. Age and social-class differences. *Psychosomatic Medicine, 28*(6), 808–821. doi:10.1097/00006842-196611000-00004.

Rosenfeld, A. G. (2004). Treatment-seeking delay among women with acute myocardial infarction: Decision trajectories and their predictors. *Nursing Research, 53*(4), 225–236. doi:10.1097/00006199-200407000-00005.

Rumsfeld, J. S., & Ho, P. M. (2005). Depression and cardiovascular disease: A call for recognition. *Circulation, 111*(3), 250–253. doi:10.1161/01.CIR.0000154573.62822.89.

Salminen-Tuomaala, M., Astedt-Kurki, P., Rekiaro, M., & Paavilainen, E. (2012). Coping – Seeking lost control. *European Journal of Cardiovascular Nursing, 11*(3), 289–296. doi:10.1016/j.ejcnurse.2011.01.005.

Sarkar, U., Ali, S., & Whooley, M. A. (2007). Self-efficacy and health status in patients with coronary heart disease: Findings from the heart and soul study. *Psychosomatic Medicine, 69*(4), 306–312. doi:10.1097/PSY.0b013e3180514d57.

Sarkar, U., Ali, S., & Whooley, M. A. (2009). Self-efficacy as a marker of cardiac function and predictor of heart failure hospitalization and mortality in patients with stable coronary heart disease: Findings from the Heart and Soul Study. *Health Psychology, 28*(2), 166–173. doi:10.1037/a0013146.

Scott, K. M., Hwang, I., Chiu, W. T., Kessler, R. C., Sampson, N. A., Angermeyer, M., . . . Nock, M. K. (2010). Chronic physical conditions and their association with first onset of suicidal behavior in the world mental health surveys. *Psychosomatic Medicine, 72*(7), 712–719. doi:10.1097/PSY.0b013e3181e3333d.

Sharp, P. B., & Salyer, J. (2012). Self-efficacy and barriers to healthy diet in cardiac rehabilitation participants and nonparticipants. *Journal of Cardiovascular Nursing, 27*(3), 253–262. doi:10.1097/JCN.0b013e31821efdc2.

Silverman, M., Nutini, J., Musa, D., Schoenberg, N. E., & Albert, S. M. (2009). "Is it half full or half empty?" Affective responses to chronic illness. *Journal of Cross-Cultural Gerontology, 24*(3), 291–306. doi:10.1007/s10823-009-9097-7.

Simmonds, R. L., Tylee, A., Walters, P., & Rose, D. (2013). Patients' perceptions of depression and coronary heart disease: A qualitative UPBEAT-UK study. *BMC Family Practice, 14*, 38. doi:10.1186/1471-2296-14-38.

Sjostrom-Strand, A., & Fridlund, B. (2007). Stress in women's daily life before and after a myocardial infarction: A qualitative analysis. *Scandinavian Journal of Caring Sciences, 21*(1), 10–17. doi:10.1111/j.1471-6712.2007.00433.x.

So, S. S., & La Guardia, J. G. (2011). Matters of the heart: Patients' adjustment to life following a cardiac crisis. *Psychology & Health, 26*(Suppl 1), 83–100. doi:10.1080/08870441003690456.

Soh, K. C., & Lee, C. (2010). Panic attack and its correlation with acute coronary syndrome – More than just a diagnosis of exclusion. *Annals of the Academy of Medicine, Singapore, 39*(3), 197–202.

Steinke, E. E., & Wright, D. W. (2006). The role of sexual satisfaction, age, and cardiac risk factors in the reduction of post-MI anxiety. *European Journal of Cardiovascular Nursing, 5*(3), 190–196. doi:10.1016/j.ejcnurse.2005.12.002.

Steptoe, A., & Brydon, L. (2009). Emotional triggering of cardiac events. *Neuroscience & Biobehavioral Reviews, 33*(2), 63–70. doi:10.1016/j.neubiorev.2008.04.010.

Tindle, H. A., Chang, Y. F., Kuller, L. H., Manson, J. E., Robinson, J. G., Rosal, M. C., . . . Matthews, K. A. (2009). Optimism, cynical hostility, and incident coronary heart disease and mortality in the Women's Health Initiative. *Circulation, 120*(8), 656–662. doi:10.1161/CIRCULATIONAHA.108.827642.

Tsay, S. L., & Chao, Y. F. (2002). Effects of perceived self-efficacy and functional status on depression in patients with chronic heart failure. *Journal of Nursing Research, 10*(4), 271–278. doi:10.1097/01.JNR.0000347608.76047.7a.

Tully, P. J., & Cosh, S. M. (2013). Generalized anxiety disorder prevalence and comorbidity with depression in coronary heart disease: A meta-analysis. *Journal of Health Psychology, 18*(12), 1601–1616. doi:10.1177/1359105312467390.

Walton, J. (2002). Discovering meaning and purpose during recovery from an acute myocardial infarction. *DCCN Dimensions of Critical Care Nursing, 21*(1), 36–43. doi:10.1097/00003465-200201000-00012.

Weisberg, R. B. (2009). Overview of generalized anxiety disorder: Epidemiology, presentation, and course. *Journal of Clinical Psychiatry, 70*(Suppl 2), 4–9. doi:10.4088/JCP.s.7002.01.

Wikman, A., Bhattacharyya, M., Perkins-Porras, L., & Steptoe, A. (2008). Persistence of posttraumatic stress symptoms 12 and 36 months after acute coronary syndrome. *Psychosomatic Medicine, 70*(7), 764–772. doi:10.1097/PSY.0b013e3181835c07.

Worden, J. W. (2008). *Grief counseling and grief therapy, fourth edition: A handbook for the mental health practitioner*. New York: Springer Publishing Company.

Anxiety, Depression, and Psychological Adjustment After an Acute Cardiac Event

Barbara M. Murphy, Rosemary O. Higgins, and Alun C. Jackson

Contents

Abstract

Psychological adjustment following acute cardiac events such as acute myocardial infarction (AMI) and coronary artery bypass graft surgery (CABGS) has received increasing attention in the last three decades. While physical recovery remains the highest priority, psychological recovery is now considered a primary

B.M. Murphy (✉)
Heart Research Centre, Melbourne, VIC, Australia

Department of Psychology, University of Melbourne, Melbourne, VIC, Australia

Faculty of Health, University of Newcastle, NSW, Australia
e-mail: barbara.murphy@heartresearchcentre.org

R.O. Higgins
Heart Research Centre, Melbourne, VIC, Australia

Department of Physiotherapy, University of Melbourne, Melbourne, VIC, Australia
e-mail: rosemary.higgins@heartresearchcentre.org

A.C. Jackson
Heart Research Centre, North Melbourne, VIC, Australia

Centre on Behavioral Health, University of Hong Kong, Pokfulam, Hong Kong
e-mail: alun.jackson@heartresearchcentre.org

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_57

concern for health professionals working in cardiac rehabilitation and secondary prevention. The prevalence of anxiety and depression in people who have had a cardiac event is up to four times higher than in the general population. Post-event anxiety and depression both confer an increased mortality risk, highlighting the importance of identifying these patients early in order to ensure appropriate treatment. In recent years it has been recommended that all cardiac patients be screened for depression after a cardiac event. However, there are some inherent problems with routine depression screening, particularly if undertaken soon after the event. There are risks of both unnecessary treatment of patients with transient symptoms and non-identification of patients whose symptoms appear later after physical recovery. This chapter outlines evidence regarding the prevalence and impacts of anxiety and depression in cardiac patients and issues regarding depression screening. Some alternative ways of identifying patients at risk of depression are discussed.

Keywords
Anxiety • Depression • Emotional adjustment • Distress • Screening

Prevalence of Anxiety and Depression

Many studies document high levels of both anxiety and depression in patients at the time of or soon after an acute cardiac event (Andrew et al. 2000; Barefoot et al. 2000; Berkman et al. 2003; Frasure-Smith and Lesperance 2003; Thombs et al. 2006). A 2006 review of 24 studies involving over 14,000 patients reported prevalence of depression in patients hospitalized after acute myocardial infarction (AMI). Prevalence rates varied depending on the assessment method. Across the eight studies that used a standardized diagnostic interview, the prevalence of major depression varied from 16 % to 27 %, with a weighted prevalence of 19.8 % (Thombs et al. 2006). The largest of the included studies – the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study, which involved over 9,000 patients – reported a prevalence of 20 % (Berkman et al. 2003). Across the 17 studies that used a validated questionnaire, the prevalence of "clinically significant depression" varied from 10 % to 47 %, with variation depending on the instrument used (Thombs et al. 2006). When depression was classified as Beck Depression Inventory (BDI) scores $\geq$10, the prevalence rates were relatively high, ranging from 20 % to 37 %, with a weighted prevalence of 31 %. In contrast, when depression was classified as Hospital Anxiety and Depression Scale – Depression (HADS-D) scores $\geq$8, the prevalence was considerably lower, ranging from 11 % to 17 %, with a weighted prevalence of 15.5 % (Thombs et al. 2006). Given these variations, it is difficult to categorically report prevalence rates for in-hospital depression post-cardiac event. However, it is generally agreed that 15–20 % of patients meet diagnostic criteria for major depression while in hospital after acute myocardial infarction (AMI) or coronary artery bypass graft surgery (CABGS) (Colquhoun et al. 2013; Lichtman

et al. 2008), with many more showing elevated depressive symptoms (Barefoot et al. 2000; Carney and Freedland 2003; Frasure-Smith and Lesperance 2003).

Relatively few studies have reported prevalence rates for in-hospital anxiety. In studies of CABGS patients, both presurgical and postsurgical anxiety rates tend to be reported. In some cases, anxiety is shown to remit after surgery. For example, in a German study of 142 CABGS patients, with anxiety classified as Hospital Anxiety and Depression Scale – Anxiety (HADS-A) scores $\geq$8, the presurgical rate was 34 % (Krannich et al. 2007). By 10 days postsurgery, the prevalence of anxiety had reduced, albeit nonsignificantly, to 25 % (Krannich et al. 2007). Symptom remission was more likely in younger than in older patients (Krannich et al. 2007). However, in other studies, anxiety rates increase after surgery. For example, in an Australian study of 147 CABGS patients, with anxiety classified using the Depression, Anxiety and Stress Scale (DASS), the preoperative prevalence of mild to severe anxiety was 27 %, whereas the postoperative prevalence was significantly higher at 45 % (Andrew et al. 2000). The inclusion of patients with "mild" symptoms (DASS anxiety scores 8–9) may have inflated these rates: excluding these patients, the presurgical and postsurgical prevalence of moderate to severe anxiety (DASS anxiety $\geq$10) was 20 % and 33 %, respectively (Andrew et al. 2000). In addition, some patients awaiting surgery have either generalized anxiety disorder (GAD) or panic disorder, as assessed by structured diagnostic interview. A recent review indicated prevalence rates varying from 2 % to 10.2 % for GAD and 10.8 % for panic disorder presurgery (Tully and Baker 2012). The review confirmed that many more patients have subclinical anxiety symptoms both pre- and postsurgery (Tully and Baker 2012).

These rates of in-hospital post-event anxiety and depression are considerably higher than seen in the general community. For example, approximately 5 % of Australian adults report a depressive illness and around 4 % anxiety-related problems (AIHW 2012). Similarly, the prevalence of major depression in American adults is approximately 5 % (American Psychiatric Association 2013; Egede 2007). In a study comparing AMI and CABGS patients with healthy adults, rates of anxiety and depression were significantly higher in both patient groups (Moser et al. 2010). It appears that rates of anxiety and depression among cardiac patients are up to four times that seen in the general population.

Impacts of Anxiety and Depression on Health Behaviors, Morbidity, and Mortality

Modifiable risk factors account for up to 90 % of the overall risk of acute myocardial infarction (AMI) (Yusuf et al. 2004). In patients with established coronary heart disease, modifiable risk factors affect the progression of the disease and the likelihood of a future event, while lifestyle changes improve risk factor profiles and prognosis (Euroaspire II Study Group 2001). In particular, smoking cessation reduces cardiac patients' mortality risk by 36 % after 5 years (Critchley and Capewell 2003) and by 50 % after 10 years (Cavender et al. 1992). Increasing

physical activity also reduces the risk of further events and death (Iestra et al. 2005; Moholdt et al. 2008), as does reducing dietary fat intake (Iestra et al. 2005; Mead et al. 2006). Nonetheless, the prevalence of unhealthy lifestyles and modifiable risk factors remains high in cardiac populations (Euroaspire II Study Group 2001; Murphy et al. 2011).

Post-event anxiety and depression put cardiac patients at a distinct disadvantage in terms of engagement in activities that promote health and well-being. Compared with their nondepressed counterparts, depressed patients are more likely to smoke (Gravely-Witte et al. 2009; Kronish et al. 2006; Murphy et al. 2012) and to relapse after quitting (Perez et al. 2008). They consume higher levels of dietary fat (Murphy et al. 2012; Ziegelstein et al. 2000) and engage in less physical activity (Allan et al. 2007; Kronish et al. 2006; Murphy et al. 2012; Ziegelstein et al. 2000) than those who are not depressed. Similarly, anxious patients have higher smoking rates (Kuhl et al. 2009; Murphy et al. 2012; Perez et al. 2008) and dietary fat intake (Murphy et al. 2012), although, once sociodemographic factors are taken into account, their physical activity levels tend to be similar to those of non-anxious patients (Kuhl et al. 2009; Murphy et al. 2012).

In addition to their poor health behaviors, depressed patients are less adherent to recommended treatments (DiMatteo et al. 2000). First, they show poorer medication adherence than nondepressed patients, being more likely to forget to take their medications and to skip doses and less likely to take medication as prescribed (Gehi et al. 2005; Kronish et al. 2006). Second, they are disinclined to attend cardiac rehabilitation programs (Frasure-Smith et al. 1993; Kronish et al. 2006; Whitmarsh et al. 2003; Blumenthal et al. 1999; Lane et al. 2001) and, if they do attend, are more likely to discontinue (Blumenthal et al. 1999; Kronish et al. 2006). Both medication adherence (Ho et al. 2006) and attendance at cardiac rehabilitation (Beauchamp et al. 2013; Denollet and Brutsaert 2001) have been shown to impact positively on survival.

It is not surprising then that cardiac patients who are anxious or depressed after an acute cardiac event have poorer morbidity and mortality outcomes than their non-anxious and nondepressed counterparts (van Melle et al. 2004; Barth et al. 2004). For example, anxious patients are at increased risk of hospital readmission within 30 days of discharge after CABGS (Murphy et al. 2008b) and of reinfarction following a first AMI (Strik et al. 2003). In terms of mortality outcomes, presurgical anxiety has been shown to predict all-cause mortality, independent of age and comorbid disease (Tully et al. 2008a). Post-event anxiety has also been shown to predict cardiac mortality up to 3 years after a first event, independent of other risk factors (Strik et al. 2003). A recent review included four studies reporting associations between generalized anxiety disorder (GAD) and cardiac morbidity and mortality among CHD patients (Tully et al. 2013). The earliest study, involving 804 acute coronary syndrome (ACS) patients, reported a 2.29 increased risk of re-event or death at 2 years in patients shown to have GAD at 2 months post-event (Frasure-Smith and Lesperance 2008). The largest study, involving over 1,000 CHD patients, demonstrated a 74 % increased risk of re-event or death, with adjustment for confounders, among patients with GAD

(Martens et al. 2010). An Australian study of 158 CABGS patients showed that GAD conferred a threefold increased risk of in-hospital re-events and death, after adjustment for confounders (Tully et al. 2011). Contrary to other findings, a 2011 study of 436 ACS patients found that GAD was associated with a reduced risk of death over 5 years post-event, suggesting that GAD may have a protective effect (Parker et al. 2011). Likewise, a study of over 2,000 cardiac patients referred for exercise testing found that elevated anxiety as assessed by the HADS-A was associated with lower 5-year mortality (Herrmann et al. 2000). While it increases risks via physiological mechanisms (Olafiranye et al. 2011), anxiety may simultaneously encourage help-seeking behaviors that reduce risk (Herrmann et al. 2000). Consistent with this view, it has been suggested that some forms of anxiety, particularly generalized anxiety about health, might actually improve cardiac medication adherence (DiMatteo et al. 2000).

Depressed patients are similarly at risk of reinfarction after AMI (Frasure-Smith et al. 1993; Strik et al. 2003) and of a recurrent cardiac event and hospital readmission in the first 12 months after bypass (Connerney et al. 2001; Tully et al. 2008b). Likewise, numerous studies conducted in the late 1990s and early 2000s demonstrated that post-event depression predicts mortality up to 10 years later (Barefoot et al. 2000; Frasure-Smith et al. 1999; Welin et al. 2000). Two meta-analyses published in 2004 confirmed the earlier findings, demonstrating that depression more than doubles the risk of mortality after a cardiac event (Barth et al. 2004; van Melle et al. 2004). One meta-analysis included 20 studies of patients with a range of CHD diagnoses, with the length of follow-up varying from 3 months to 10 years (Barth et al. 2004). The authors reported an unadjusted odds ratio of 2.24 between depression and all-cause mortality (Barth et al. 2004). The other meta-analysis was restricted to studies of post-AMI patients, involved 6,367 patients across 16 cohorts, and endpoints within 2 years (van Melle et al. 2004). The authors reported odds ratios for all-cause and cardiac mortality of 2.38 and 2.59, respectively (van Melle et al. 2004). Of note was the finding that the association between depression and mortality was more pronounced in studies undertaken prior to 1992, possibly due to improved treatments for CHD which may simultaneously reduce the negative physiological impact of depression (Carney et al. 2004; van Melle et al. 2004).

Indeed, the mechanisms whereby depression might adversely affect patients' outcomes have been well documented and debated. In particular, depression and CHD share several biological mechanisms. Depressed patients have higher levels of biomarkers that promote atherosclerosis, reduced heart rate variability suggesting increased sympathetic activity, increased C-reactive protein, an indicator of increased inflammatory response, altered serotonergic pathways, and altered platelet aggregability (Carney et al. 1988; Lichtman et al. 2008; Sheps and Rozanski 2005; Soufer et al. 2002; Taylor 2010). It has also been postulated that CHD and depression have common genetic patterns related to serotonin and inflammatory responses (McCaffery et al. 2006). Together with their behavioral disadvantage, depressed patients are also socioeconomically disadvantaged through their lower income and education, manual occupations, and social isolation (Cheok

et al. 2003), all of which are associated with increased mortality risk (Brummet et al. 2003; Case et al. 1992). Importantly though, it has been suggested that more research is needed on possible mechanisms underlying the relationship between depression and mortality (Carney et al. 2004).

So what of the role of cardiac disease severity in explaining the association between post-event depression and mortality? Is it possible that depressed patients are at increased risk of re-events and earlier death largely because of their advanced atherosclerosis? Unfortunately, some studies have not adequately controlled for disease severity in investigating the causal relationship between depression and death. Only six of the studies included in the meta-analysis by Barth and colleagues controlled for disease severity, using either ejection fraction (Carney et al. 2003; Connerney et al. 2001; Welin et al. 2000), Killip class (Frasure-Smith et al. 1993, 1995), or a combined hazard score including ejection fraction and other indicators of myocardial damage (Barefoot et al. 2000). A further two controlled for previous AMI (Herrmann et al. 2000; Irvine et al. 1999). Six also controlled variously for other potential confounders, including age (Barefoot et al. 2000; Carney et al. 2003; Herrmann et al. 2000; Ladwig et al. 1994), smoking status (Carney et al. 2003; Frasure-Smith et al. 1993, 1995; Welin et al. 2000), diabetes (Carney et al. 2003), hypertension (Herrmann et al. 2000; Welin et al. 2000), and hypercholesterolemia (Welin et al. 2000). In the meta-analysis, the adjusted odds ratio remained significant but dropped to 1.76 indicating that depression conferred a 75 % increased risk of death rather than the doubling of risk seen prior to adjustment (Barth et al. 2004). Nonetheless, depression remained predictive independent of disease severity. The meta-analysis by van Melle and colleagues involved only bivariate analyses and thus did not take into account the effects of possible confounders such as disease severity, diabetes, smoking, and other elevated risk factors. Several authors have noted the importance of adjusting for confounders, particularly disease severity (Lane et al. 2005; Murphy et al. 2013). The postulated physiological and biochemical mechanisms for the link between post-event depression and mortality suggest that it is imperative that disease severity is accounted for in such studies.

Identification of Depression in Cardiac Patients

Given their poorer prognosis, it is important to identify and support patients who are anxious or depressed after their cardiac event. This section focuses on strategies for identifying depressed cardiac patients in particular and discusses the inherent difficulties in ensuring accurate identification. The treatment of anxious and depressed patients is discussed in other chapters.

Current Depression Screening Guidelines

In light of the high prevalence and prognostic importance of post-event depression, it has been proposed that all cardiac patients should be screened for depression

around the time of their cardiac event. Specifically, in 2008, the American Heart Association recommended that all cardiac patients be screened for depression "in various settings, including the hospital, physician's office, clinic, and cardiac rehabilitation centre" (Lichtman et al. 2008). Australian guidelines, released in 2013, similarly recommend routine depression assessments "at first presentation and again at the next follow-up appointment," with repeat assessments recommended on a yearly basis (Colquhoun et al. 2013). The Australian guidelines specifically recommend a screen 2–3 months after the cardiac event (Colquhoun et al. 2013).

Both guidelines recommend using the Patient Health Questionnaire (PHQ) for screening, with endorsement of either or both of the PHQ-2 items warranting administration of the full PHQ-9. The PHQ-9 has been shown to have good sensitivity and specificity when used with cardiac patients (Gilbody et al. 2008). It can be completed in less than 5 min and yields both a provisional depression diagnosis and a severity score (Lichtman et al. 2008). The items correspond with the nine features of depression used in determining a diagnosis of major depressive disorder (MDD), as outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (American Psychiatric Association 2013).

A positive screen requires specific action, depending on the severity of depression indicated. For patients with mild symptoms (PHQ $<$ 10), a "wait and watch" protocol applies, with rescreening during a subsequent medical appointment recommended (Colquhoun et al. 2013; Lichtman et al. 2008). For patients with high scores (PHQ $\geq$ 10), referral for more comprehensive clinical evaluation by a professional qualified in the diagnosis and management of depression is advised (Colquhoun et al. 2013; Lichtman et al. 2008).

Problems with Depression Screening in Cardiac Patients

Since the release of the depression screening guidelines, there has been some debate as to the appropriateness of depression screening recommendations. Some authors have noted that there is insufficient evidence that routine depression screening is beneficial, with no clear evidence of positive patient outcomes (Ski and Thompson 2011; Thombs et al. 2009; Tully and Baker 2012). Indeed, shortly after the American guidelines were released, a systematic review reported that no trials had tested the impacts of depression screening on either depression or CHD outcomes (Thombs et al. 2008). A systematic review of five trials of "screen and refer" protocols undertaken in the primary care setting concluded that while screening improves detection and increases treatment, it does not improve depression symptoms or patient outcomes (Gilbody et al. 2008). As noted by Thombs and colleagues, screening protocols "cannot be advocated until a thorough evaluation of risk and benefit is completed" (Thombs et al. 2009). Clearly more research on the impact of depression screening is required.

In addition, it has been noted that there would be significant costs if screening and referral guidelines were strictly followed, both in terms of burden on the service system and negative impacts on the patient. In particular, Thombs and Ziegelstein

highlight the perils of false-positive assessment, including "unnecessary diagnostic testing, adverse effects and costs of inappropriate treatment, and the sequelae of being incorrectly labeled" (Thombs and Ziegelstein 2010). Thombs and colleagues also note that such a practice "would be unduly resource intensive" and, to be effective, would require significant changes in current models of care (Thombs et al. 2008).

While the hospital stay may represent an opportune time for depression screening from a practical standpoint, the risks of misclassification are particularly high at this time (Hasnain et al. 2011; Murphy et al. 2013; Ski and Thompson 2011; Tully and Higgins 2014). As noted above, there is a possibility of "false-positive" classification of patients with transient in-hospital distress symptoms. Hasnain and colleagues state that "screening too close to the cardiac event would likely categorize a larger number of patients as depressed than it might if it was done later" (Hasnain et al. 2011). In addition, there is a possibility of "false-negative" classification of patients who have delayed depressive symptoms which appear during convalescence, in the period after hospital discharge. In a recent review, Hare and colleagues argue that "reported depression is often repressed or suppressed in hospital because of initial denial of affect" (Hare et al. 2013).

Two issues are at work in regard to early misclassification: first, whether the presenting symptoms are actually depression or, instead, a normal bereavement response to the life-threatening event, which would more accurately be described as "mourning" (Freud 1917), "normal sadness" (Horwitz and Wakefield 2005, 2007), or "adjustment disorder" (Goble et al. 1989; Hare et al. 2013), and, second, the course of the depressive symptoms in the period after hospital discharge, that is, whether the symptoms are transient, chronic, or persistent (Murphy et al. 2008a, 2013; Tully and Higgins 2014). Both these issues are discussed in the following section.

High Incidence of Transient "Normal" Distress

Many patients experience a strong emotional reaction at the time of or soon after an acute cardiac event. Common emotional responses include shock, low or fluctuating mood, sadness, worry, guilt, and anger (Goble et al. 1989; Hare et al. 2013; Higgins et al. 2007). Mood change is displayed by tiredness, irritability, tearfulness, loss of pleasure in usual activities, withdrawal from others, early waking and other sleep disturbances, and changes in appetite and sex drive (Goble et al. 1989; Hare et al. 2013; Higgins et al. 2007). Cognitive changes that typically co-occur include confusion and forgetfulness, inability to concentrate, nightmares, reduced self-esteem, concerns about role changes, particularly regarding paid work, physical health and independence, and pessimism about the future (Goble et al. 1989; Hare et al. 2013; Higgins et al. 2007).

These mood changes and associated symptoms can be considered part of the normal emotional reaction to the cardiac event. It has been noted that "after acute cardiac illness, depression is a normal response to loss, threat of other losses, and awareness of mortality" (Goble et al. 1989). Indeed, Goble and colleagues argue that "after acute AMI, depression is to be expected. . . is not an abnormal reaction and is not an illness" (Goble et al. 1989). More recent authors have similarly agreed that symptoms characteristically associated with depression – fatigue, loss of

appetite, reduced activity, insomnia, and difficulty concentrating – may occur as a normal reaction to illness, hospitalization, or significant loss (Hare et al. 2013; Horwitz and Wakefield 2005, 2007; Thombs et al. 2006; Tully and Baker 2012; Tully and Higgins 2014).

Indeed, many of the symptoms of common distress or bereavement that typically follow the acute event closely mirror the criteria for a diagnosis of depression. This overlap underscores the difficulties of accurate diagnosis close to the cardiac event. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (American Psychiatric Association 2013), for a diagnosis of major depressive disorder (MDD), at least five of the nine symptoms listed in Box 1 need to be present nearly every day for the previous 2 weeks. These symptoms are very similar to the "normal emotional reactions" outlined earlier. Several authors have noted the conceptual overlap between "normal sadness or distress" and depression (Goble et al. 1989; Hare et al. 2013; Horwitz and Wakefield 2007; Murphy et al. 2014; Thombs et al. 2006; Tully and Baker 2012). In their book *The Loss of Sadness*, Horwitz and Wakefield argue that the "recent explosion of putative depressive disorder... is largely a product of classifying many instances of normal sadness as mental disorders" (Horwitz and Wakefield 2007).

Given the similarity between the diagnostic criteria and the emotional reactions that commonly accompany a cardiac event, the challenge for health professionals is to differentiate a "normal common reaction" from "depression," particularly when patients are assessed during hospitalization or soon after discharge. It has been noted that "the separation of normal sadness and depressive disorder is a sensible and legitimate, indeed a crucial one" (Horwitz and Wakefield 2007). Understanding the course of symptoms can assist health professionals in distinguishing between the two conditions.

Box 1: DSM Criteria for Major Depression

- Depressed mood or irritable (feels sad or empty or appears tearful)
- Decreased interest of pleasure
- Change in weight or appetite
- Change in sleep
- Change in activity
- Fatigue of loss of energy
- Guilt/worthlessness
- Diminished concentration
- Thoughts of death or suicide

The Course of Depression: Persistence, Resolution, and Delay

Many studies have investigated the course of depression after a cardiac event, tracking patients at various points during the first 12 months after hospital discharge. These studies point to the transient nature of depressive symptoms for many

patients, reinforcing the notion of a normal emotional reaction that passes with time. When patients are reassessed within the first 2 months of their cardiac event, persistence of depression is quite prevalent: typically, around 60 % (Davis and Jensen 1988) to 70 % (Lauzon et al. 2003) of patients who are depressed in hospital remain so at 2 months. However, when patients are reassessed at later timepoints, depression persistence is less likely. For example, of 30 patients with in-hospital major depression in Schleifer and colleagues' study of 190 AMI patients, major depression persisted in only 11 (36 %) by 3–4 months post-event (Schleifer et al. 1989). This constitutes less than 6 % of the full baseline sample, a rate similar to that seen in the general population. In a Norwegian study of 288 AMI patients, rates of both anxiety and depression at 3, 6, 12, and 18 months post-event were no higher than seen in the general population (Hanssen et al. 2009). Indeed, in regard to depressive symptoms, AMI patients showed significantly lower HADS-D scores than the reference group at the 3- and 12-month assessments (Hanssen et al. 2009).

Some studies have used statistical modeling techniques to track the possible trajectories of depression in patients after AMI and CABGS. These studies have similarly shown considerable resolution of in-hospital depressive symptoms. For example, in an Australian cohort of 184 CABGS patients, all 26 (14 %) patients who were above threshold for depression in hospital followed a trajectory of symptom resolution, mostly in the first 2–3 months, and were under threshold by the 6-month mark (Murphy et al. 2008a). Similarly, in a cohort of 160 AMI and CABGS patients, all 27 (17 %) who were above threshold in hospital showed resolution by 6 months (Murphy et al. 2014). In a Netherlands study of 475 AMI patients, where five depression trajectories were identified, a lower but still substantial 26 % of patients who were depressed in hospital showed remission of symptoms over the 12 months after their event (Kaptein et al. 2006). These findings suggest that, for many patients, in-hospital depressive symptoms resolve during convalescence. Several authors have agreed that early depressive symptoms remit spontaneously for many cardiac patients (Hare et al. 2013; Tully and Baker 2012).

At the same time, other patients who are not depressed in hospital go on to become depressed in the months that follow. For example, in a cohort of 555 CABGS patients, 36 (6.5 %) developed depression in 6 months after discharge, representing 9 % of initially nondepressed patients (Blumenthal et al. 2003). Similarly, in a cohort of 123 CABGS patients who were nondepressed at baseline, 22 (10 %) had developed depression by 6 months (Peterson et al. 2002). Likewise, in the cohort of 184 CABGS patients, 26 (14 %) who were not depressed in hospital had become depressed by the 6-month mark, representing 16 % of the initially nondepressed patients (Murphy et al. 2008a). These findings suggest that between 10 % and 16 % of initially nondepressed CABGS patients go on to develop depression by 6 months after surgery.

It is useful to overlay a trauma framework when considering trajectories of depressive symptoms after an acute cardiac event. While much of the early trauma research focused on responses to external events such as war, terrorism, accident, assault, and natural disasters, more recent studies have considered acute health crises as "traumatic" events (Tedstone and Tarrier 2003). Traumatic events are

defined as events that are out of the ordinary, leave people with a perceived lack of control or sense of powerlessness, and create long-lasting problems leading to a sense of hopelessness (Cavalcanti-Ribeiro et al. 2012). Some of the common psychological problems associated with traumatic events are intrusive thoughts and memories, flashbacks, hypervigilance, mental and behavioral avoidance, sadness, and sleep problems (Joseph 2011). Depending upon the nature of the stressor, its intensity, severity, and duration of suffering or threat, psychological responses such as anxiety, fear, guilt, anger, and irritability may be present for a long time after the threat has receded (Tedeschi and Calhoun 2004). Thoughts and feelings are affected, especially if the event was sudden (such as an AMI), with initial reactions of shock, psychological numbness, disbelief, anger, fear, and worry. Anxiety is one of the most commonly reported responses and tends to be associated with a perception of significant threat to life or health (Tedeschi and Calhoun 1995). Depressive symptoms – including sadness, low energy, and decreased interest in life – are also common and tend to be associated with the perception of significant loss (Hodgkinson and Stewart 1991). It is not necessarily the type of event but rather an individual's perception of it and response to it in the aftermath that renders it as stressful or traumatic.

According to trauma theory, there are four typical responses to a traumatic event such as an acute cardiac event or, indeed, other life-threatening illnesses or unexpected diagnosis of disease. First, there are those – such as the patients described earlier – "who recover." Second, there are those with "chronic" symptoms, whose early depression symptoms persist beyond the period of physical recovery. Third, there are those with "delayed" symptoms, as outlined above, which do not appear until further into the convalescence period. And finally, there are "resilient" patients who do not experience depressive symptoms after their acute event. These four typical responses to trauma are depicted in Fig. 1.

There is some evidence in the cardiac literature that only patients whose symptoms are present beyond initial convalescence after the acute event – those with either chronic or delayed symptoms – are at increased mortality risk (Blumenthal et al. 2003; Murphy et al. 2008a, b; Tully and Baker 2012). In the US study of CABGS patients, those whose in-hospital depression resolved in the first 6 months had a 5-year mortality risk of 10 %, identical to that of nondepressed patients, whereas those whose in-hospital depression persisted had almost twice that mortality risk (Blumenthal et al. 2003). Patients with "new" depression had an intermediate mortality risk of 14 % (Blumenthal et al. 2003). In a 3-year follow-up of 124 CABGS patients, the rates of re-events and death were significantly higher in those with "new" depression at 6 months: the 3-year re-event/mortality rate was 14 % in those who developed "new" depression compared to 3 % in those who remained nondepressed over the 6-month post-event period (Peterson et al. 2002). In a 12-year follow-up of 180 Australian AMI and CABGS patients, there was a high 64 % mortality among those whose in-hospital depression persisted or worsened and a low 14 % mortality rate among those whose in-hospital symptoms resolved (Murphy et al. 2013). Indeed, the death rate among those with remitted depression was lower than that among patients who were nondepressed in hospital

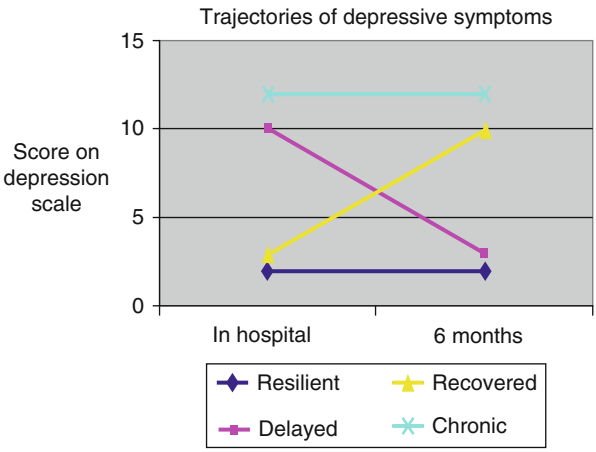


Fig. 1 Four typical trajectories of depressive symptoms after an acute cardiac event

and remained so during convalescence (Murphy et al. 2013). These findings suggest that in-hospital depressive symptoms do not necessitate a poor prognosis and further point to the probability of misclassification of "at-risk" patients if identification is based purely on an in-hospital assessment.

Indications for Risk Stratification

Given the risks of and problems associated with misclassification, it is important that strategies are adopted to ensure accurate identification of depressed patients. First and foremost, it has been recommended that systems be established for repeat screening of cardiac patients further into convalescence, so that identification is not based purely on a single, in-hospital screen (Colquhoun et al. 2013; Hare et al. 2013; Murphy et al. 2013; Ski and Thompson 2011). Ideal opportunities for repeat screening include during patients' attendance at cardiac rehabilitation programs and regular visits to the general practitioner, family physician, and cardiologist (Hare et al. 2013; Murphy et al. 2013). It has also been suggested that psychologists undertake opportune depression screening in presenting cardiac patients (Tully and Higgins 2014).

Second, it would seem prudent that health professionals be alert to patients at higher risk of depression, using sociodemographic and medical characteristics as identifiers or "red flags." It has been noted that "risk stratification of patients who screen positive for depression soon after an acute cardiac event is essential to prevent unnecessary intervention" (Hasnain et al. 2011). Patients who are at higher risk of developing depression after a cardiac event could potentially be flagged upon admission to or discharge from hospital and at later points during convalescence.

Several sociodemographic and medical characteristics have been identified as risk factors for anxiety and depression after an acute cardiac event. Female cardiac patients (Burker et al. 1995; Cheok et al. 2003; Duits et al. 1998; Keresztes et al. 2003; Mallik et al. 2005; Strik et al. 2004) and those who are younger

(Cheok et al. 2003; Gallagher et al. 2003; Mallik et al. 2005; Strik et al. 2004) consistently show higher rates of depression than males and older patients, respectively. Social isolation, lack of social support, and living alone also increase the risk of post-event depression (Burker et al. 1995; Cheok et al. 2003; Frasure-Smith et al. 2000). Unemployment also confers increased risk (Cheok et al. 2003; Gallagher et al. 2003), as does poor physical health and lower physical functioning (Cheok et al. 2003; Mallik et al. 2005), the presence of comorbidities (Mallik et al. 2005; Watkins et al. 2003), and other associated conditions such as diabetes (Frasure-Smith et al. 1999, 2000). While relatively few studies have identified predictors of post-event anxiety, female gender (Duits et al. 1998; Moser et al. 2010) and low education (Moser et al. 2010) have been identified as significant risk factors. There is some evidence that AMI patients experience more anxiety and depression than CABGS patients in early convalescence (Westin et al. 1997), although there is no evidence that this difference is sustained (Moser et al. 2010; Westin et al. 1997).

Some studies have specifically focused on the identification of red flags for persistent, worsening, or new depressive symptoms in the post-event period, as a means of identifying patients at high risk of chronic or delayed depression (Murphy et al. 2008a, 2014). Key red flags include having a history of depression or anxiety, younger age (aged <55), living alone or other indicators of social isolation, poorer self-rated health, financial difficulties, diabetes and other comorbid conditions, smoking, and compounded loss (Murphy et al. 2008a, c, 2014). Key red flags for increased depression risk are shown in Box 2. Several authors have similarly emphasized the importance of the patients' mental health history as a strong indicator of depression risk post-event (Martens et al. 2008; Spijkerman et al. 2005). Rather than relying on depression screen results in isolation, health practitioners could be guided by the presence or absence of these red flags as to whether a particular patient is at heightened risk of a poor depression trajectory. Patients who screen positive and also present with specific red flags could be stratified for more rigorous follow-up, rescreening, referral, and treatment. Simultaneously patients who initially screen negative but who present with red flags for increased depression risk could be targeted for repeat screening.

Box 2: Red Flags for Increased Depression Risk

- History of anxiety or depression
- Age ≤ 55 years
- Living alone or lack of social support
- Poor self-rated health
- Financial difficulty
- Diabetes
- Other comorbid conditions
- Smoking
- Recent bereavement or compounded loss

Implications for Clinical Practice

What are the implications of these findings in terms of clinical practice? Given that early distress resolves for many patients, patients who present with early symptoms can be reassured that their distress, worry, and other changes in mood and behaviors are likely to be transient and can be considered part of a "normal adjustment response." Normalizing common emotional reactions to a cardiac event may well enhance psychological recovery and warrant empirical investigation. Already there is some evidence that it is desired by patients. A study of 160 Australian cardiac patients demonstrated that over 80 % want to be told about what to expect emotionally after they leave hospital (Murphy et al. 2015). The symptoms commonly experienced by patients after the event – low or fluctuating mood, tearfulness, loss of pleasure in usual activities, sleep disturbance, reduced self-esteem, changes in appetite and sex drive, concerns about role changes, and worries about the future (Goble et al. 1989; Higgins et al. 2007) – are typical of a normal grief response to an experience of loss or trauma (Goble et al. 1989). "Prevention and management depend on the patient's learning that a depressed mood is a normal temporary response to the illness… and that recovery is the rule" (Goble et al. 1989).

Nonetheless, identification of depressed patients is essential. Given that one in five patients goes on to experience serious depression and is thereby at increased morbidity and mortality risk, patients also need to be alerted that depression is possible. If patients are alerted to this risk early on, before hospital discharge, they may be better placed to identify depressive symptoms if and when they arise. Again this hypothesis warrants empirical investigation.

Health professionals can be guided by both the trajectories of the symptoms, based on repeat screens, and the presence of other risk indicators or red flags as to whether a particular patient is likely to be experiencing a normal emotional reaction or is, indeed, likely to be depressed. Stratification of high-risk patients toward more rigorous follow-up, referral, and treatment may improve patient outcomes without unduly burdening the health system and warrants further investigation.

The importance of repeat screening cannot be overemphasized. Health professionals across a range of healthcare settings need to be equipped to undertake depression assessment. These include cardiologists, who see the patient on multiple occasions from the time of the event, physicians and practice nurses working in general practice, and nurses and other health professionals working both on the hospital ward and in cardiac rehabilitation. Approaches might include routine screening for all presenting patients or, in some settings, targeted screening of high-risk patients.

References

AIHW. (2012). *Australia's health 2012. Australia's health no. 13. Cat. no. AUS 156*. Canberra: AIHW.

Allan, J. L., Johnston, D. W., Johnston, M., & Mant, D. (2007). Depression and perceived behavioural control are independent predictors of future activity and fitness after coronary syndrome events. *Journal of Psychosomatic Research, 63*, 501–508.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual for Mental Disorders fifth edition (DSM-5)*. Arlington: American Psychiatric Association.

Andrew, M. J., Baker, R. A., Kneebone, A. C., & Knight, J. L. (2000). Mood state as a predictor of neuropsychological deficits following cardiac surgery. *Journal of Psychosomatic Research, 48* (6), 537–546.

Barefoot, J. C., Brummet, B. H., Helms, M. J., Mark, M. D., Siegler, I. C., & Williams, R. B. (2000). Depressive symptoms and survival of patients with coronary artery disease. *Psychosomatic Medicine, 62*, 790–795.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine, 66*, 802–013.

Beauchamp, A., Worcester, M., Ng, A., Murphy, B., Tatoulis, J., Grigg, L., . . . Goble, A. (2013). Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up. *Heart*. 9, 620–25. Published online 4 Dec 2012. doi:10.1136/heartjnl-2012-303022.

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catellier, D., Cowan, M. J., . . . Schneiderman, N. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. *JAMA, 289*(23), 3106–3116.

Blumenthal, J. A., Babyak, M. A., Moore, K. A., Craighead, W. E., Herman, S., Khatri, P., . . . Krishnan, K. R. (1999). Effects of exercise training on older patients with major depression. Archives of Internal Medicine*, 159*(19), 2349–2356.

Blumenthal, J. A., Lett, H. S., Babyak, M. A., White, W., Smith, P. K., Mark, D. B., . . . Newman, M. F. (2003). Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet, 362*(9384), 604–609.

Brummet, B. H., Barefoot, J. C., & Vitaliano, P. P. (2003). Associations among social support, income and depression: The UNC Alumni Heart Study. *International Journal of Behavioral Medicine, 10*, 239–250.

Burker, E. J., Blumenthal, J. A., Feldman, M., Burnett, R., White, W., Smith, L. R., . . . Reves, J. G. (1995). Depression in male and female patients undergoing cardiac surgery. *British Journal of Clinical Psychology, 34*, 119–128.

Carney, R. M., & Freedland, K. E. (2003). Depression, mortality, and medical morbidity in patients with coronary heart disease. *Biological Psychiatry, 54*, 241–247.

Carney, R. M., Rich, M. W., teVelde, A., Saini, J., Clark, K., & Freedland, K. E. (1988). The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. *Journal of Psychosomatic Research, 32*(2), 159–164.

Carney, R. M., Blumenthal, J. A., Catellier, D., Freedland, K. E., Berkman, L. F., Watkins, L. L., . . . Jaffe, A. S. (2003). Depression as a risk factor for mortality after acute myocardial infarction. *American Journal of Cardiology, 92*, 1277–1281.

Carney, R. M., Freedland, K. E., & Sheps, D. S. (2004). Depression is a risk factor for mortality in coronary heart disease: Editorial. *Psychosomatic Medicine, 66*(6), 799–801.

Case, R. B., Moss, A. J., Case, N., McDermott, M., & Eberly, S. (1992). Living alone after myocardial infarction, impact on prognosis. *JAMA, 267*, 515–519.

Cavalcanti-Ribeiro, P., Andrade-Nascimento, M., Morais-de-Jesus, M., Melquiades de Medeiros, G., Daltro-Oliveira, R., Oliveira Conceicao, J., & Castro Quarantini, L. (2012). Post-traumatic stress disorder as a comorbidity: Impact on disease outcome. *Expert Review Neurotherapy, 12* (8), 1023–1037.

Cavender, J. B., Rogers, W. J., Fisher, L. D., Gersh, B. J., Coggin, C. J., & Myers, W. O. (1992). Effect of smoking on survival and morbidity in patients randomized to medical or surgical

therapy in the coronary artery surgery study (CASS): 10-Year follow-up. *Journal of the American College of Cardiology, 20*, 287–294.

Cheok, F., Schrader, G., Banham, D., Marker, J., & Hordacre, A. L. (2003). Identification, course, and treatment of depression after admission for a cardiac condition: Rationale and patient characteristics for the Identifying Depression As a Comorbid Condition (IDACC) project. *American Heart Journal, 146*(6), 978–984.

Colquhoun, D. M., Bunker, S. J., Clark, D. M., Glozier, N., Hare, D. L., Hickie, I. B., . . . Branagan, M. G. (2013). Screening, referral and treatment for depression in patients with coronary heart disease: A consensus statement from the National Heart Foundation of Australia. *Medical Journal of Australia, 198*(9). doi:10.5694/mja13.10153.

Connerney, I., Shapiro, P. A., McLaughlin, J. S., Bagiella, E., & Sloan, R. P. (2001). Relation between depression after coronary artery bypass surgery and 12-month outcome: A prospective study. *Lancet, 358*, 1766–1771.

Critchley, J. A., & Capewell, S. (2003). Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: A systematic review. *JAMA, 290*(1), 86–97. doi:10.1001/jama.290.1.86290/1/86 [pii].

Davis, T., & Jensen, L. (1988). Identifying depression in medical patients. *Image – The Journal of Nursing Scholarship, 20*, 191–195.

Denollet, J., & Brutsaert, D. L. (2001). Reducing emotional distress improves prognosis in coronary heart disease. *Circulation, 104*, 2018–2023.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine, 160*(14), 2101–2107. doi: ioi90679 [pii].

Duits, A. A., Duivenvoorden, H. J., Boeke, S., Taams, M. A., Mochtar, B., Krauss, X. H., . . . Erdman, R. A. (1998). The course of anxiety and depression in patients undergoing coronary artery bypass graft surgery. *Journal of Psychosomatic Research, 45*(2), 127–138.

Egede, L. E. (2007). Major depression in individuals with chronic medical disorders: Prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *General Hospital Psychiatry, 29*, 409–416.

Euroaspire II Study Group. (2001). Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. *European Heart Journal, 22*(7), 554–572. doi:10.1053/euhj.2001.2610. S0195668X01926107 [pii].

Frasure-Smith, N., & Lesperance, F. (2003). Depression and other psychological risks following myocardial infarction. *Archives of General Psychiatry, 60*, 627–636.

Frasure-Smith, N., & Lesperance, F. (2008). Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Archives of General Psychiatry, 65*(1), 62–71.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1993). Depression following myocardial infarction. Impact on 6-month survival. *JAMA, 270*, 1819–1825.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1995). Depression and 18-month prognosis after myocardial infarction. *Circulation, 91*, 999–1005.

Frasure-Smith, N., Lesperance, F., Juneau, M., Talajic, M., & Bourassa, M. G. (1999). Gender, depression, and one-year prognosis after myocardial infarction. *Psychosomatic Medicine, 61*, 26–37.

Frasure-Smith, N., Lesperance, F., Gravel, G., Masson, A., Juneau, M., Talajic, M., & Bourassa, M. G. (2000). Social support, depression, and mortality during the first year after myocardial infarction. *Circulation, 101*, 1919–1924.

Freud, S. (1917). Mourning and melancholia. In J. Strackey (Ed.), *The standard edition of the complete psychological works of Sigmund Freud* (pp. 243–258). London: Hogarth Press.

Gallagher, R., McKinley, S., & Dracup, K. (2003). Effects of a telephone counseling intervention on psychosocial adjustment in women following a cardiac event. *Heart and Lung, 32*, 79–87.

Gehi, A., Haas, D., Pipkin, S., & Whooley, M. A. (2005). Depression and medication adherence in outpatients with coronary heart disease: Findings from the Heart and Soul Study. *Archives of Internal Medicine, 165*, 2508–2513.

Gilbody, S. D., Sheldon, T. D., & House, A. D. (2008). Screening and case-finding instruments for depression: A meta-analysis. *CMAJ, 178*, 997–1003.

Goble, A. J., Biddle, N., & Worcester, M. U. C. (1989). Depression after acute cardiac illness. *Quality of Life and Cardiovascular Care, 5*, 60–65.

Gravely-Witte, S., Stewart, D., Suskin, N., & Grace, S. (2009). The association among depressive symptoms, smoking status and antidepressant use in cardiac outpatients. *Journal of Behavioral Medicine, 32*, 478–490.

Hanssen, T. A., Nordrehaug, J. E., Eide, G. E., Bjelland, I., & Rokne, B. (2009). Anxiety and depression after acute myocardial infarction: An 18-month follow-up study with repeated measures and comparison with a reference population. *European Journal of Cardiovascular Prevention and Rehabilitation, 16*, 651–659.

Hare, D. L., Toukhsati, S. R., Johansson, P., & Jaarsma, T. (2013). Depression and cardiovascular disease: A clinical review. *European Heart Journal*. doi:10.1093/eurheartj/eht462. published online 4 December.

Hasnain, M., Vieweg, W. V. R., Lesnefsky, E. J., & Pandurangi, A. K. (2011). Depression screening in patients with coronary heart disease: A critical evaluation of the AHA guidelines. *Journal of Psychosomatic Research, 71*, 6–12.

Herrmann, C., Brand-Driehorst, S., Buss, U., & Ruger, U. (2000). Effects of anxiety and depression on 5-year mortality in 5,057 patients referred for exercise testing. *Journal of Psychosomatic Research, 48*(4–5), 455–462. doi: S0022-3999(99)00086-0 [pii].

Higgins, R. O., Murphy, B. M., Nicholas, A., Worcester, M. U., & Lindner, H. (2007). Emotional and adjustment issues faced by cardiac patients seen in clinical practice: A qualitative survey of experienced clinicians. *Journal of Cardiopulmonary Rehabilitation and Prevention, 27*(5), 291–297. doi:10.1097/01.HCR.0000291296.62894.e5.

Ho, M., Spertus, J. A., Masoudi, F. A., Reid, K. J., Peterson, E. D., Magid, D. J., . . . Rumsfeld, J. S. (2006). Impact of medication therapy discontinuation on mortality after myocardial infarction. *Archives of Internal Medicine, 166*, 1842–1847.

Hodgkinson, P. E., & Stewart, M. (1991). *Coping with catastrophe*. London: Routledge.

Horwitz, A. V., & Wakefield, J. C. (2005). The age of depression. *National Affairs, 158*, online.

Horwitz, A. V., & Wakefield, J. C. (2007). *The loss of sadness: How psychiatry transformed normal sorrow into depressive disorder*. New York: Oxford University Press.

Iestra, J. A., Kromhout, Y. T., van der Schouw, D. E., Grobbee, H. C., Boshuizen, H. C., & van Staveren, W. A. (2005). Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: A systematic review. *JAMA, 112*, 924–934.

Irvine, J., Basinski, A., Baker, B., Jandciu, S., Paquette, M., & Cairns, J. (1999). Depression and risk of sudden cardiac death after myocardial infarction: Testing for the confounding effects of fatigue. *Psychosomatic Medicine, 61*, 729–737.

Joseph, S. (2011). *What doesn't kill us: The new psychology of posttraumatic growth*. London: Piatkus.

Kaptein, K. I., de Jong, P., van den Brink, R., & Korf, J. (2006). Course of depressive symptoms after myocardial infarction and cardiac prognosis: A latent class analysis. *Psychosomatic Medicine, 68*(5), 662–668.

Keresztes, P. A., Merritt, S. L., Holm, K., Penckofer, S., & Patel, M. (2003). The coronary artery bypass experience: Gender differences. *Heart and Lung, 32*(5), 308–319.

Krannich, J. H., Weyers, P., Lueger, S., Herzog, M., Bohrer, T., & Elert, O. (2007). Presence of depression and anxiety before and after coronary artery bypass graft surgery and their relationship to age. *BMC Psychiatry, 7*, 47.

Kronish, I. M., Rieckmann, N., Halm, E. A., Shimbo, D., Vorchheimer, D., Haas, D. C., & Davidson, K. W. (2006). Persistent depression affects adherence to secondary prevention

behaviors after acute coronary syndromes. *Journal of General Internal Medicine, 21*(11), 1178–1183.

Kuhl, E. A., Fauerbach, J. A., Bush, D. E., & Ziegelstein, R. C. (2009). Relation of anxiety and adherence to risk-reducing recommendations following myocardial infarction. *The American Journal of Cardiology, 103*, 1629–1634.

Ladwig, K. H., Roll, G., Breithardt, G., Budde, T., & Borggrefe, M. (1994). Post-infarction depression and incomplete recovery 6 months after acute myocardial infarction. *Lancet, 343* (8888), 20–23.

Lane, D., Carroll, D., Ring, C., Beevers, D. G., & Lip, G. Y. (2001). Mortality and quality of life 12 months after myocardial infarction: Effects of depression and anxiety. *Psychosomatic Medicine, 63*(2), 221–230.

Lane, D., Ring, C., Lip, G. Y. H., & Carroll, D. (2005). Depression, indirect clinical markers of cardiac disease severity, and mortality following myocardial infarction. *Heart, 91*, 531–532.

Lauzon, C., Beck, C. A., Huynh, T., Dion, D., Racine, N., Carignan, S., … Pilote, L. (2003). Depression and prognosis following hospital admission because of acute myocardial infarction. *CMAJ, 168*(5), 547–552.

Lichtman, J. H., Bigger, J. T., Blumenthal, J., Frasure-Smith, N., Kaufman, P. G., Lesperance, F., … Froelicher, E. S. (2008). Depression and coronary heart disease. Recommendations for screening, referral, and treatment. A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation, 118*, 1768–1775.

Mallik, S., Krumholz, H. M., Lin, Z. Q., Kasl, S. V., Mattera, J. A., Roumains, S. A., & Vaccarino, V. (2005). Patients with depressive symptoms have lower health status benefits after coronary artery bypass surgery. *Circulation, 111*(3), 271–277.

Martens, E. J., Smith, O. R., Winter, J., Denollet, J., & Pederson, S. S. (2008). Cardiac history, prior depression personality predict course of depressive symptoms after myocardial infarction. *Psychological Medicine, 38*(2), 257–264.

Martens, E. J., De Jonge, P., Na, B., Cohen, B. E., Lett, H. S., & Whooley, M. A. (2010). Scared to death? Generalised anxiety disorder and cardiovascular events in patients with stable coronary heart disease: The heart and soul study. *Archives of General Psychiatry, 67*(7), 750–758.

McCaffery, J. M., Frasure-Smith, N., & Dube, M. P. (2006). Common genetic vulnerability to depressive symptoms and coronary artery disease: A review and development of candidate genes related to inflammation and serotonin. *Psychosomatic Medicine, 68*, 187–200.

Mead, A., Atkinson, G., Albin, D., Alphey, D., Baic, S., Boyd, O., … Hooper, L. (2006). Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease – Evidence from systematic reviews of randomized controlled trials (second update, January 2006). *Journal of Human Nutrition and Dietetics, 19*(6), 401–419. doi:JHN726 [pii] 10.1111/j.1365-277X.2006.00726.x.

Moholdt, T., Wisloff, U., Nilsen, T. I. L., & Slordahl, S. A. (2008). Physical activity and mortality in men and women with coronary heart disease: A prospective population-based cohort study in Norway (the HUNT study). *European Journal of Cardiovascular Prevention and Rehabilitation, 15*, 639–645.

Moser, D. K., Dracup, K., Evangelista, L. S., Zambroski, C. H., Lennie, T. A., Chung, M. L., … Heo, S. (2010). Comparison of prevalence of symptoms of depression, anxiety and hostility in elderly heart failure, myocardial infarction and coronary artery bypass graft surgery patients. *Heart Lung, 39*(5), 378–385.

Murphy, B. M., Elliott, P. C., Higgins, R. O., Le Grande, M. R., Worcester, M. U., Goble, A. J., & Tatoulis, J. (2008a). Anxiety and depression after coronary artery bypass graft surgery: Most get better, some get worse. *European Journal of Cardiovascular Prevention and Rehabilitation, 15*(4), 434–440. doi:10.1097/HJR.0b013e3282fbc945.

Murphy, B. M., Elliott, P. C., Le Grande, M. R., Higgins, R. O., Ernest, C. S., Goble, A. J., … Worcester, M. U. (2008b). Living alone predicts 30-day hospital readmission after coronary

artery bypass graft surgery. *European Journal of Cardiovascular Prevention and Rehabilitation, 15*(2), 210–215. doi:10.1097/HJR.0b013e3282f2dc4e.

Murphy, B. M., Elliott, P. C., Worcester, M. U., Higgins, R. O., Le Grande, M. R., Roberts, S. B., & Goble, A. J. (2008c). Trajectories and predictors of anxiety and depression in women during the 12 months following an acute cardiac event. *British Journal of Health Psychology, 13* (Pt 1), 135–153. doi:10.1348/135910707X173312.

Murphy, B.M., Higgins, R.O., Jackson, A.C., Edington, J., Jackson, A., Worcester, M.U. (2015). Patients want to know about the 'cardiac blues'. *Australian Family Physician, 44*(11), 826–832.

Murphy, B. M., Worcester, M. U., Goble, A. J., Mitchell, F., Navaratnam, H., Higgins, R. O., . . . Le Grande, M. R. (2011). Lifestyle and physiological risk factor profiles six weeks after an acute cardiac event: Are patients achieving recommended targets for secondary prevention? *Heart, lung & Circulation, 20*(7), 446–451. doi:10.1016/j.hlc.2011.02.004.

Murphy, B. M., Le Grande, M., Navaratnam, H., Higgins, R., Elliott, P., Turner, A., . . . Goble, A. (2012). Are poor health behaviours in anxious and depressed cardiac patients explained by sociodemographic factors? *European Journal of Preventive Cardiology, 20*(6), 995–1003. doi:10.1177/2047487312449593.

Murphy, B. M., Rogerson, M., Worcester, M. U. C., Elliott, P. C., Higgins, R. O., Le Grande, M. R., . . . Goble, A. (2013). Predicting mortality 12 years after an acute cardiac event: Comparison between in-hospital and 2-month assessment of depressive symptoms in women. *Journal of Cardiopulmonary Rehabilitation and Prevention, 33*, 160–167. doi:10.1097/HCR.013e318283927f.

Murphy, B. M., Ludeman, D., Elliott, P., Judd, F., Humphreys, J., Edington, J., . . . Worcester, M. (2014). 'Red flags' for persistent or worsening anxiety and depression after an acute cardiac event: A 6 month longitudinal study in regional and rural Australia. *European Journal of Preventive Cardiology, 21*(9), 1079–1089. doi:10.1177/2047487313493058.

Olafiranye, O., Jean-Louis, G., Zizi, F., Nunes, J., & Vincent, M. T. (2011). Anxiety and cardiovascular risk: Review of epidemiological and clinical evidence. *Mind Brain, 2*(1), 32–37.

Parker, G., Hyett, M., Hadzi-Pavlovic, D., Brotchie, H., & Walsh, W. (2011). GAD is good? Generalised anxiety disorder predicts superior five-year outcome following an acute coronary syndrome. *Psychiatry Research, 188*(3), 383–389.

Perez, G. H., Nicolau, J. C., Romano, B. W., & Laranjeira, R. (2008). Depression: A predictor of smoking relapse in a 6-month follow-up after hospitalization for acute coronary syndrome. *European Journal of Cardiovascular Prevention and Rehabilitation, 15*, 89–94.

Peterson, J. C., Charlson, M., Williams-Russo, P., Krieger, K., Pirraglia, P., Meyers, B., . . . Alexopoulos, G. S. (2002). New post-operative depressive symptoms and long-term cardiac outcomes after coronary artery bypass surgery. *American Journal of Geriatric Psychiatry, 10*, 192–198.

Schleifer, S. J., Macari-Hinson, M. M., Coyle, D. A., Slater, W. R., Kahn, M., Gorlin, R., & Zucker, H. D. (1989). The nature and course of depression following myocardial infarction. *Archives of Internal Medicine, 149*(8), 1785–1789.

Sheps, D. S., & Rozanski, A. (2005). From feeling blue to clinical depression: Exploring the pathogenicity of depressive symptoms and their management in cardiac practice. *Psychosomatic Medicine, 67*(Suppl 1), S2–S5.

Ski, C. F., & Thompson, D. R. (2011). Beyond the blues: The need for integrated care pathways. *European Journal of Cardiovascular Prevention and Rehabilitation, 18*, 218–221.

Soufer, R., Arrighi, J. A., & Burg, M. M. (2002). Brain, behaviour, mental stress, and the neurocardiac interaction. *Journal of Nuclear Cardiology, 9*, 650–662.

Spijkerman, T. A., van der Brink, R. H. S., Jansen, J. H. C., Crijns, H. J. G. M., & Ormel, J. (2005). Who is at risk of post-MI depressive symptoms? *Journal of Psychosomatic Research, 58*(5), 425–432.

Strik, J. J., Denollet, J., Lousberg, R., & Honig, A. (2003). Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *Journal of the American College of Cardiology, 42*(10), 1801–1807.

Strik, J. J., Lousberg, R., Cheriex, E. C., & Honig, A. (2004). One year cumulative incidence of depression following myocardial infarction and impact on cardiac outcome. *Journal of Psychosomatic Research, 56*, 59–66.

Taylor, C. B. (2010). Depression, heart rate related variables and cardiovascular disease. *International Journal of Psychophysiology, 78*(1), 80–88.

Tedeschi, R. G., & Calhoun, L. G. (1995). *Trauma and transformation: Growing in the aftermath of suffering*. Thousand Oaks: Sage.

Tedeschi, R. G., & Calhoun, L. G. (2004). Posttraumatic growth: A new perspective on psychotraumatology. *Psychiatric Times, 21*(4), 945–960.

Tedstone, J. E., & Tarrier, N. (2003). Posttraumatic stress disorder following medical illness and treatment. *Clinical Psychological Review, 23*, 409–448.

Thombs, B. D., & Ziegelstein, R. C. (2010). Screening in cardiovascular care. In A. J. Mitchell & J. C. Coyne (Eds.), *Screening for depression in clinical practice: An evidence-based guide*. New York: Oxford University Press.

Thombs, B. D., Bass, E. B., Ford, D. E., Stewart, K. J., Tsilidis, K. K., Patel, U., ... Ziegelstein, R. C. (2006). Prevalence of depression in survivors of acute myocardial infarction: Review of the evidence. *Journal of General Internal Medicine, 21*, 30–38.

Thombs, B. D., de Jonge, P., Coyne, J. C., Whooley, M. A., Frasure-Smith, N., Mitchell, A. J., ... Ziegelstein, R. C. (2008). Depression screening and patient outcomes in cardiovascular care. *JAMA, 300*(18), 2161–2171.

Thombs, B. D., Jewett, L. R., Knafo, R., Coyne, J. C., & Ziegelstein, R. C. (2009). Learning from history: A commentary on the American Heart Association Science Advisory on depression screening. *American Heart Journal, 158*(4), 503–505.

Tully, P. J., & Baker, R. A. (2012). Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: A contemporary and practical review. *Journal of Geriatric Cardiology, 9*, 197–208.

Tully, P. J., & Higgins, R. (2014). Depression screening, assessment and treatment for patients with coronary heart disease: A review for psychologists. *Australian Psychologist, X*, xx-xx.

Tully, P. J., Baker, R. A., & Knight, J. L. (2008a). Anxiety and depression as risk factors for mortality after coronary artery bypass surgery. *Journal of Psychosomatic Research, 64*, 285–290.

Tully, P. J., Baker, R. A., & Turnbull, D. (2008b). The role of depression and anxiety symptoms and hospital readmissions after cardiac surgery. *Journal of Behavioral Medicine, 31*, 281–290.

Tully, P. J., Pederson, S. S., Winefield, H. R., Baker, R. A., Turnbull, D. A., & Denollet, J. (2011). Cardiac morbidity risk and depression and anxiety: A disorder, symptom and trait analysis among cardiac surgery patients. *Psychology, Health & Medicine, 16*(3), 333–345.

Tully, P. J., Cosh, S. M., & Baune, B. T. (2013). A review of the effects of worry and generalised anxiety disorder upon cardiovascular health and coronary heart disease. *Psychology, Health & Medicine, 18*(6), 627–644.

van Melle, J. P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G. P., Ormel, J., van Veldhuisen, D. J., ... van den Berg, M. P. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosom Med, 66*, 814–822.

Watkins, L. L., Schneiderman, N., Blumenthal, J. A., Sheps, D. S., Catellier, D., Taylor, C. B., & Freedland, K. E. (2003). Cognitive and somatic symptoms of depression are associated with medical comorbidity in patients after acute myocardial infarction. *American Heart Journal, 146*(1), 48–54.

Welin, C., Lappas, G., & Wilhelmsen, L. (2000). Independent importance of psychosocial factors for prognosis after myocardial infarction. *Journal of Internal Medicine, 247*(6), 629–639.

Westin, L., Carlsson, R., Israelsson, B., Willenheimer, R., Cline, C., & McNeil, T. F. (1997). Quality of life in patients with ischaemic heart disease: A prospective controlled study. *Journal of Internal Medicine, 242*(3), 239–247.

Whitmarsh, A., Koutantji, M., & Sidell, K. (2003). Illness perceptions, mood and coping in predicting attendance at cardiac rehabilitation. *British Journal of Health Psychology, 8*(Pt 2), 209–221.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., & Lanas, F. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*(9438), 937–952.

Ziegelstein, R. C., Fauerbach, J. A., Stevens, S. S., Romanelli, J., Richter, D. P., & Bush, D. E. (2000). Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Archives of Internal Medicine, 160*(12), 1818–1823.

Quality of Life in Survivors of Myocardial Infarction

Magdalena Anna Lazarewicz, Dorota Wlodarczyk, and Geir Arild Espnes

Contents

Abstract

The concepts of quality of life and health-related quality of life (HRQoL) are wildly used in literature but lack agreed formal definitions. It is however broadly accepted that they are complex, multidimensional, and dynamic constructs,

M.A. Lazarewicz (✉) • D. Wlodarczyk
Department of Medical Psychology, Medical University of Warsaw, Warsaw, Poland
e-mail: magdalena.lazarewicz@wum.edu.pl; magda.lazarewicz@gmail.com; dorota.wlodarczyk@wum.edu.pl

G.A. Espnes
Center for Health Promotion Research, Department of Social Work and Health Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Australian National University, Canberra, ACT, Australia
e-mail: Geir.Arild.Espnes@svt.ntnu.no; geirae@svt.ntnu.no

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_63

which should be assessed on the basis of positive and negative indicators. The term HRQoL is used to clarify the health-disease context of the analyzed QoL. Both generic and disease-specific instruments are used for HRQoL measurement.

Results of the studies on the level and changes in HRQoL after MI are inconsistent. Some studies show HRQoL as being minimally affected by MI, while others indicate major reduction in at least some of its dimensions. Moreover, minor fluctuations to significant changes in HRQoL's different dimensions are reported. The dynamic of these changes varies depending on the period since an MI and between different dimensions of HRQoL.

A number of clinical, sociodemographic, and psychosocial characteristics are recognized as predictors of HRQoL in MI survivors. Among sociodemographic characteristics, age, gender, and education are of a special interest with higher education predicting better HRQoL, but age and gender's role being unclear. Among psychosocial resources, e.g., self-esteem and various social resources were recognized as strong predictors of HRQoL, with higher levels of psychosocial resources predicting better HRQoL.

More work still needs to be performed to fully understand the dynamics and complexity of quality of life in the context of myocardial infarction and CVD in general. But the results support a need for a comprehensive and patient-centered medical practice.

Keywords

Quality of life • Health-related quality of life • Psychosocial resources • Self-esteem • Social cohesion • Social support • General life satisfaction • Myocardial infarction

Introduction

Progress in medicine, pharmacology, and technology allowed to eliminate many infectious diseases and allows to conduct increasingly sophisticated medical procedures and life-saving surgeries. The advances in the last 20–30 years in medical therapies of myocardial infarction and its sequelae (ranging from improvement of accurate medication to successful heart transplants) are indisputable. This triumph has, however, automatically triggered a new clinical challenge: a need to consider the long-term quality of life of the growing number of long-term MI survivors rather than only suppress morbidity or mortality in this group. A need for broadening the perspective on the goals in cardiac practice has been recognized by the European Society of Cardiology and reflected by including maintenance and improvement of quality of life as treatment goals in the guidelines for patients with different heart diseases (Fox et al. 2006; Swedberg et al. 2005). A focus on the constellation of challenges that patients face during treatment and recovery period, on their ways of coping with these challenges and the achieved outcomes (in terms of physical, psychological, social, and spiritual functioning), became a priority for many practitioners and researchers (Fox et al. 2006; Swedberg et al. 2005).

Nowadays, a shift from concentrating solely on prolonging the patient's life to also focusing on the quality of years added to life is observed in a medical and health sciences. A good example of this conceptual transition is the process of changes in the USA federal government's *Healthy People* reports (as cited in Drewnowski and Evans 2001). In the *Healthy People 2000* report (U.S. Department of Health and Human Services [U.S. DHHS] 1991), the main goal of primary and secondary health promotion was to increase the span of healthy life, with the focus on mortality and morbidity data and symptom checklists as the principal measures of ill health. In the *Healthy People 2010* and *2020* reports (U.S. DHHS, 1998, 2008), the emphasis is on overall well-being, with helping people to increase life expectancy and to improve their quality of life across all life stages. Similar tendencies are observed in Europe and are, e.g., reflected in the *Horizon 2020* – the new research and innovation program for 2014–2020 (European Commission 2012). This conceptual transition is also reflected by patients increasing expectations to receive comprehensive information about the consequences of disease and therapy, including the impact of both upon aspects of their quality of life (Fayers and Machin 2007).

In this chapter the concept of quality of life will be discussed, the differences between general and health-related quality of life will be indicated, and ways of measuring quality of life for clinical and research goals will be presented. This introduction will be followed by a presentation of a state-of-the-art knowledge on health-related quality of life in cardiovascular patients, especially MI survivors.

Introducing the Concept of Quality of Life

The concept of quality of life (QoL) was rarely mentioned in the literature until the twentieth century (Fayers and Machin 2007). Though Shaw, an early commentator on the subject, noted in 1900 that "happiness" could be "sacrificed" for quality of life: "Life at its noblest leaves mere happiness far behind; and indeed cannot endure it . . .Happiness is not the object of life: life has no object: it is an end in itself; and courage consists in the readiness to sacrifice happiness for an intenser quality of life" (as cited in Fayers and Machin 2007, p. 6). As Fayers and Machin (2007) suggest, this note made by Shaw in 1900 indicates that by his time, "quality of life" had become a familiar term that did not require further explanation. In fact, some modern investigators argue that, at least in the Western world, most people are generally familiar with the term "quality of life" and intuitively understand what it comprises, and thus no formal definition is needed (Fayers and Machin 2007). Such approach, even though satisfactory for a general deliberation, seems insufficient for the goals of scientific research and clinical practice. Thus, numerous attempts across many disciplines (not only medical, health and social sciences, or philosophy but also economy, geography, literature, architecture, banking, or advertising) were made to clarify the concept of quality of life (Bowling 2001).

In medical, health, and health-related social sciences, quality of life has been defined as, e.g., the degree of human needs satisfaction (Hörnquist 1982), the sum

of those aspects of life, and human function considered essential for living fully (Mor 1987), "…the degree to which a person enjoys the important possibilities of his or her life in the area of …*being* ["who one is" on the physical, psychological, and spiritual components], …*belonging* [the fit between a person and his or her physical, social, and community environments] …and *becoming* [whether one achieves one's personal goals, hopes, and aspirations]" (Raphael et al. 2001, p. 181). Finally, according to WHO quality of life is "an individual's perception of their position in life in context of the culture and value system in which they live and in relation to their goals, expectations, standard, and concerns" (1995, p. 1405). QoL has been referred to or used interchangeably with such terms as "personal well-being", "health status" (Bergner 1987), or "life satisfaction" (Campbell 1981). When operationalized, its measurements range from assessment of functional ability, physical and social activity, or activities of daily living (historically assessed by healthcare staff) through physical and psychological symptoms checklists, pain, sexual performance, and impact of illness to emotional, role, social, and cognitive functioning and self-assessment of global life satisfaction (Fayers and Machin 2007).

The above presentation of a variety of definitions, terms, and measurements serves to highlight the lack of agreement within the literature regarding what exactly quality of life is: what are its indicators and what is its true nature. It is often addressed as a vague or amorphous concept (Fayers and Machin 2007). Nevertheless, even in the absence of a formally agreed definition of QoL, some common trends in its conceptualization and operationalization are observed. Ever since the review of QoL concepts, formulation of the definition and suggestions for ways of assessment of QoL has been published by the World Health Organization Quality Of Life Assessment Group (WHO 1995, the definition was already cited above), and there is a consensus between the medical, health, and social sciences' researchers about some of the characteristics of this construct. It is nowadays broadly accepted that QoL:

- Is a complex and multidimensional concept, incorporating a physical dimension, social dimension, psychological dimension, and, still somewhat less frequently considered, spiritual dimension (WHO 1995)
- Should be assessed from the patient's perspective, thus, on the basis of subjective rather than "objective" indicators and on the basis of the person's global evaluations of behaviors, states, and capacities and satisfaction/dissatisfaction with behaviors, states, and capacities rather than simply on the basis of the person's report of functioning (Fayers and Machin 2007; WHO 1995)
- Includes both positive (e.g., mobility, role functioning, positive feelings, general contentment) and negative dimensions (e.g., dependence on medication, fatigue, pain, negative feelings) (Bowling 2001; WHO 1995)
- Is rather dynamic than static (Moons et al. 2006)

Moreover, in the healthcare setting, to emphasize the key interest in health aspects, a term "health-related quality of life" (HRQoL) is frequently used to

remove ambiguity. Within HRQoL, in the context of a specific disease, a term "*disease*-specific QoL" (e.g., MI-specific QoL) or "HRQoL after a *disease*" (e.g., HRQoL after MI) may be used, to indicate that unique aspects of a particular disease are also considered. The use of such terms clearly distinguishes between the patient-reported outcomes in health/disease and quality of life in its more general sense, which would also include such aspects as adequacy of income, housing, or perceptions of immediate environment (Bowling 2001; Fayers and Machin 2007).

Health-Related Quality of Life

HRQoL focuses on an impact of perceived health status on the ability to lead a fulfilling life (Bullinger et al. 1993). Its theoretical framework is embedded in a WHO's definition of health as a "state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity" (1946, p. 100). Having such roots, HRQoL is a concept incorporating positive (optimal) as well as negative (pathological) aspects of well-being and life. It is multidimensional, embracing physical, psychological, and social functioning, overall life satisfaction/well-being, and perception of health status, with additional dimensions including satisfaction with treatment, intimacy, sexual functioning, sleep disturbance, pain, and symptoms (Bowling 2001). Anxiety and depression are often incorporated to HRQoL as its aspects particularly important to patients with chronic or advanced diseases (Fayers and Machin 2007). HRQoL is a dynamic construct, because as health status changes, perspectives on personal needs, relationships, experiences, and generally on life also change (Sherwood et al. 1977 as cited in Bowling 2001).

In the clinical setting, HRQoL – as a subjective patient-reported outcome measure – is an important information additional to morbidity, response to treatment, and survival (the "classic" and "hard" clinical outcome measures) (Fayers and Machin 2007). Considering this patient-reported outcome, one is not only looking at how to prevent death but also at ways to improve life. The incorporation of the values only known by patients into research and clinical practice reflects a movement toward a more patient-centered care (Sullivan 2003). Simultaneously, the assessment of HRQoL also has a prognostic significance in terms of predicting morbidity and survival (Dixon et al. 2001; Ernstsen et al. 2011; Norekvål et al. 2010; Svärdsudd and Tibblin 1990).

As in case of the general QoL concept, HRQoL also lacks an agreed formal definition. Thus, when reviewing the available research, it is important to remember that different authors understand and operationalize this concept in different ways. However, most operationalizations seem to stay in line with the already quoted WHO QoL Assessment Group's definition of QoL from 1995 and with the presented above agreed characteristics of this construct.

Measuring HRQoL in MI Survivors: Methodological Issues

Preparing for HRQoL measurement both for clinical practice and for research, it is important to begin with a clear definition of HRQoL and its operationalization. The next step is a choice (or preparation) of a questionnaire that will satisfy specific psychometric standards and perform best in providing the most appropriate and required information. Methods of developing and testing new QoL instruments and standards for adequate psychometric properties of the inventories are broadly described in the literature and will not be discussed in this chapter (see, e.g., Fayers and Machin 2007). When selecting the inventory most appropriate for the particular aim, one may choose a generic instrument, a disease-specific instrument.

Generic and Disease-Specific Instrument for HRQoL Measurement

Generic HRQoL instruments are intended for general use and are applicable for healthy and sick people and for patients with various conditions. Thus, they are a good choice when, e.g., MI survivors' QoL is to be compared with healthy people's QoL. Generic instruments are usually multidimensional (e.g., they measure physical, social, and emotional functioning as well as enquire about overall QoL). The examples of reliable and valid generic HRQoL instruments include the Nottingham Health Profile (NHP) developed by Hunt et al. (1981), the Medical Outcomes Study 36-Item Short Form (SF-36) developed by Ware et al. (1993), EuroQoL (EQ-5D) by Brooks and EuroQoL Group (1996), or WHOQOL-100 and WHOQOL-BREF developed by WHOQOL Group (1998). All of the above have a number of cultural and language adaptations allowing transcultural comparisons.

Disease-specific HRQoL instruments assess the influence of a particular disease or condition on QOL. When compared to generic instruments, they are more clinically sensitive, potentially more responsive in detecting change, and are better discriminators of differences between subgroups within a disease category (Wiebe et al. 2003). However, they will not allow comparisons with a control group of healthy people or patients with another condition. Examples of instruments designed to examine specifically the impact of angina or MI on QoL include: the Seattle Angina Questionnaire (Spertus et al. 1995), the MacNew questionnaire (Dixon et al. 2002), or the Myocardial Infarction Dimensional Assessment Scale (Thompson et al. 2002). The abovementioned questionnaires were broadly discussed by Thompson and Yu (2003).

HRQoL Scale Versus Single-Item Measures

Classical test theory has generally been fairly consistent in indicating that single items are at a relative disadvantage to multi-item measures, as more items will allow the random error of the measurement to be ruled out and therefore the results

to be more reliable and precise (Gardner et al. 1998). Single-item measures of QoL are often thought to generate less reliable responses over time (Fayers and Machin 2007), to be less responsive to specific treatment effects (Bernhard et al. 2001), and, generally, to provide less information about participants' QoL than multi-item questionnaires. The use of single-item measures also limits or at least complicates some of the analyses, as not all of the parametric tests have nonparametric equivalents. However, single-item instruments also have a number of advantages, being the simplest approach to measure QoL (Boer et al. 2004), being easier to administer (Fayers and Machin 2007), and being less burdensome to participants than multi-item measures (Cunny and Perri 1991). This simplicity and ease of use may prevent missing data and result in operational efficiency such as data entry and data analyses (Boer et al. 2004). Generally, valid, reliable, and responsive single-item questions are of great interest for use in clinical setting (especially when the participants are severely ill, have concentration problems and poor eyesight, are in pain, etc.) or when a broad set of variables are to be measured at the same time as it is, for instance, in population-based health surveys. Single-item self-rated health measures were used in a number of studies and were found to be very good predictors of future health, morbidity, mortality, and health service attendance (e.g., Idler and Benjamini 1997).

Several single-item general life satisfaction or global QoL measures were previously used in clinical and population-based studies and were compared to multi-item questionnaires. Basing on such comparisons, they were found to be instruments with good validity and reliability, moderate estimates of distribution-based responsiveness, and good anchor-based responsiveness (e.g., Boer et al. 2004, where a visual analog scale for global quality of life was used and compared to Medical Outcome Studies SF-20 and the Rotterdam Symptom Checklist, or Kuppens et al. 2008, where results of single-item measures of global life satisfaction and Satisfaction With Life Scale were compared for 37 countries).

Procedure of HRQoL Data Collection

According to the methodological recommendations for psychological testing, the HRQoL measurements should be conducted in comparable controlled settings (preferably a quiet room, in the presence of the researcher/pollster, without a third party), and the particular questionnaire should always be identical in the order of items or the way it is graphically presented. Lack of researchers control over the circumstances in which the survey is filled in may constitute a serious methodological problem. These rules, however, seem to loosen up slightly in recent years. There is, for example, a growing acceptance of arbitrary use of only selected subscales of the complete scales (e.g., Schulz and Schwarzer 2003) or of the use of electronic versions of tests or surveys posted online (i.e., "e-surveys") (Eysenbach and Wyatt 2002), which are graphically modified and obviously filled in in settings staying beyond researchers' control.

What Do We Know About Quality of Life After MI?

A number of previous studies indicated a significant prognostic role of HRQoL for morbidity and mortality in general population (Svärdsudd and Tibblin 1990) and in cardiac patients (Dixon et al. 2001; Ernstsen et al. 2011; Norekvål et al. 2010).

Level of HRQoL After MI

Simultaneously, numerous studies indicated that in many groups of cardiac patients (e.g., patients with ischemic heart disease, stable angina pectoris, coronary artery disease, or chronic heart failure), the QoL is significantly diminished (Bennett et al. 2001; Bosworth et al. 2000). However, the above remains unclear in the case of MI survivors. A systematic review of the quality of life after MI presented by Simpson and Pilote (2003) revealed that HRQoL is minimally affected by an experience of MI. On the other hand, there are examples from the population-based studies indicating significant differences between pre- and post-MI HRQoL (van Jaarsveld et al. 2001) and significant reduction in at least some dimensions of HRQoL in MI survivors compared to age-specific healthy controls, both in short-term (up to 12 months) and in longer-term perspective (one to several years after MI) (Brink et al. 2005; Pettersen et al. 2008a; Schweikert et al. 2009). Simpson and Pilote (2003) observed that in a number of studies they have reviewed, the measurement tools might not have been sensitive enough to recognize the difference/change in HRQoL.

Results from HUNT Study, one of the world's largest population-based prospective health surveys and biobanks (the Nord-Trøndelag Health Study (HUNT) is a unique database of personal and family medical histories, collected among citizens of the Nord-Trøndelag county (Norway) aged 20 years and above, during three surveys: HUNT1 in 1984–1986 period, HUNT2 in 1995–1997, and HUNT3 in 2006–2008. A total of 77,212 people attended HUNT1 (97 % response and participation rate), 65,237 people attended HUNT2 (81 %), and 50,807 people participated in HUNT3 (71 %). Currently, it is a database with information about 106,446 adults (Krokstad et al. 2012)), are also inconclusive. The authors of this chapter analyzed differences in HRQoL between MI survivors and MI-free HUNT population. In one study, differences in HRQoL of male long-term MI survivors ($n = 64$) and MI-free participants ($n = 768$) were investigated on three measurements over a period of 20 years. The analyses included indicators of somatic HRQoL (everyday life impairment and self-rated health) and general life satisfaction. Somatic HRQoL of MI survivors was significantly diminished in comparison to somatic HRQoL of MI-free men at each of the three HUNT measurements, but MI survivors and MI-free persons did not differ significantly on the level of general life satisfaction. In another study in which MI survivors ($n = 780$) and MI-free participants ($n = 44820$) HRQoL were also analyzed, when demographics, health-related factors, lifestyle factors, and psychosocial resources were controlled, MI experience predicted poorer somatic HRQoL in a short-term but not long-term

(10 years) perspective, and it was not a significant predictor of cognitive HRQoL (general life satisfaction) or emotional HRQoL (anxiety, depression, and positive affect) (Lazarewicz et al. 2014, *unpublished thesis*). To sum up, the results differed depending on the investigated indicators of HRQoL and time perspective included in the analyses.

Changes over Time in HRQoL After MI

Results of the studies also show inconsistency as to whether and how HRQoL changes over time after MI. Minor fluctuations (Eriksson et al. 2012) to significant changes in its different dimensions were reported (Kristofferzon et al. 2005). Also, reports of both deterioration and improvement in HRQoL over time can be found in the literature. Simpson and Pilote (2003) concluded that physical HRQoL (physical capacity, symptoms, functional status, and general health perceptions) declined the most after MI. However, the majority of these HRQoL domains "improved to normal levels with time" (p. 507) (the studies reviewed by Simpson and Pilote followed the patients since an MI up to max. 5 years after it). Furthermore, a gain over time was reported in such dimensions as role fulfillment, pursuit of normal and social activities (Lacey and Walters 2003), physical functioning, vitality, or social functioning (Kristofferzon et al. 2005).

These results were also confirmed in the authors' studies based on the HUNT data (Lazarewicz et al. 2014, *unpublished thesis*). In the already quoted study where changes over a period of 20 years in male MI survivors and MI-free men HRQoL were analyzed, the somatic HRQoL decreased over time in both samples, while general life satisfaction increased over time. In the case of MI survivors, this increase was especially significant over the period of the first 10 years of the study and present but insignificant in the later period. This suggests that the experience of an MI may have a delayed negative effect on general life satisfaction, suppressing its increase after a longer (over 20 years) period since an MI (while such increase in general life satisfaction was observed in MI-free participants).

Summing up, the results of the reviewed and own studies suggest that the changes in HRQoL after MI are dynamic and their direction (increase or deterioration) depends on the time since an MI experience (Pettersen et al. 2008a; Simpson and Pilote 2003) and the investigated dimension of HRQoL.

Clinical and Sociodemographic Predictors of HRQoL After MI

Apart from time since MI, previous studies report several clinical and sociodemographic characteristics that influence HRQoL in MI survivors. Among the clinical factors, the following are often found to predict lower future HRQoL of MI survivors: previous (additional) MI (Pettersen et al. 2008a), higher left ventricular ejection fraction (Pettersen et al. 2008b), high number of atherosclerosis risk

factors (hypertension, dyslipidemia, overweight, smoking) (Arendarczyk and Loboz-Grudzien 2000), type of intervention applied for MI treatment (Beck et al. 2001), readmission to hospital, manifestations of coronary heart disease other than MI, angina pectoris, additional comorbidity, and lower baseline HRQoL (Beck et al. 2001; Brink et al. 2005; Emery et al. 2004).

Sociodemographic characteristics were also often found to affect quality of life levels following MI; however, their role is not always clear. Higher education, higher socioeconomic status, and higher age usually predict higher HRQoL (Beck et al. 2001; Pettersen et al. 2008a; Simpson and Pilote 2003). However, in one of the recent studies, the quality of life scores declined with increasing age, but interestingly the decline was smaller in MI survivors than in the general population (Schweikert et al. 2009). The role of gender in predicting HRQoL after MI also remains unclear. Some studies report little differences or lack of gender differences in HRQoL (Kristofferzon et al. 2005; Lazarewicz et al. 2014, *unpublished thesis*), while others report female MI survivors having significantly lower HRQoL than male MI survivors (Brink et al. 2005; Emery et al. 2004; Pettersen et al. 2008a; Wrzesiewski and Wlodarczyk 2012). Another study reported that improvement in HRQoL (which took place after its initial deterioration) happened more slowly in female than in male MI survivors (Norris et al. 2004). Moreover, men and women were reported to have different determinants of HRQoL after MI (Pettersen et al. 2008a).

Pettersen et al. (2008b) suggest that the identified determinants of HRQoL vary between studies due to differences in patient selection, time interval between MI and HRQoL measurement, the potential predictors included, and the chosen measures of HRQoL. Notably, most of the reviewed studies have limitations regarding measurement of multidimensional QoL, the sample sizes (especially poor representation of women and of the elderly MI survivors), and, in case of the prospective studies, the lengths of a follow-up.

Positive Psychosocial Predictors of HRQoL

The majority of the studies reviewed above concentrate on a search for factors responsible for the deterioration of HRQoL. A search for factors that protect HRQoL from deterioration and stimulate its increase has only started recently but attract an increasing amount of attention. Rapidly growing interest in this area of health research reflects a growing popularity of salutogenic approach (Antonovsky 1987) and of positive psychology in general (e.g., Seligman and Csikszentmihalyi 2000; Snyder and Lopez 2005). An interest in HRQoL itself was a first step toward this more positive approach in health science. An interest in the HRQoL' positive determinants seems to be an important next step.

Investigation in the area of positive determinants of HRQoL and adaptation to chronic disease has mainly concentrated on psychological and social characteristics, often labeled as "psychosocial resources." Psychosocial resources are defined as "individual differences and social relationships that have beneficial effects on

mental and physical health outcomes" (Taylor and Broffman 2011, p. 1), on health and quality of life.

Both psychological and social factors can impact the way in which people approach life circumstances (e.g., a stressful situation such as a somatic disease), what in turn can impact their well-being and HRQoL. Such approach stays in line with, broadly discussed in the literature, Lazarus and Folkman's (1984) cognitive and transactional model of stress, in which personal and social coping resources are conceptualized as elements of the theoretical model of stress. A number of positive psychological resources, e.g., self-esteem (Rosenberg 1965), self-efficacy (Bandura 1997), dispositional optimism (Scheier and Carver 1985), and sense of coherence (Antonovsky 1987), and a number of aspects of social resources experienced within family, friends, or broader community groups, conceptualized as, e.g., social cohesion, social support, or sense of community (Schwarzer and Leppin 1991), were suggested and investigated in the literature. Including such factors in the studies of MI survivors was indicated as being of a great importance (Wrzesniewski and Wlodarczyk 2012) and an increased number of studies concentrated on selected resources and HRQoL, also in the context of cardiac patients.

For example, higher self-esteem was associated with better physical and psychosocial recovery after CABG (Artinian et al. 1993). It was also a significant predictor of quality of life 1–2 years after such surgery (Dantas et al. 2002). In a study, that focused on older adults (over 60 years old) with CVD, higher self-esteem was significantly associated with subsequent maintenance or improvement of physical and psychosocial function over a 12-months period, especially among women (it was a stronger predictor of physical and psychosocial functioning than demographic and clinical factors) (Forthofer et al. 2001). In a cross-sectional study investigating a group of 96 female MI survivors, higher self-esteem significantly predicted higher multidimensional QoL (four dimensions were specified: health and functioning, socioeconomics, psychological and/or spiritual, and family life) (Wingate 1995).

Good social resources were also found to have a positive effect on various aspects of HRQoL in cardiac patients (Bennett et al. 2001; Emery et al. 2004). Lack of social support after a coronary event was found to be related to poorer physical and mental outcome both in men (Conn et al. 1991) and in women (Lett et al. 2005). However, the results are not fully consistent when gender and age differences are considered (e.g., Emery et al. 2004). The absence of a spouse, partner, or confidant was often associated with greater depression, and this relation was found particularly strong for men (e.g., Frasure-Smith et al. 1999). In other study (where other measures were used), lower social support was also associated with more depressive symptoms and worse health status over the first year of acute MI recovery, but it was particularly significant for women (Leifheit-Limson et al. 2010).

The authors' research on the already quoted HUNT population ($n = 55{,}253$) (Lazarewicz et al. 2014, *unpublished thesis*) confirms a significant predictive role of self-esteem (as an example of a psychological resource) and social cohesion (as an example of social resource) for somatic, cognitive, and emotional dimensions of MI survivors' HRQoL both in cross-sectional and 10-year perspective.

To sum up, studies investigating the association of psychosocial resources with cardiac patients' HRQoL have generally linked lower (limited) psychosocial resources to poorer HRQoL and higher (broader) psychosocial resources to better HRQoL, not only to its emotional or cognitive dimension but also to its somatic dimension. It is however worth noticing that these psychosocial predictors of HRQoL seem to be overlapping with psychological and social aspects of HRQoL and are conceptualized as such by some authors. It may be argued, for example, that social cohesion is not a predictor of HRQoL but rather its social aspect understood as "individuals' perception of the interpersonal relationships and social roles in their life" (WHO 1995, p. 1405). Self-esteem is also sometimes incorporated in the QoL construct as its "specific aspect" (Fayers and Machin 2007). This problem seems to mainly reflect the great complexity of the quality of life construct.

Clinical Implications

In order to accurately address MI survivors' long-term HRQoL, cardiac rehabilitation practice should support development of psychosocial resources, e.g., growth or at least prevention from deterioration of self-esteem and development or redefinition of the social context of life. These resources are challenging to act upon, but possible to be addressed by healthcare professionals. For instance, on the daily communication level, self-esteem may be supported by accurate (not infantilizing) use of positive reinforcements (praising during rehabilitation and treatment, e.g., "I am really impressed with how well you are coping." "Following all these recommendation may be challenging. You are doing great."). Selective optimization with compensation processes (Freund and Baltes 1998), selecting important areas of functioning, learning new skills to optimize performance and compensate for these deficits, should also be supported and reinforced. This may prevent the patient from concentrating solely on experienced losses (e.g., deterioration in physical fitness, need to give up old habits) and help with redefining or defining new areas of life which may serve as bases for building specific self-esteem. Awareness of the healthcare professionals of MI survivors' level of social resources (e.g., social cohesion) is also vital. Creating an optimal social environment in the medical or social welfare setting may contribute to better HRQoL including lower everyday life impairment.

Generally, results of the reviewed studies on HRQoL in MI survivors and other CVD patients support a need for a comprehensive, holistic, interdisciplinary, and patient-centered medical practice, transcending the examination room and including changes and interventions on the community level.

Conclusion

The concept of quality of life is wildly used in the literature but lacks agreed formal definition. However, most of its recent operationalizations stay in line with the WHO QoL Assessment Group's definition of QoL, which states that it is "an

individual's perception of their position in life in context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns" (1995, p. 1405). It is complex and multidimensional dynamic construct, which should be assessed on the basis of positive and negative subjective indicators. The term health-related quality of life is often used to clarify the health-disease context of the analyzed QoL.

Prior research has documented profound negative effects of poor HRQoL on morbidity and mortality in general population and in cardiac patients, and numerous studies indicate that in many groups of cardiac patients, HRQoL is significantly diminished. However, it is unclear in the case of MI survivors. Some studies show HRQoL as being only minimally affected by an experience of MI, while others indicate major reduction in at least some of its dimensions both in short- and longer-term perspective. Results of the studies also show inconsistencies as to whether and how HRQoL changes over time after MI: minor fluctuations to significant changes in its different dimensions were reported. The dynamic of these changes probably varies depending on the period since an MI (after initial deterioration, there is an improvement) and between different dimensions of HRQoL.

A number of clinical and sociodemographic characteristics are recognized as predictors of HRQoL in MI survivors. Among sociodemographic characteristics, age, gender, and education are of a special interest with higher education predicting better HRQoL, but age and gender's role being unclear. However, in most studies, higher age and male gender predict better HRQoL, and a gradual improvement in HRQoL (often observed after its initial deterioration after MI) seems to happen more slowly in female than in male MI survivors.

A growing interest in the importance of psychosocial resources for HRQoL in general population and in MI survivors is also observed. Among others, self-esteem and various social resources were recognized as strong predictors of HRQoL (often stronger than clinical and demographic factors), with higher levels of psychosocial resources predicting better health and quality of life outcomes.

However, more work still needs to be performed to fully understand the dynamics and complexity of quality of life in the context of myocardial infarction and CVD in general. Due to a prior concentration mainly on pathology and prevention of loss, especially little is known about the positive correlates and determinants of health-related quality of life. Moreover, results of many studies should be interpreted or generalized with caution, because they often had some methodological limitations. They were mainly cross-sectional. Prospective studies often covered only a short period of time (usually a couple of month up to a year after an MI). Moreover, most of the reviewed studies concentrate predominantly on middle age male populations, with female and elderly MI patients often not being included or being underrepresented. The studies recognizing a need for investigation of HRQoL in female and elderly MI survivors often studied only women (or older patients), making gender and age comparisons impossible. Only some studies had a control group which allowed to check if recognized relations or differences were indeed specific for MI survivors. Furthermore, in many of the reviewed studies, QoL or HRQoL was not clearly defined, or a construct similar but not identical to HRQoL

(e.g., self-rated psychosocial adaptation or function) was measured as an outcome. Thus, to fully understand the dynamics of change in HRQoL after MI and the relations between psychosocial resources and HRQoL in both sexes and different age groups, more research is still needed, especially work balancing pathogenic and salutogenic orientations in reasonable-sized samples of women and oldest old of both sexes.

References

Antonovsky, A. (1987). *Unravelling the mystery of health: How people manage stress and stay well*. San Francisco: Jossey-Bass.

Arendarczyk, M., & Loboz-Grudzien, K. (2000). Jakość życia chorych w dwa lata po zawale serca 2. Ocena wpływu czynników [Quality of life two years after MI. Assessment of predictors impact]. *Polski Merkuriusz Lekarski, 44*, 94–97.

Artinian, N. T., Duggan, C., & Miller, P. (1993). Age differences in patient recovery patterns following coronary artery bypass surgery. *American Journal of Critical Care, 2*, 453–461.

Bandura, A. (1997). *Self-efficacy: The exercise of control*. New York: Freeman.

Beck, C. A., Joseph, L., Belisle, P., & Pilote, L. (2001). Predictors of quality of life 6 months and 1 year after acute myocardial infarction. *American Heart Journal, 142*(2), 271–279.

Bennett, S. J., Perkins, S. M., Lane, K. A., Deer, M., Brater, D. C., & Murray, M. D. (2001). Social support and health-related quality of life in chronic heart failure patients. *Quality of Life Research, 10*, 671–682.

Bergner, M. (1987). Development, testing and use of the sickness impact profile. In S. R. Walker & R. M. Rosser (Eds.), *Quality of life: Assessment and application* (pp. 79–94). Lancaster: MTP Press.

Bernhard, J., Sullivan, M., Hürny, C., Coates, A. S., & Rudenstam, C.-M. (2001). Clinical relevance of single item quality of life indicators in cancer clinical trials. *British Journal of Cancer, 84*, 1156–1165.

Bosworth, H. B., Siegler, I. C., Olsen, M. K., Brummett, B. H., Barefoot, J. C., Williams, R. B., et al. (2000). Social support and quality of life in patients with coronary artery disease. *Quality of Life Research, 9*, 829–839.

Bowling, A. (2001). *Measuring disease* (2nd ed.). Philadelphia: Open University Press.

Brink, E., Grankvist, G., Karlson, B. W., & Hallberg, L. R. (2005). Health-related quality of life in women and men one year after acute myocardial infarction. *Quality of Life Research, 14*(3), 749–757.

Brooks, R., & EuroQoL Group. (1996). EuroQoL: The current state of play. *Health Policy, 37*, 53–72.

Bullinger, M., Anderson, R., Cella, D., & Aaronson, N. (1993). Developing and evaluating cross-cultural instruments from minimum requirements to optimal models. *Quality of Life Research, 2*, 451–459.

Campbell, A. (1981). *The sense of well-being in America: Recent patterns and trends*. New York: McGraw-Hill.

Conn, V. S., Taylor, S. G., & Abele, P. B. (1991). Myocardial infarction survivors: Age and gender differences in physical health, psychosocial state and regimen adherence. *Journal of Advanced Nursing, 16*, 1026–1034.

Cunny, K. A., & Perri, M. (1991). Single-item vs. multi-item measures of quality of life. *Psychological Reports, 69*, 127–130.

Dantas, R. A., Motzer, S. A., & Ciol, M. A. (2002). The relationship between quality of life, sense of coherence and self-esteem in persons after coronary artery bypass graft surgery. *International Journal of Nursing Studies, 39*(7), 745–755.

de Boer de, A. G. E. M., van Lanschot, J. J. B., Stalmeier, P. F. M., van Sandick, J. W., Hulscher, J. B. F., de Haes, J. C. J. M., & Sprangers, M. A. G. (2004). Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Quality of Life Research, 13*, 311–320.

Dixon, T., Lim, L. L., & Heller, R. F. (2001). Quality of life: An index for identifying high-risk cardiac patients. *Journal of Clinical Epidemiology, 54*, 952–960.

Dixon, T., Lim, L. L., & Oldridge, N. B. (2002). The MacNew heart disease health-related quality of life instrument: Reference data for users. *Quality of Life Research, 11*, 173–183.

Drewnowski, A., & Evans, W. J. (2001). Nutrition, physical activity, and quality of life in older adults: Summary. *Journal of Gerontology, 56*(Spec. 2), 89–94.

Emery, C. F., Frid, D. J., Engebretson, T. O., Alonzo, A. A., Fish, A., Ferketich, A. K., et al. (2004). Gender differences in quality of life among cardiac patients. *Psychosomatic Medicine, 66*(2), 190–197.

Eriksson, M., Asplund, K., Hochwälder, J., & Svedlund, M. (2012). Changes in hope and health-related quality of life in couples following acute myocardial infarction: A quantitative longitudinal study. *Scandinavian Journal of Caring Sciences, 27*, 295–302. doi:10.1111/j.1471-6712.2012.01032.x.

Ernstsen, L., Nilsen, S. M., Espnes, G. A., & Krokstad, S. (2011). The predictive ability of self-rated health on ischaemic heart disease and all-cause mortality in elderly women and men: The Nord-Trøndelag Health Study (HUNT). *Age and Ageing, 40*, 105–111. doi:10.1093/ageing/afq141.

European Commission. (2012). *FP7 cooperation work programme: Health 2013*. ftp://ftp.cordis.europa.eu/pub/fp7/health/docs/fp7-health-wp-2013_en.pdf. Assessed 12 Sept 2013.

Eysenbach, G., & Wyatt, J. (2002). Using the internet for surveys and health research. *Journal of Medical Internet Research, 4*(2), e13. doi:10.2196/jmir.4.2.e13.

Fayers, P. M., & Machin, D. (2007). *Quality of life. The assessment, analysis and interpretation of patient-reported outcomes*. Chichester: Wiley.

Forthofer, M. S., Janz, N. K., Dodge, J. A., & Clark, N. M. (2001). Gender differences in the associations of self esteem, stress and social support with functional health status among older adults with heart disease. *Journal of Women & Aging, 13*(1), 19–37. doi:10.1300/J074v13n01_03.

Fox, K., Garcia, M. A., Ardissino, D., Buszman, P., Camici, P. G., Crea, F., et al. (2006). Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *European Heart Journal, 27*(11), 1341–1381.

Frasure-Smith, N., Lesperance, F., Juneau, M., Talajic, M., & Bourassa, M. G. (1999). Gender, depression, and one-year prognosis after myocardial infarction. *Psychosomatic Medicine, 61*(1), 26–37.

Freund, A. M., & Baltes, P. B. (1998). Selection, optimization, and compensation as strategies of life-management: Correlations with subjective indicators of successful aging. *Psychology and Aging, 13*, 531–543.

Gardner, D. G., Cumming, L. L., Dunham, R. B., & Pierce, J. L. (1998). Single-item versus multiple-item measurement scales: An empirical comparison. *Education and Psychological Measurement, 58*, 898–915.

Hörnquist, J. O. (1982). Quality of life: Concept and assessment. *Scandinavian Journal of Social Medicine, 18*, 69–79.

Hunt, S. M., McKenna, S. P., McEwen, J., Williams, J., & Papp, E. (1981). The Nottingham health profile: Subjective health status and medical consultations. *Social Science & Medicine. Part A: Medical Psychology & Medical Sociology, 15*(3), 221–229. doi:10.1016/0271-7123(81)90005-5.

Idler, E. L., & Benjamini, Y. (1997). Community studies reporting associations between self-rated health and mortality: Additional studies, 1995–1998. *Research on Aging and Health, 21*, 392–401.

Kristofferzon, M. L., Lofmark, R., & Carlsson, M. (2005). Coping, social support and quality of life over time after myocardial infarction. *Journal of Advanced Nursing, 52*(2), 113–124.

Krokstad, S., Langhammer, A., Hveem, K., Holmen, T. L., Midthjell, K., Stene, T. R., et al. (2012). Cohort profile: The HUNT study, Norway. *International Journal of Epidemiology*, *41*(4). doi:10.1093/ije/dys095.

Kuppens, P., Realo, A., & Diener, E. (2008). The role of positive and negative emotions in life satisfaction judgment across nations. *Journal of Personality and Social Psychology, 95*(1), 66–75.

Lacey, E. A., & Walters, S. J. (2003). Continuing inequality: Gender and social class influences on self-perceived health after a heart attack. *Journal of Epidemiology & Community Health, 57*, 622–627.

Lazarewicz, M. A., Wlodarczyk, D., Espnes, G. A. (2014). Changes in QoL in female and male MI-survivors: The role of age, self-esteem and social embeddedness. A prospective study based on HUNT 1, 2 and 3. Warsaw: Medical University of Warsaw (*unpublished doctoral thesis available in the university library*).

Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and coping*. New York: Springer.

Leifheit-Limson, E. C., Reid, K. J., Kasl, S. V., Lin, H., Jones, P. G., Buchanan, D. M., et al. (2010). The role of social support in health status and depressive symptoms after acute myocardial infarction: Evidence for a stronger relationship among women. *Circulation Cardiovascular Quality and Outcomes, 3*(2), 143–150. doi:10.1161/CIRCOUTCOMES.109.899815.

Lett, H. S., Blumenthal, J. A., Babyak, M. A., Strauman, T. J., Robins, C., & Sherwood, A. (2005). Social support and coronary heart disease: Epidemiologic evidence and implications for treatment. *Psychosomatic Medicine, 67*, 869–878.

Moons, P., Budts, W., & DeGeest, D. (2006). Critique on the conceptualization of quality of life: A review and evaluation of different conceptual approaches. *International Journal of Nursing Studies, 43*, 891–901.

Mor, V. (1987). Cancer patients' quality of life over the disease course: Lessons from the real world. *Journal of Chronic Disease, 40*(6), 535–544.

Norekvål, T. M., Fridlund, B., Rokne, B., Segadal, L., Wentzel-Larsen, T., & Nordrehaug, J. E. (2010). Patient-reported outcomes as predictors of 10-year survival in women after acute myocardial infarction. *Health and Quality of Life Outcomes, 8*, 140–150.

Norris, C. M., Ghali, W. A., Galbraith, P. D., Graham, M. M., Jensen, L. A., Knudtson, M. L., & the APPROACH Investigators. (2004). Women with coronary artery disease report worse health-related quality of life outcomes compared to men. *Health and Quality of Life Outcomes, 2*, 21. doi:10.1186/1477-7525-2-21 (2004).

Pettersen, K. I., Reikvam, A., Rollag, A., & Stavem, K. (2008a). Understanding sex differences in health-related quality of life following myocardial infarction. *International Journal of Cardiology, 130*, 449–456.

Pettersen, K. I., Kvan, E., Rollag, A., Stavem, K., & Reikvam, A. (2008b). Health-related quality of life after myocardial infarction is associated with level of left ventricular ejection fraction. *BMC Cardiovascular Disorder, 8*, 28. doi:10.1186/1471-2261-8-28 (2008).

Raphael, D., Renwick, R., Brown, I., Steinmetz, B., Sehdev, H., & Phillips, S. (2001). Making the links between community, structure and individual well-being: Community quality of life in Riverdale, Toronto, Canada. *Health and Place, 7*, 179–196.

Rosenberg, M. (1965). *Society and the adolescent self-image*. Princeton: Princeton University Press.

Scheier, M. F., & Carver, C. S. (1985). Optimism, coping and health: Assessment and implications of generalized outcome expectancies. *Health Psychology, 4*, 219–247.

Schulz, U., & Schwarzer, R. (2003). Soziale Unterstützung bei der Krankheitsbewältigung. Die Berliner Social Support Skalen (BSSS) [Social support in coping with illness: The Berlin Social Support Scales (BSSS)]. *Diagnostica, 49*, 73–82.

Schwarzer, R., & Leppin, A. (1991). Social support and health: A theoretical and empirical overview. *Journal of Personal and Social Relationships, 8*, 99–127.

Schweikert, B., Hunger, M., Meisinger, C., Konig, H. H., Gapp, O., & Holle, R. (2009). Quality of life several years after myocardial infarction: Comparing MONICA/KORA registry to the general population. *European Heart Journal, 30*(4), 436–443.

Seligman, M. E., & Csikszentmihalyi, M. (2000). Positive psychology. An introduction. *The American Psychologist, 55*(1), 5–14.

Sherwood, S. J., Morrison, J., Mor, V., & Gutkin, C. (1977). *Compendium of Measures for Describing and Assessing Long Term Care Populations*. Boston, MA: Hebrew Rehabilitation Center for the Aged.

Simpson, E., & Pilote, L. (2003). Quality of life after acute MI: A systematic review. *Canadian Journal of Cardiology, 19*(5), 507–511.

Snyder, S. R., & Lopez, J. (2005). *Handbook of positive psychology*. New York: Oxford University Press.

Spertus, J. A., Winder, J. A., Dewhurst, T. A., Deyo, R. A., Prodzinski, J., McDonell, M., & Fihn, S. D. (1995). Development and evaluation of the Seattle Angina questionnaire: A new functional status measure for coronary artery disease. *Journal of the American College of Cardiology, 25*, 333–341.

Sullivan, M. (2003). The new subjective medicine: Taking the patient's point of view on health care and health. *Social Science & Medicine, 56*(7), 1595–1604.

Svärdsudd, K., & Tibblin, G. (1990). Is quality of life affecting survival? The study of men born in 1913. *Scandinavian Journal of Primary Health Care, 1*, 55–60.

Swedberg, K., Cleland, J., Dargie, H., Drexler, H., Follath, F., Komajda, M., et al. (2005). Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *European Heart Journal, 26*(11), 1115–1140. doi:10.1093/eurheartj/ehi204.

Taylor, S. E., & Broffman, J. I. (2011). Chapter one – psychosocial resources: Functions, origins, and links to mental and physical health. *Advances in Experimental Social Psychology, 44*, 1–57.

Thompson, D. R., & Yu, C.-M. (2003). Quality of life in patients with coronary heart disease-I: Assessment tools. *Health and Quality of Life Outcomes, 1*, 42. doi:10.1186/1477-7525-1-42.

Thompson, D. R., Jenkinson, C., Roebuck, A., Lewin, R. J. P., Boyle, R. M., & Chandola, T. (2002). Development and validation of a short measure of health status for individuals with acute myocardial infarction: The myocardial infarction dimensional assessment scale (MIDAS). *Quality of Life Research, 11*, 535–543.

U.S. Department of Health and Human Services. (1998). *Healthy People 2010 Objectives: Draft for Public Comment*. Washington, DC: U.S. Government Printing Office.

U.S. Department of Health and Human Services. (2008). *Phase I Report Recommendations For The Framework And Format Of Healthy People 2020*. Washington, DC: U.S. Government Printing Office.

van Jaarsveld, C. H., Sanderman, R., Miedema, I., Ranchor, A. V., & Kempen, G. I. (2001). Changes in health-related quality of life in older patients with acute myocardial infarction or congestive heart failure: A prospective study. *Journal of the American Geriatrics Society, 49*, 1052–1058.

Ware, J. E., Snow, K. K., Kosinski, M., & Gandek, B. (1993). *SF-36® health survey manual and interpretation guide*. Boston: New England Medical Center, The Health Institute.

Wiebe, S., Guyatt, G., Weaver, B., Matijevic, S., & Sidwell, C. (2003). Comparative responsiveness of generic and specific quality-of-life instruments. *Journal of Clinical Epidemiology, 56*, 52–60.

Wingate, S. (1995). Quality of life for women after a myocardial infarction. *Heart & Lung, 24*(6), 467–473.

World Health Organization. (1946). *WHO definition of Health*. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19–22 June 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 Apr 1948.

World Health Organization. (1995). World Health Organization Quality of Life assessment (WHOQOL): Position paper from the World Health Organization. *Social Science & Medicine, 41*(10), 1403–1409.

World Health Organization Quality of Life Group. (1998). Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychological Medicine, 28*(3), 551–558.

Wrzesniewski, K., & Włodarczyk, D. (2012). Sense of coherence as a personality predictor of quality of life in men and women after MI. [Poczucie koherencji jako osobowościowy predykator jakości życia kobiet i mężczyzn po zawale serca]. *Polish Heart Journal [Kardiologia Polska], 70*(2), 157–163.

Psychological Consultation for Patients with Implantable Cardioverter Defibrillator: Confounding Challenges of Cardiac Disease, Technology, and the Patient Experience

Amanda Whited, Samuel F. Sears, John Cahill, and Mihail G. Chelu

Contents

Abstract

Sudden cardiac arrest is a common and often lethal event, claiming roughly 400,000 lives annually in the United States alone. Implantable cardioverter defibrillators (ICDs) represent a significant technological advance in the medical arena and are the best available intervention for sudden cardiac arrest and subsequent prevention of sudden cardiac death. Over the last two decades, research has increasingly focused on understanding how living with an ICD

A. Whited • S.F. Sears (✉)
Department of Psychology, East Carolina University, Greenville, NC, USA

Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Greenville, NC, USA
e-mail: whitedam@ecu.edu; searss@ecu.edu

J. Cahill
Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Greenville, NC, USA
e-mail: cahillj@ecu.edu

M.G. Chelu
Department of Medicine, University of Utah, Salt Lake City, UT, USA
e-mail: mgchelu@gmail.com

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_25

presents unique and serious psychological challenges for many patients benefiting from this lifesaving technology. Employing a biopsychosocial model in caring for these patients' psychological health helps address relevant factors that can contribute to their psychologically distressed presentation, including cardiac disease burden, ICD treatment delivery (i.e., shock), psychiatric (s) disorder or symptoms, health behaviors, and disruption of day-to-day life or social functioning. This chapter highlights known, common psychological risks for ICD patients, which include depression, anxiety, and compromised quality of life. It further explores some key considerations or groups that are associated with risk for psychological distress, such as pediatric ICD patients, devices under recall, and end-of-life issues. Several relevant assessment measures are provided to assist providers in identifying which psychological risks are realities for each particular patient. In total, this information is designed to lend knowledge and confidence to consulting mental health providers, leaving them well equipped to deliver state-of-the-art assessment of ICD patients – a medically complex, and often psychologically distressed, group of individuals.

Keywords

Anxiety • Depression • Device acceptance • Device technology • Implantable cardioverter defibrillator • Post-traumatic stress disorder • Quality of life • Shock anxiety

Introduction

Sudden cardiac arrest remains the most significant life threat for adults in the developed world with as many as 400,000 Americans experiencing a cardiac arrest each year (Go et al. 2014). The implantable cardioverter defibrillator (ICD) has evolved since its approval by the US Food and Drug Administration (FDA) in 1988 (precursory implantable defibrillators were first approved in 1985) to be the best available intervention for preventing sudden cardiac death. Large trials have shown greater benefit from the ICD in regard to mortality when compared to medications (Bardy et al. 2005; Moss et al. 2002). Subsequent to increased sophistication and effectiveness of ICDs, more patients are surviving potentially lethal arrhythmias and living longer. In the wake of optimized patient survival, psychological hazards that accompany living with an ICD readily emerged. In other words, although ICDs provide protection in terms of *quantity* of life (i.e., years of survival), they also confer risk of psychological distress and compromised *quality* of life for patients if patient centric approaches are not engaged. Further, the presence of the underlying cardiac disease substrate confounds clear attributions and targets of psychological treatment. Both the disease and treatment can be challenging to manage for patients. Modern health psychology can provide strategies for ICD patients as they simultaneously cope with the potential for life-threatening arrhythmias, cardiac disease management, and psychological challenges. The purpose of the current chapter is to review the significant medical and psychosocial factors to be considered in the psychological consultation with patients with ICDs.

Medical Background and the Biopsychosocial Model for ICD Patients

Recent approximations place ICD implantations at an occurrence of 12,537 per month, which extrapolates out to roughly 150,000 implants per year (Kremers et al. 2013). The ICD system consists of endovascular leads and a pulse generator implanted under the skin typically in the subclavicular region. The ICD allows for individual patient programming using one to three leads inserted in the right atrium, right ventricle, and/or left ventricle (branches of the coronary sinus). The different types of ICDs are often referred to by the number of chambers of the heart that they are monitoring (single chamber, dual chamber, and biventricular pacemakers/cardiac resynchronization therapy (CRT)), which depends on each patient's specific needs and condition.

ICDs provide a "black box" level of information about cardiac functioning that is reminiscent of a flight recorder on an airplane. Health personnel can examine information such as atrial and ventricular rate and rhythm information, differential pacing and shock programmability, and system checks using remote systems via landline or wireless data transfer. The rapid technological innovation of the ICD is a medical success story of the past few decades, resulting in smaller devices with greater diagnostic and treatment precision.

Patients with ICDs have an increasingly broad range of medical diagnoses, but they all share the propensity for potentially life-threatening arrhythmias. For example, some patients are implanted following sudden cardiac arrest (i.e., secondary prevention), while others are implanted as a prophylactic measure before sudden cardiac arrest or any other triggering event has occurred (i.e., primary prevention). Also, some patients may have a chronic course of severe disease prior to implantation, whereas others may have subjectively felt healthy prior to an acute event that necessitated ICD implantation. Further, there is a great range within a specific diagnosis that precipitates consideration of ICD implantation, as well as in disease burden and course following implantation. These medical complexities contribute to a complicated array of psychological considerations of which providers should be aware when caring for patients before, amidst, and after ICD implantation. Fortunately, researchers have shown an increased commitment over time to understanding these hazards.

The empirical basis for the assessment and care of ICD patients has been steadily growing, and a biopsychosocial conceptualization is needed in the context of psychological consultation for these patients (Kirian et al. 2012; Stutts et al. 2007; Sears et al. 2009a). As noted above, there are a range of medical factors to consider, including device indication, history of device therapy or therapies (i.e., shock), cardiac disease severity/prognosis, surgical history, neurological deficits related to hypoxia, and comorbid diseases (e.g., pulmonary hypertension, chronic kidney disease). Moving beyond the medical realm into psychosocial concerns, the following are some common domains or complaints to identify: anxiety, depression, quality of life, psychiatric history, risk for self-harm, coping skills, social support strengths and deficits, financial distress, and general and health literacy.

A final and critical element of enlisting the biopsychosocial perspective in consultation on ICD patients is understanding health behaviors that frequently influence both medical and psychosocial realms. Some key behaviors include tobacco use, alcohol use, drug use, physical activity level, medication adherence, dietary restriction adherence, and monitoring of medical parameters per provider instructions (e.g., blood pressure, weight). Approaching each patient with a biopsychosocial viewpoint maximizes identification of key issues of concern and highly tailored case conceptualization and subsequent treatment planning.

Psychological Functioning and the ICD

Depression and Anxiety. Patients with cardiac illness, or other chronic health conditions, experience a significant level of distress above and beyond the level that is seen in their relatively healthy counterparts. The prevalence of these issues has been shown to be upward of 15–20 % in cardiac illness (see Rozanski et al. 2005). By comparison, psychological distress in ICD patients is much higher. There is a general consensus across studies that psychological distress is present in 25–33 % of patients with ICDs. A recent, systematic review specifically of anxiety and depression in ICD patients demonstrated that approximately 20 % of ICD patients are subject to clinically significant distress in point prevalence studies (Magyar-Russell et al. 2011). More specifically, between 11 % and 28 % had either an anxiety or depressive disorder when structured interviews were used. Estimates ranged more broadly for anxiety (i.e., 8–63 %) and depression (5–41 %) when questionnaires were the mode of assessment. Regardless of the specific study cited, the consulting psychologist can have a relatively high index of suspicion diagnostically for anxiety and depression in ICD patients.

Longitudinal assessment of psychological functioning has also been studied but definitive conclusions are difficult to draw. For example, when attempting to characterize the trajectories of distress in ICD patients over the first 1.5 years after implantation, type D personality (tendency toward high negative affect and social inhibition) and anxiety sensitivity predicted upward trends in distress (van den Broek et al. 2014). The persistence of anxiety has been demonstrated (Pedersen et al. 2011a), but some evidence also shows reductions in anxiety in ICD patients over time (Lang et al. 2014; Pedersen et al. 2009a). For depression, symptoms may decrease over time in ICD patients (Pedersen et al. 2009a); however, there appears to be a great deal of individual variance, with some patients who maintain psychological distress within the first months or years after implantation (e.g., Pedersen et al. 2011a, b; Suzuki et al. 2010). A number of factors have been shown to influence anxiety, depression, or a mixture thereof, including type D personality, disease severity, comorbidity burden, and ICD shock (Hoogwegt et al. 2013; Jacq et al. 2009; Pedersen et al. 2009a; Schulz et al. 2013).

Post-traumatic Stress Disorder. PTSD has garnered increasing attention among the anxiety disorders (Sears et al. 2011). Initial research indicated that PTSD was prevalent and influential on survival (Ladwig et al. 2008). Significant

levels of PTSD symptoms at the time of implantation have been found to be just over 20 %, and these rates were somewhat reduced at 6- (12 %) and 12-month (13 %) follow-up intervals (Kapa et al. 2010). There are likely two factors that have caused focus on PTSD. First, for those receiving ICDs as secondary prevention, the index event that precipitated implantation (e.g., sudden cardiac arrest) is often traumatic for patients. Second, the experience of ICD shock itself can be traumatic and trigger related symptoms of anxiety, hypervigilance, avoidance of feared activities, and other hallmark symptoms that can be conceptualized within the framework of PTSD. The confound between disease process and diagnosis, rather than shock itself, may be the more prevalent contributor to PTSD symptoms, as shock has at times failed to be linked to PTSD symptoms (Habibovic et al. 2012; Ladwig et al. 2008). Recently, shock anxiety (specific fears of ICD shocks) was associated with PTSD symptoms, which lends credence to the possibility that an acute stress reaction to shock, not simply experiencing shock, could be a key ingredient in development of PTSD (Morken et al. 2014).

Longitudinal research examining predictors of PTSD at 18-month postimplantation in a Dutch sample of ICD patients found that type D personality and general baseline anxiety were significant predictors, whereas shock was not a significant predictor (Habibovic et al. 2012). Prospective research has attempted to describe two sets of predictors of PTSD, one relevant to predicting PTSD at the time of implantation and another relevant to predicting PTSD at follow-up (von Känel et al. 2011). Female sex, depression, and dissociation around the time of trauma predicted PTSD symptoms at the time of implantation, whereas greater PTSD symptoms at implantation, alexithymia, and experiencing five or more shocks predicted PTSD at follow-up. The authors also reported that PTSD symptoms increased in prevalence from the time of implantation to follow-up, suggesting that chronicity may be a germane issue when considering PTSD in ICD patients.

Type D Personality. Type D personality research has increased in popularity over recent years as research teams have set out to understand the ICD patient experience. Some estimates have placed the prevalence of type D personality around 21–23 % in ICD patients (e.g., Pedersen et al. 2008, 2010). Being a personality factor, the focus has not been on how ICDs change one's personality, but rather how one's personality affects the ICD patient experience. Patients with type D personality have shown a range of poorer outcomes, including more anxiety and depression (Habivovic et al. 2012; Pedersen et al. 2011a, 2013a). It may represent a more macro level of distress overall, or susceptibility to distress from the potential stressors living with an ICD can present and subsequently experience increased psychological morbidity. However, some recent reports have revealed difficulty with the primary measure of type D personality (see Suls 2014). Nonetheless, the existing research base employing type D constructs in ICD patient research is significant and highlights the consideration of psychological factors in patient care.

Quality of Life. Significant large-scale randomized studies have indicated that the quality of life of ICD patients is at least equal to, if not better than, the quality of

life in patients treated with anti-arrhythmic drug therapy (e.g., Irvine et al. 2002; Schron et al. 2002; Sears et al. 2009a). The importance of this conclusion cannot be overstated because patients often have to make the decision about receiving an ICD in short order. ICDs have a known survival advantage so patients are asked to consider the quality of life impact likely as the second most significant consideration. These data indicate that the ICD becomes an increasingly more desirable choice as long as the downsides of treatment with an ICD could be mitigated. The experience of ICD shock is often faulted, and initial research consistently focused on that theme. A cluster of studies has shown a linear relationship between frequency of ICD shocks and psychological distress (e.g., Passman et al. 2007; van den Broek et al. 2008), whereas another group of studies has failed to show an association between shock and psychological distress (e.g., Piotrowicz et al. 2007; Crössmann et al. 2007). Overall, the evidence suggests that for patients who meet the threshold of five or more shocks, this is the cut point where detriments in quality of life tend to be most reliably shown (e.g., de Ornelas Maia et al. 2013; Irvine et al. 2002; Passman et al. 2007).

A number of intuitive factors have been shown to be negatively related to quality of life in ICD patients, such as anxiety and depression (e.g., Dickerson et al. 2010; Wong et al. 2014; Hallas et al. 2010), whereas optimism and positive health expectations may be protective for quality of life (Sears et al. 2004). The reason for implantation of an ICD has also been consistently identified in the clinical context as a potentially important factor in the quality of life outcome. Debate persisted for some time regarding whether primary prevention patients' quality of life was impacted differently than that of patients receiving ICDs for secondary prevention. However, a review of the evidence concluded that patients receiving ICDs for either indication were not significantly different in regard to quality of life outcomes (Pedersen et al. 2009b).

Type of device has been related to quality of life outcomes as well. A meta-analysis delineated quality of life outcomes in patients with ICDs versus CRT-D devices. CRT-D devices provide continual treatment for patients with heart failure via biventricular pacing in addition to acute provision of shock as needed, the former being a unique feature of CRT-D devices that is not offered by ICDs. The meta-analysis showed that patients with CRT-D devices, particularly with moderate to severe heart failure, had significantly better reports of quality of life than ICD patients (Chen et al. 2012). However, as a study published around the time of that review indicates, there may be subtleties when understanding differences in quality of life based on device type. Ford and colleagues showed that patients with CRT-D devices reported poorer physical and disease-specific quality of life compared to ICD patients; but CRT-D therapy was associated with improved mental quality of life over time, a finding not shared in the subset of ICD-only patients in that study (Ford et al. 2014). Therefore, a range of factors impact quality of life for ICD patients, so it is important to consider both medical and psychological contributors when understanding the degree of functional impairment ICD patients are experiencing. Understanding how a patient's quality of life is impacted by living with a device is a paramount task when embracing the biopsychosocial model

because the patient typically seeks or warrants professional psychological assistance because their quality of life is compromised.

Demographic and Patient Factors

Stratifying risk based on sex and age has been addressed by a wide range of studies. Although the evidence is mixed to a degree (see Bostwick and Sola 2007), many studies demonstrate that ICD patients who are female and/or are younger at the time of implantation could be more likely to experience distress and disrupted quality of life when compared to male and/or older counterparts. The link between female sex and greater risk may be attributable to negative impacts, body image (e.g., scars), social role shifts, greater awareness of bodily sensations, or greater levels of pain and functional limitation in the context of caregiving duties (e.g., Brouwers et al. 2011). However, the investigation of gender is often difficult as most studies include a vast majority of male patients, and needed analyses may be underpowered to detect valid sex differences. Young age (less than 50 years of age) also places ICD patients at potential risk for poorer adjustment (Sears et al. 2001; Dubin et al. 1996). Several reasons for the age difference have been offered and include body image concerns, disruption of quality of life (e.g., via numerous medical visits), avoidance of physical activities, and higher rates of emotional distress. Relative to analysis of sex and age differences, little research addresses racial differences in ICD recipients. In one sample, African Americans had poorer psychological response profiles to ICDs when compared to whites (Wilson et al. 2013). Specifically, African Americans reported lower acceptance of their devices and higher shock-related anxiety. They also demonstrated less knowledge of their devices in comparison to whites. Although differences among races, ethnicities, or cultures have not gained traction in similar magnitude of that gained by sex and age research with ICD patients, this is an important next direction for the field as it attempts to understand the ICD patient experience in increasing levels of detail to optimize patient adjustment and understanding.

Special Populations and Considerations

Pediatric Patients. The challenges of coping with cardiac disease and an ICD are particularly salient in the pediatric context (Sears et al. 2001, 2009). Children with ICDs have consistently demonstrated increased and specific psychological challenges in ICD patient research. Although the strength of conclusions remains limited by the relatively small samples of ICD patients available in single centers, researchers have delineated concerns spanning both affective and behavioral problems. In a study of children with ICDs or pacemakers, increased risk was demonstrated for anxiety in ICD patients (27 % vs. 11 % respectively), but not for depressive symptoms (Webster et al. 2014). The type of device was not a significant predictor of distress after controlling for possible confounds, and parental distress

was not different between groups. Another study showed that 22 % of their pediatric ICD patient sample experienced problematic anxiety (Stefanelli et al. 2002), which, when combined with the previous study, estimates that the likelihood of psychological distress in children with ICDs is to be between 22 % and 27 %.

Researchers have sought to examine whether the distress is meaningfully different than in children with other chronic diseases. Pediatric patients with ICDs do appear to be uniquely impacted by living with a device in some ways. Although rates of depression and anxiety in children with ICDs were not shown to be significantly different than in children with chronic illness (DeMaso et al. 2004), lower physical functioning, psychosocial functioning, and quality of life have been demonstrated in pediatric ICD patients when compared to healthy or chronically ill reference groups (DeMaso et al. 2004; Sears et al. 2011b). Within the same studies, parental reports echoed these findings, showing that parents of children with ICDs also perceived that their children were negatively impacted in those domains. In fact, parent reports of negative impacts were higher than the children's reports in some instances (Sears et al. 2011b). In the largest study on quality of life with pediatric ICD patients, Sears et al. (2011b) further demonstrated that the occurrence of ICD shock and medical severity were not predictive of patient distress. Additionally, sex differences emerged in that study, with girls reporting lower physical, psychosocial, and cardiac quality of life than boys. A separate, and smaller, study did not find sex differences in children's adjustment to living with an ICD, but ICD shock was linked to depressive symptoms (Koopman et al. 2012). That study also provided some evidence of increased anxiety, depression, and sleep problems in children with ICDs relative to normative samples. Although some findings may be mixed, clarification and specificity will be better accomplished as research in this population accumulates over time. Nonetheless, the pattern of increased risk for negative psychosocial impact in pediatric ICD patients is clear.

Despite the limited nature of research with pediatric ICD samples, specific pediatric ICD patient concerns have begun to emerge. Perhaps the most significant finding from any of these studies is that approximately 84.7 % of these young ICD patients reported strong avoidance behaviors in an attempt to manage anxiety (Sears et al. 2011b). In addition, Koopman et al. (2012) highlighted some specific worries that provide some additional insights into pediatric ICD patients. For example, the majority of pediatric ICD patients endorsed the following: "I am afraid of being alone if the ICD fires and I need help," and "I'm nervous that if I exercise, my heart might start beating faster and make the ICD fire." This statement highlights the role of fear generalization beyond simply ICD shock and extends to behaviors that would be associated with even normative exertions or normal elevation of heart rate. These types of survey responses could provide specific targets of information and strategies in designing a pediatric treatment study.

Devices Under Recall and Leads Under Advisory. Although such events are rare, ICDs have at times been subject to "field actions" or "recalls" due to evidence of malfunctions or increased risk of adverse events, some of which could cause death. Naturally, some researchers have set out to examine how this affects the patient

psychologically. Although there is some mixed evidence, studies of better quality indicate that significant differences fail to emerge between those with and without devices under recall in psychological functioning or quality of life (e.g., Undavia et al. 2008). However, there is some evidence to show that quality of life for those with class I recall (most severe risk for adverse events) may be particularly negatively affected. ICD device and lead reliability is constantly monitored internationally by the device manufacturers and adverse events are routinely reported.

The weak link in the ICD system has long been the use of intracardiac leads. Some leads are placed under advisory due to risk of fracture and subsequent malfunction, which may take the form of inappropriate shock. Similar to the findings with recalled devices, patients with leads under advisory do not demonstrate poorer psychological functioning compared to patients with ICD leads that are not under advisory (Birnie et al. 2009; Keren et al. 2011). However, patients with leads that actually fractured did show poorer psychological functioning when compared to those without leads under recall, implicating the inappropriate shocks that these patients received as a result of the lead fracture(s) (Keren et al. 2011).

Phantom Shocks. Phantom shocks are instances when patients perceive the occurrence of shock when objective evidence of shock is absent. Given the understandably confusing nature of this experience, it is a clinical issue that demands delicate attention, particularly as patients may feel they are being dismissed or that their symptoms are not taken to be "real." A recent study from the Netherlands followed over 600 ICD patients for nearly 3 years and reported a rate of phantom shock at 5 % (Kraaier et al. 2012). Patients who have experienced ICD shock storms (multiple back-to-back shocks) may be more likely to subsequently experience phantom shock (Jacob et al. 2012). In regard to psychological distress, both depression and anxiety have been associated with phantom shock, and the experience of phantom shock may be a permutation of reexperiencing, a hallmark symptom of PTSD (Jacob et al. 2012; Prudente et al. 2006). However, such linkages were not found between psychological distress and phantom shock in one recent investigation (Starrenburg et al. 2014). The evidence in its totality suggests, however, that patients who present with an episode of phantom shock should be considered at risk for psychological distress. Unfortunately, the probability of phantom shocks does not appear to be reduced via rehabilitation intervention based on limited available evidence (Berg et al. 2013).

End-of-Life Issues. With improvements in ICD technology, the number of patients implanted with ICDs has increased, as has the number of years patients are living with ICDs. This, combined with focus on patient-centered perspective in caring for ICD patients, has led to efforts in exploring the role of ICDs near the end of life. Evidence shows that physicians often fail to address device deactivation with their ICD patients when considering end-of-life care (Goldstein et al. 2004; Nambisan and Chao 2004). Alarmingly, a recent study showed that in ICD patients at the end of life, 31 % received ICD shock within the final 24 h of life (Westerdahl et al. 2014). Further, of patients with do-not-resuscitate orders, ICD devices were active and available to deliver shock in over half of the study patients; nearly 25 % of those patients experienced ICD shock in the last 24 h of life. There have been

Table 1 Assessment tools for measuring quality of life and psychological distress

	Measure	Source or reference	Concept measured	Subscales	No. of items
Device-specific measures	Aquarel questionnaire	Stofmeel et al. 2001	Device acceptance (pacemaker only)	Cognition, chest discomfort, dyspnea, arrhythmias	20
	Florida patient acceptance scale	Burns et al. 2005	Device acceptance	Return to function, device-related distress, body image concerns	18
	Florida shock anxiety scale	Kuhl et al. 2006	Device-specific anxiety	Consequence of shock, trigger of shock	10
	ICD patient concerns questionnaire	Frizelle et al. 2006	Device-related concerns	Device-specific concerns, perceived limitations	20
	Unnamed	Luderitz et al. 1993	Device acceptance	N/A	8
Generic measures	Cardiac anxiety questionnaire	Eifert et al. 2000	Disease-specific anxiety	Fear, avoidance, heart-focused attention	18
	Hospital anxiety and depression scale	See Bjelland et al. 2002	Depression and anxiety in nonpsychiatric medical settings	Anxiety, depression	14
	Beck depression inventory II	Beck et al. 1996	Depression	N/A	21
	Beck anxiety inventory	Beck et al. 1988	Anxiety	N/A	21
	State-trait anxiety inventory	Spielberger et al. 1983	Anxiety	State anxiety, trait anxiety	40
	Patient health questionnaire (PHQ-9)	Spitzer et al. 1999	Depression	N/A	9
	Impact of event scale – revised	Weiss and Marmer 1997	Post-traumatic stress	Avoidance, hyperarousal, intrusion	22
	PTSD checklist	Weathers et al. 1994	Post-traumatic stress	N/A	17

recent efforts to systematically address this clinical shortfall, including a consensus statement on the management of devices amidst end of life (Lampert et al. 2010). Concerted efforts to proactively and empathically address this topic are particularly critical given that many patients are not aware that deactivation is even an option at

end of life (Pedersen et al. 2013b). There is evidence that patients feel that education around deactivation is desirable (Pedersen et al. 2013b) and that patients may favor deactivation when they understand the overall function of their ICD (Dodson et al. 2013). Ultimately, the risk is high for acutely and severely compromised quality of life during the end-of-life phase if patients are not adequately informed about both their devices and device management during the end of life.

Assessment Tools

A variety of tools are available to measure psychological distress and adjustment in ICD recipients. Some tools are generic and are ostensibly applicable to all individuals, medical and nonmedical. Others have been developed for utilization specifically with ICD patients. The latter can be particularly beneficial as some generic measures fail to capture the complexities of the incomparable ICD patient experience. Generic measures are certainly relevant in some patient presentations, however. ICD patients naturally will vary in their presentation, with some patients having psychological distress history or current complaints that are attributable to issues that are distinct from their ICD experience. So in an effort to understand each patient's presentation fully, it is essential to be flexible in one's selection of assessment tools to aid in case conceptualization. Given the prevalence of anxiety and depression in ICD patients, as well as the importance of quality of life, as outlined above, these are the measures likely to provide the most benefit in understanding the psychological concerns of your patients. Table 1 provides a summary of recommended measures for consideration when objectively exploring the psychological presentation of ICD patients.

Conclusions

ICDs save lives and have been one of the most rapidly innovating technologies in recent history. The patient experience with the ICD readily intertwines the process of cardiac disease with the implantation of a technology. Psychological aspects are inherently central to understanding and producing the best possible health outcomes. Approximately one in five ICD patients experiences significant psychological distress (Magyar-Russell et al. 2011), but very few receive treatment (see Hoogwegt et al. 2012; Magyar-Russell et al. 2011). Therefore, both medical and mental health providers have an obligation to be aware of the psychological hazards likely to be faced by ICD patients so that the need for treatment can be recognized and referral for effective services can be facilitated. Chapter "▶ Adding Psychological Intervention to High-Tech Care for Patients with Implantable Cardioverter Defibrillators" in this edition outlines available treatments for these patients' needs.

References

Bardy, G. H., Lee, K. L., Mark, D. B., Poole, J. E., Packer, D. L., Boineau, R., . . ., Ip, J. H. (2005). Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. *New England Journal of Medicine, 352,* 225–237.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology, 56*, 893–897.

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. (1996). Comparison of beck depression inventories –IA and –II in psychiatric outpatients. *Journal of Personality Assessment, 67*, 588–597.

Berg, S. K., Moons, P., Zwisler, A. D., Winkel, P., Pedersen, B. D., Pedersen, P. U., & Svendsen, J. H. (2013). Phantom shocks in patients with implantable cardioverter defibrillator: Results from a randomized rehabilitation trial (COPE-ICD). *Europace, 15*, 1463–1467.

Birnie, D. H., Sears, S. F., Green, M. S., Lemery, R., Gollob, M. H., & Amyotte, B. (2009). No long-term psychological morbidity living with an implantable cardioverter defibrillator under advisory: The Medtronic marquis experience. *Europace, 11*, 26–30.

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *Journal of psychosomatic research, 52*(2), 69–77.

Bostwick, J. M., & Sola, C. L. (2007). An updated review of implantable cardioverter/defibrillators, induced anxiety, and quality of life. *Psychiatric Clinics of North America, 30*, 677–688.

Brouwers, C., Van den Broek, K. C., Denollet, J., & Pedersen, S. S. (2011). Gender disparities in psychological distress and quality of life among patients with an implantable cardioverter defibrillator. *Pacing and Clinical Electrophysiology, 34*, 798–803.

Burns, J. L., Serber, E. R., Keim, S., & Sears, S. F. (2005). Measuring patient acceptance of implantable cardiac device therapy. *Journal of cardiovascular electrophysiology, 16*(4), 384–390.

Chen, S., Yin, Y., & Krucoff, M. W. (2012). Effect of cardiac resynchronization therapy and implantable cardioverter defibrillator on quality of life in patients with heart failure: A meta-analysis. *Europace, 14*, 1602–1607.

Crössmann, A., Pauli, P., Dengler, W., Kühlkamp, V., & Wiedemann, G. (2007). Stability and cause of anxiety in patients with an implantable cardioverter-defibrillator: A longitudinal two-year follow-up. *Heart & Lung, 36*, 87–95.

de Ornelas Maia, A. C. C., Soares-Filho, G., Pereira, V., Nardi, A. E., & Silva, A. C. (2013). Psychiatric disorders and quality of life in patients with implantable cardioverter defibrillators: A systematic review. *The Primary Care Companion for CNS Disorders, 15,* PCC.12r01456.

DeMaso, D. R., Lauretti, A., Spieth, L., Van Der Feen, J. R., Jay, K. S., Gauvreau, K., ... Berul C. I. (2004). Psychosocial factors and quality of life in children and adolescents with implantable cardioverter-defibrillators. *The American Journal of Cardiology, 93,* 582–587.

Dickerson, S. S., Kennedy, M., Wu, Y. W. B., Underhill, M., & Othman, A. (2010). Factors related to quality-of-life pattern changes in recipients of implantable defibrillators. *Heart & Lung, 39*, 466–476.

Dodson, J. A., Fried, T. R., Van Ness, P. H., Goldstein, N. E., & Lampert, R. (2013). Patient preferences for deactivation of implantable cardioverter-defibrillators. *JAMA Internal Medicine, 173*, 377–379.

Dubin, A. M., Batsford, W. P., Lewis, R. J., & Rosenfeld, L. E. (1996). Quality of life in patients receiving implantable cardioverter defibrillators at or before age 40. *Pacing and Clinical Electrophysiology, 19*, 1555–1559.

Eifert, G. H., Thompson, R. N., Zvolensky, M. J., Edwards, K., Frazer, N. L., Haddad, J. W., & Davig, J. (2000). The Cardiac Anxiety Questionnaire: development and preliminary validity. *Behaviour Research and Therapy, 38*(10), 1039–1053.

Ford, J., Sears, S., Ramza, B., Reynolds, D. W., Nguyen, P., Fedewa, M., . . ., Murray, C. (2014). The Registry Evaluating Functional Outcomes of Resynchronization Management (REFORM): Quality of life and psychological functioning in patients receiving cardiac resynchronization therapy. *Journal of Cardiovascular Electrophysiology, 25,* 43–51.

Frizelle, D. J., Lewin, B., Kaye, G., & Moniz-Cook, E. D. (2006). Development of a measure of the concerns held by people with implanted cardioverter defibrillators: The ICDC. *British Journal of Health Psychology, 11*, 293–301.

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Blaha, M. J., on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, et al. (2014). Heart disease and stroke statistics – 2014 update: A report from the American Heart Association. *Circulation, 129*, e28–e292.

Goldstein, N. E., Lampert, R., Bradley, E., Lynn, J., & Krumholz, H. M. (2004). Management of implantable cardioverter defibrillators in end-of-life care. *Annals of Internal Medicine, 141*, 835–838.

Habibović, M., van den Broek, K. C., Alings, M., Van der Voort, P. H., & Denollet, J. (2012). Posttraumatic stress 18 months following cardioverter defibrillator implantation: Shocks, anxiety, and personality. *Health Psychology, 31*, 186–193.

Hallas, C. N., Burke, J. L., White, D. G., & Connelly, D. T. (2010). A prospective one year study of changes in neuropsychological functioning following implantable cardioverter defibrillator surgery. *Circulation. Arrhythmia and Electrophysiology, 3*, 170–177.

Hoogwegt, M. T., Kupper, N., Theuns, D. A., Zijlstra, W. P., Jordaens, L., & Pedersen, S. S. (2012). Undertreatment of anxiety and depression in patients with an implantable cardioverter-defibrillator: Impact on health status. *Health Psychology, 31*, 745–753.

Hoogwegt, M. T., Kupper, N., Jordaens, L., Pedersen, S. S., & Theuns, D. A. (2013). Comorbidity burden is associated with poor psychological well-being and physical health status in patients with an implantable cardioverter-defibrillator. *Europace, 15*, 1468–1474.

Irvine, J., Dorian, P., Baker, B., O'Brien, B. J., Roberts, R., Gent, M., . . ., Connolly, S. J. (2002). Quality of life in the Canadian implantable defibrillator study (CIDS). *American Heart Journal, 144,* 282–289.

Jacob, S., Panaich, S. S., Zalawadiya, S. K., McKelvey, G., Abraham, G., Aravindhakshan, R., . . ., Marsh, H. M. (2012). Phantom shocks unmasked: clinical data and proposed mechanism of memory reactivation of past traumatic shocks in patients with implantable cardioverter defibrillators. *Journal of Interventional Cardiac Electrophysiology, 34*, 205–213.

Jacq, F., Foulldrin, G., Savouré, A., Anselme, F., Baguelin-Pinaud, A., Cribier, A., & Thibaut, F. (2009). A comparison of anxiety, depression and quality of life between device shock and nonshock groups in implantable cardioverter defibrillator recipients. *General Hospital Psychiatry, 31*, 266–273.

Kapa, S., Rotondi-Trevisan, D., Mariano, Z., Aves, T., Irvine, J., Dorian, P., & Hayes, D. L. (2010). Psychopathology in patients with ICDs over time: Results of a prospective study. *Pacing and Clinical Electrophysiology, 33*, 198–208.

Keren, A., Sears, S. F., Nery, P., Shaw, J., Green, M. S., Lemery, R., . . ., Birnie, D. H. (2011). Psychological adjustment in ICD patients living with advisory fidelis leads. *Journal of Cardiovascular Electrophysiology, 22,* 57–63.

Kirian, K., Sears, S. F., & DeAntonio, H. (2012). Sudden cardiac arrest: A biopsychosocial approach to patient management of ventricular fibrillation and implantable cardioverter defibrillators. In: Ellen A. Dornelas (Ed) *Stress Proof the Heart* (pp. 25–43). Springer: New York.

Koopman, H. M., Vrijmoet-Wiersma, C. M. J., Langius, J. N. D., van den Heuvel, F., Clur, S. A., Blank, C. A., . . ., ten Harkel, A. D. J. (2012). Psychological functioning and disease-related quality of life in pediatric patients with an implantable cardioverter defibrillator. *Pediatric Cardiology, 33,* 569–575.

Kraaier, K., Starrenburg, A. H., Verheggen, R. M., Van Der Palen, J., & Scholten, M. F. (2012). Incidence and predictors of phantom shocks in implantable cardioverter defibrillator recipients. *European Heart Journal, 33*, 542–542.

Kremers, M. S., Hammill, S. C., Berul, C. I., Koutras, C., Curtis, J. S., Wang, Y., . . ., Rumself, J. (2013). The national ICD registry report: Version 2.1 including leads and pediatrics for years 2010 and 2011. *Heart Rhythm, 10*, e59–e65.

Kuhl, E. A., Dixit, N. K., Walker, R. L., Conti, J. B., & Sears, S. F. (2006). Measurement of patient fears about implantable cardioverter defibrillator shock: an initial evaluation of the Florida Shock Anxiety Scale. *Pacing and clinical electrophysiology, 29*(6), 614–618.

Ladwig, K. H., Baumert, J., Marten-Mittag, B., Kolb, C., Zrenner, B., & Schmitt, C. (2008). Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. *Archives of General Psychiatry, 65*, 1324–1330.

Lampert, R., Hayes, D. L., Annas, G. J., Farley, M. A., Goldstein, N. E., Hamilton, R. M., . . ., Zellner, R. (2010). HRS expert consensus statement on the management of cardiovascular implantable electronic devices (CIEDs) in patients nearing end of life or requesting withdrawal of therapy. *Heart Rhythm, 7,* 1008–1026.

Lang, S., Becker, R., Wilke, S., Hartmann, M., Herzog, W., & Loewe, B. (2014). Anxiety disorders in patients with implantable cardioverter defibrillators: Frequency, course, predictors, and patients' requests for treatment. *Pacing and Clinical Electrophysiology, 37*, 35–47.

Luderitz, B., Werner, J., Deister, A., Marneros, A., & Manz, M. (1993). Patient acceptance of the implantable cardioverter defibrillator in ventricular tachyarrhythmias. *Pacing and Clinical Electrophysiology, 6*, 1815–1821.

Magyar-Russell, G., Thombs, B. D., Cai, J. X., Baveja, T., Kuhl, E. A., Singh, P. P., . . ., Ziegelstein, R. C. (2011). The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: a systematic review. *Journal of Psychosomatic Research, 71,* 223–231.

Morken, I. M., Bru, E., Norekvål, T. M., Larsen, A. I., Idsoe, T., & Karlsen, B. (2014). Perceived support from healthcare professionals, shock anxiety and post-traumatic stress in implantable cardioverter defibrillator recipients. *Journal of Clinical Nursing, 23*, 450–460.

Moss, A. J., Zareba, W., Hall, J., Klein, H., Wilber, D. J., Cannom, D. S., . . ., Andrews M. L., for the MADIT II Investigators. (2002). Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *New England Journal of Medicine, 346,* 877–883

Nambisan, V., & Chao, D. (2004). Dying and defibrillation: A shocking experience. *Palliative Medicine, 18*, 482–483.

Passman, R., Subacius, H., Ruo, B., Schaechter, A., Howard, A., Sears, S. F., & Kadish, A. (2007). Implantable cardioverter defibrillators and quality of life: Results from the defibrillators in nonischemic cardiomyopathy treatment evaluation study. *Archives of Internal Medicine, 167*, 2226–2232.

Pedersen, S. S., Theuns, D. A., Erdman, R. A., & Jordaens, L. (2008). Clustering of device-related concerns and Type D personality predicts increased distress in ICD patients independent of shocks. *Pacing and Clinical Electrophysiology, 31*, 20–27.

Pedersen, S. S., van den Berg, M., Erdman, R. A., Van Son, J., Jordaens, L. U. C., & Theuns, D. A. (2009a). Increased anxiety in partners of patients with a cardioverter-defibrillator: The role of indication for ICD therapy, shocks, and personality. *Pacing and Clinical Electrophysiology, 32*, 184–192.

Pedersen, S. S., Sears, S. F., Burg, M. M., & Van Den Broek, K. C. (2009b). Does ICD indication affect quality of life and levels of distress? *Pacing and Clinical Electrophysiology, 32*, 153–156.

Pedersen, S. S., Theuns, D. A., Jordaens, L., & Kupper, N. (2010). Course of anxiety and device-related concerns in implantable cardioverter defibrillator patients the first year post implantation. *Europace, 12*, 1119–1126.

Pedersen, S. S., van den Broek, K. C., Theuns, D. A., Erdman, R. A., Alings, M., Meijer, A., . . . Denollet, J. (2011a). Risk of chronic anxiety in implantable defibrillator patients: A multicenter study. *International Journal of Cardiology, 147,* 420–423.

Pedersen, S. S., Hoogwegt, M. T., Jordaens, L., & Theuns, D. A. (2011b). Relation of symptomatic heart failure and psychological status to persistent depression in patients with implantable cardioverter-defibrillator. *The American Journal of Cardiology, 108*, 69–74.

Pedersen, S. S., Hoogwegt, M. T., Jordaens, L., & Theuns, D. A. (2013a). Pre-implantation psychological functioning preserved in majority of implantable cardioverter defibrillator patients 12 months post implantation. *International Journal of Cardiology, 166*, 215–220.

Pedersen, S. S., Chaitsing, R., Szili-Torok, T., Jordaens, L., & Theuns, D. A. (2013b). Patients' perspective on deactivation of the implantable cardioverter-defibrillator near the end of life. *The American Journal of Cardiology, 111*, 1443–1447.

Piotrowicz, K., Noyes, K., Lyness, J. M., McNitt, S., Andrews, M. L., Dick, A., . . ., Zareba, W. (2007). Physical functioning and mental well-being in association with health outcome in patients enrolled in the multicenter automatic defibrillator implantation trial II. *European Heart Journal, 28,* 601–607.

Prudente, L. A., Reigle, J., Bourguignon, C., Haines, D. E., & DiMarco, J. P. (2006). Psychological indices and phantom shocks in patients with ICD. *Journal of Interventional Cardiac Electrophysiology, 15*, 185–190.

Rozanski, A., Blumenthal, J. A., Davidson, K. W., Saab, P. G., & Kubzansky, L. (2005). The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology. *Journal of the American College of Cardiology, 45*, 637–651.

Schron, E. B., Exner, D. V., Yao, Q., Jenkins, L. S., Steinberg, J. S., Cook, J. R., . . . Powell, J. (2002). Quality of life in the antiarrhythmics versus implantable defibrillators trial impact of therapy and influence of adverse symptoms and defibrillator shocks. *Circulation, 105,* 589–594.

Schulz, S. M., Massa, C., Grzbiela, A., Dengler, W., Wiedemann, G., & Pauli, P. (2013). Implantable cardioverter defibrillator shocks are prospective predictors of anxiety. *Heart & Lung, 42*, 105–111.

Sears, S. F., Burns, J. L., Handberg, E., Sotile, W. M., & Conti, J. B. (2001). Young at heart: Understanding the unique psychosocial adjustment of young implantable cardioverter defibrillator recipients. *Pacing and Clinical Electrophysiology, 24*, 1113–1117.

Sears, S. F., Serber, E. R., Lewis, T. S., Walker, R. L., Conners, N., Lee, J. T., . . ., Conti, J. B. (2004). Do positive health expectations and optimism relate to quality-of-life outcomes for the patient with an implantable cardioverter defibrillator? *Journal of Cardiopulmonary Rehabilitation and Prevention, 24,* 324–331.

Sears, S. F., Matchett, M., & Conti, J. B. (2009a). Effective management of ICD patient psychosocial issues and patient critical events. *Journal of Cardiovascular Electrophysiology, 20*, 1297–1304.

Sears, S. F., Amant, J. B., & Zeigler, V. (2009b). Psychosocial considerations for children and young adolescents with implantable cardioverter defibrillators: An update. *Pacing and Clinical Electrophysiology, 32*, S80–S82.

Sears, S. F., Hauf, J. D., Kirian, K., Hazelton, G., & Conti, J. B. (2011a). Posttraumatic stress and the implantable cardioverter-defibrillator patient: What the electrophysiologist needs to know. *Circulation. Arrhythmia and Electrophysiology, 4*, 242–250.

Sears, S. F., Hazelton, A. G., St Amant, J., Matchett, M., Kovacs, A., Vazquez, L. D., . . ., Bryant, R. M. (2011b). Quality of life in pediatric patients with implantable cardioverter defibrillators. *The American journal of cardiology, 107*, 1023–1027.

Spielberger, C. D., Gorssuch, R. L., Lushene, P. R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the state-trait anxiety inventory*. Palo Alto: Consulting Psychologists Press Inc.

Spitzer, R. L., Kroenke, K., Williams, J. W., & Patient Health Questionnaire Primary Care Study Group. (1999). Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. *JAMA, 282*, 1737–1744.

Starrenburg, A., Kraaier, K., Pedersen, S., Scholten, M., & Palen, J. (2014). Psychological indices as predictors for phantom shocks in implantable cardioverter defibrillator recipients. *Pacing and Clinical Electrophysiology, 37*, 768–773.

Stefanelli, C. B., Bradley, D. J., Leroy, S., Dick, M., Serwer, G. A., & Fischbach, P. S. (2002). Implantable cardioverter defibrillator therapy for life-threatening arrhythmias in young patients. *Journal of Interventional Cardiac Electrophysiology, 6*, 235–244.

Stofmeel, M. A., Post, M. W., Kelder, J. C., Grobbee, D. E., & van Hemel, N. M. (2001). Psychometric properties of the Aquarel: A disease-specific quality of life questionnaire for pacemaker patients. *Journal of Clinical Epidemiology, 54*, 157–165.

Stutts, L. A., Cross, N. J., Conti, J. B., & Sears, S. F. (2007). Examination of research trends on patient factors in patients with implantable cardioverter defibrillators. *Clinical Cardiology, 30*, 64–68.

Suls, J. (2014). An informative failure to replicate – the Type D is distressed: A comment on Meyer et al. *Annals of Behavioral Medicine, 48*, 140–141.

Suzuki, T., Shiga, T., Kuwahara, K., Kobayashi, S., Suzuki, S., Nishimura, K., . . ., Hagiwara, N. (2010). Prevalence and persistence of depression in patients with implantable cardioverter defibrillators: A 2-year Longitudinal Study. *Pacing and Clinical Electrophysiology, 33,* 1455–1461.

Undavia, M., Goldstein, N. E., Cohen, P., Sinthawanarong, K., Singson, M., Bhutani, D., . . ., Mehta, D. (2008). Impact of implantable cardioverter-defibrillator recalls on patients' anxiety, depression, and quality of life. *Pacing and Clinical Electrophysiology, 31,* 1411–1418.

van den Broek, K. C., Nyklíček, I., Van Der Voort, P. H., Alings, M., & Denollet, J. (2008). Shocks, personality, and anxiety in patients with an implantable defibrillator. *Pacing and Clinical Electrophysiology, 31*, 850–857.

van den Broek, K. C., Kupper, N., van der Voort, P. H., Alings, M., Denollet, J., & Nyklíček, I. (2014). Trajectories of perceived emotional and physical distress in patients with an implantable cardioverter defibrillator. *International Journal of Behavioral Medicine, 21*, 149–159.

von Känel, R., Baumert, J., Kolb, C., Cho, E. Y. N., & Ladwig, K. H. (2011). Chronic posttraumatic stress and its predictors in patients living with an implantable cardioverter defibrillator. *Journal of Affective Disorders, 131*, 344–352.

Weathers, F. W., Litz, B. T., Herman, D., Huska, J., & Keane, T. (1994). *The PTSD checklist-civilian version (PCL-C)*. Boston: National Center for PTSD.

Webster, G., Panek, K. A., Labella, M., Taylor, G. A., Gauvreau, K., Cecchin, F., . . ., DeMaso, D. R. (2014). Psychiatric functioning and quality of life in young patients with cardiac rhythm devices. *Pediatrics, 133,* e964–e972.

Weiss, D. S., & Marmer, C. R. (1997). The impact of events scale-revised. In J. Wilson & T. Keane (Eds.), *Assessing psychological trauma and PTSD* (pp. 344–362). New York: Guilford.

Westerdahl, A. K., Sjöblom, J., Mattiasson, A. C., Rosenqvist, M., & Frykman, V. (2014). Implantable cardioverter-defibrillator therapy before death high risk for painful shocks at end of life. *Circulation, 129*, 422–429.

Wilson, M. H., Engelke, M. K., Sears, S. F., Swanson, M., & Neil, J. A. (2013). Disease-specific quality of life – patient acceptance: Racial and gender differences in patients with implantable cardioverter defibrillators. *Journal of Cardiovascular Nursing, 28*, 285–293.

Wong, F. M. F., Sit, J. W. H., Wong, E. M. L., & Choi, K. C. (2014). Factors associated with health-related quality of life among patients with implantable cardioverter defibrillator: Identification of foci for nursing intervention. *Journal of Advanced Nursing*. doi:10.1111/jan.12434.

Psychological Effects of Invasive Cardiac Surgery and Cardiac Transplantation

Marra G. Ackerman and Peter A. Shapiro

Contents

Abstract

Psychiatric symptoms are common after cardiac surgery, particularly adjustment disorders, major depressive disorder, posttraumatic stress disorder, delirium, and cognitive disorders. Depression has been reported in up to 37 % of patients after

M.G. Ackerman (✉)
New York–Presbyterian Hospital, New York University Langone Medical Center, New York, NY, USA
e-mail: marra.ackerman@nyumc.org

P.A. Shapiro
Department of Psychiatry, Columbia University Medical Center, Columbia University, New York, NY, USA
e-mail: pas3@columbia.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_26

coronary artery bypass graft surgery and up to 63 % of patients after cardiac transplantation. PTSD has a prevalence of 15–25 % in postoperative cardiac patients and 10–17 % among posttransplant patients. The reported incidence of delirium among postoperative cardiac patients ranges from 10 % to 50 %. Postsurgical psychopathology confers significant morbidity and mortality. This chapter will review the prevalence, clinical features, and treatment of the most common psychiatric disorders after open-heart surgery (including coronary artery bypass graft and valve repair procedures) and orthotopic heart transplant.

Keywords
Depression • Delirium • Posttraumatic stress disorder • Sexual dysfunction • Cognition • Coronary artery bypass surgery • Heart valve surgery • Heart transplantation • Left ventricular assist device

Introduction

Coronary artery disease is the leading cause of death and disability in the developed world, as a result of myocardial infarction, congestive heart failure, and sudden cardiac death. Significant additional morbidity and mortality result from valvular heart disease, congenital and familial heart diseases, and various acquired cardiomyopathies. Coronary artery bypass surgery and valve repair and replacement procedures are common, may be lifesaving, and may enhance quality of life, even in patients for whom no benefit with respect to survival is expected; for example, coronary artery bypass for obstructive lesions outside the left anterior descending artery or left main coronary artery reduces the frequency of angina and improves functional status without changing survival. For selected patients, heart transplantation provides an escape route from end-stage heart disease when other therapeutic options are exhausted. However, with the number of heart transplant procedures performed annually limited by lack of organ donors, heart transplantation is not an option for most patients dying of heart failure. Implanted mechanical cardiac support therapies such as left ventricular assist devices, originally deployed as "bridge to transplant," now also serve as "destination therapy." All of these surgical procedures have associated risks of psychiatric and psychological morbidity, especially mood disorders, anxiety and stress-related symptoms, delirium, and neurocognitive impairment (Go et al. 2014; Murray and Lopez 1997).

Post-CABG/Valve Surgery

Depression

- Depression is common following coronary artery bypass graft (CABG) surgery, with reported rates of up to 37 % of patients endorsing depressive symptoms at hospital discharge (24 % incidence for mild depression, 4.2 % for moderate

depression, and 1 % with severe depression). Reduced preoperative left ventricular ejection fraction, physical inactivity, baseline depression, and a prolonged hospital stay are associated with depression (Horne et al. 2013). Significantly, depression has been linked with worse postoperative outcomes, including prolonged hospitalization (Poole et al. 2014), recurrent hospitalization, unmanageable pain, failure to return to previous level of activity (Burg et al. 2003), and increased recurrent cardiovascular event and mortality rates (Blumenthal et al. 2003; Connerney et al. 2010; Peterson et al. 2002). In a 5-year follow-up study of over 800 patients, new onset depression following surgery, failure to achieve remission of depressive symptoms 6 months after surgery, and severe depression symptoms were associated with increased mortality (Blumenthal et al. 2003). In a longitudinal cohort study of 302 post-CABG patients, major depressive disorder immediately after surgery was associated with a nearly twofold increase in cardiac mortality at 10-year follow-up (Connerney et al. 2010).

There is some evidence to suggest that patients suffering from depression before surgery may experience a reduction in symptoms afterward, related to improved physical functioning (Nemati and Astaneh 2011; Rothenhausler 2010). In a 2003 review of the literature, anxiety and depression seemed to improve from preoperative to postoperative assessments. However, levels of anxiety and depression remained higher among patients with preoperative anxiety and depressive syndromes than in those patients without identified psychopathology before surgery (Pignay-Demaria et al. 2003).

Depression Treatment

Serotonin reuptake inhibitors (SSRIs), specifically sertraline and citalopram, have been shown to be safe and at least modestly effective for treatment of depression in patients with coronary artery disease, and these agents are favored as first-line pharmacotherapy for depression in patients with coronary heart disease (CHD) or congestive heart failure (CHF) (Glassman et al. 2002; Lesperance et al. 2007). Electrocardiographic QTc prolongation is associated with increasing citalopram dose (Castro et al. 2013) and may increase the risk of torsade de pointes, leading to a United States Food and Drug Administration warning against the use of citalopram in doses above 40 mg daily. The clinical significance of this finding remains controversial (Pae et al. 2014; Zivin et al. 2013). In a recent randomized controlled trial of 361 patients, antidepressant therapy with escitalopram 10 mg resulted in improvement in depressive symptoms and overall quality of life as well as reduction in postoperative pain 6 months after CABG. There was no adverse effect on all-cause morbidity and mortality. No adverse events beyond typical side effects expected for SSRIs were identified (Chocran et al. 2013). Despite known effects of SSRIs on platelet serotonin storage and possible interactions with warfarin, a study of 246 patients taking SSRIs at the time of CABG found no effect of SSRI use on the rate of abnormal bleeding events (Xiong et al. 2010).

Other studies of depression treatment in CHF and coronary artery disease patients have provided equivocal evidence of the value of other antidepressants including nefazodone, bupropion, mirtazapine, venlafaxine, and tricyclic agents. None of these medicines have been subject to clinical trials in patients following coronary bypass or valve surgery. Tricyclic agents increase risk of orthostatic hypotension and cardiac conduction disturbances, and bupropion and venlafaxine may increase blood pressure (for reviews, see Shapiro 2008; 2009).

Non-pharmacological Treatments for Depression

There is a paucity of literature on non-pharmacologic treatments of depression after cardiac surgery. Rollman and colleagues (2009) conducted a randomized, controlled study of a telephone-delivered collaborative care intervention with 302 post-CABG patients with depression. The collaborative care arm included a telephone intervention conducted by a nurse manager who reviewed patients' psychiatric history, provided education, and described treatment options, which included an educational workbook, pharmacotherapy, monitoring of symptoms, or referral to a mental health specialist. Patients in the collaborative care arm of the study were significantly more likely than patients receiving usual care to have a 50 % or greater reduction in depressive symptoms (50 % vs. 29.6 %, $p < 0.001$, NNT = 4.9) (Rollman et al. 2009).

It may be possible to apply the limited data on psychotherapy interventions in post-MI patients to postsurgical patients. The ENRICHD trial, a large randomized trial of a cognitive-behavioral psychotherapy intervention in acute post-MI patients with depression, demonstrated that a brief cognitive-behavioral psychotherapy intervention (generally, six to ten psychotherapy sessions over 6 months) was associated with a statistically significant though clinically modest effect on depression symptoms as compared to usual care. The intervention had no effect on the rate of recurrent MI or cardiac death over the mean follow-up period of 3.5 years (Berkman et al. 2003).

In the CREATE trial, a randomized controlled trial, interpersonal psychotherapy was compared to clinical management alone, and citalopram to pill placebo in a 2×2 factorial design in 284 patients with stable CAD and major depression. Interpersonal psychotherapy was not found to be more effective than clinical management visits in reducing depression symptoms, while citalopram was superior to placebo (Lesperance et al. 2007).

Health-Related Quality of Life

Elective CABG is generally associated with significant improvements in health-related quality of life (HRQOL) relative to the preoperative period, except among patients with persistent depression or cognitive deficits (Jokinen et al. 2010; Rothenhausler 2010; Tully et al. 2009; Azzopardi and Lee 2009). The presence of depressive symptoms in both the preoperative and postoperative period is associated with poorer quality of life after cardiac surgery (Goyal et al. 2005). This

association does not provide grounds for causal inferences. Female patients are also more likely to manifest impairments in HRQOL both before and after cardiac surgery than age-matched male counterparts (Martin 2006).

While CABG has been shown to be effective in improving most domains of HRQOL, sexual dysfunction continues to be problematic for many patients post-operatively. Lindau et al. (2012) investigated sexual function in the year following acute myocardial infarction and found that 48 % of men and 59 % of women reported decreased frequency of sexual activity, and 11 % of men and 13 % of women did not return to sexual activity (Lindau et al. 2012). In a study of 100 patients who underwent CABG, only 57 % of patients reported satisfaction with their sexual function prior to surgery and 62 % 8 years after CABG (Lukkarinen and Lukkarinen 2007). There is some evidence to suggest that patients who undergo off-pump procedures are less likely to report sexual dysfunction than patients undergoing traditional CABG (Mohamed et al. 2009).

Anxiety Disorders

Anxiety after cardiac surgery is common, and the differential diagnosis of anxiety symptoms is broad, including primary anxiety disorders, delirium presenting with restlessness or fear, and anxiety secondary to a general medical condition. For the clinician evaluating "anxiety" after cardiac surgery, it is essential to first consider the possibility of delirium or postoperative anxiety as a manifestation of a general medical condition, such as hypoxia, substance withdrawal, infection, or metabolic derangement. Anxiety can also be iatrogenic, i.e., secondary to various medications, particularly steroids or beta-2 agonists, or withdrawal from anesthetics. Withdrawal from sedatives can become a particular problem when trying to wean patients from the ventilator. Sedative tapering and discontinuation can result in either withdrawal symptoms or emergence delirium, either of which can result in difficulty weaning. Withdrawal from alcohol or illicit substances can also present as anxiety and should be considered especially in the setting of hemodynamic instability, tremulousness, or cognitive changes. More broadly, anxiety is a common presentation of postoperative delirium (for review, see Shapiro et al. 2008).

Some studies have actually found improvements in anxiety following cardiac surgery. A 2003 review found that new onset of anxiety symptoms in the setting of planned surgery tended to improve after surgery, but patients with elevated preoperative anxiety levels continued to have elevated rates of anxiety as compared to patients without identified psychopathology prior to surgery (Pignay-Demaria et al. 2003).

Primary Anxiety Disorders

One of the most common anxiety-related diagnoses in cardiac surgery patients is adjustment disorder with anxious mood. Adjustment disorders present with mood and/or anxiety symptoms which are subjectively distressing or interfere with ordinary functioning, occur within 3 months of a precipitating stressor, and last

less than 6 months after resolution of the stressor and its consequences; symptoms do not meet criteria for another disorder. Adjustment disorder with anxiety can have preoperative onset (i.e., the anticipation of surgery may be anxiety provoking) or occur after surgery (i.e., problems during recovery may precipitate anxiety). Manifest postoperative anxiety can also represent an underlying anxiety disorder, most often a pre-existing disorder such as generalized anxiety disorder, panic disorder, or a simple phobia. It is uncommon for these disorders to have first onset in this setting. However, posttraumatic stress disorder does have an increased incidence after cardiac surgery.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a syndrome of abnormal, intrusive reexperiencing, avoidance alterations of mood and cognition and alterations of arousal and reactivity with onset following a traumatic exposure. (DSM5 criteria specify that the exposure is to actual or threatened death, serious injury, or sexual violence, which represents a narrowing of the definition of a traumatic event compared to that found in DSM-IV.) Events in the process of cardiac surgery and intensive care unit hospitalization, such as painful line placements or cardioversion, may be experienced as traumas and precipitate PTSD. PTSD has a prevalence of 15–25 % in postoperative cardiac patients (Schelling et al. 2003; Rothenhausler et al. 2005; Tarsitani et al. 2012). PTSD has negative effects on health-related quality of life (Schelling et al. 2003). In patients with implanted cardioverter defibrillators, a diagnosis of PTSD was independently associated with two- to fourfold increase in mortality (Ladwig et al. 2008). A recent study examined the impact of beta-blockers on the risk for PTSD after cardiac surgery. In this cohort of 121 patients, female patients who were not treated with beta-blockers during the perioperative period were much more likely to experience PTSD symptoms than those patients who had been prescribed beta-blockers (36.2 ± 11.9 % vs. 20.3 ± 7.4 %, $p = 0.001$). However, no correlation between beta-blocker use and PTSD symptoms was found among male study participants (Tarsitani et al. 2012).

Treatment of Anxiety Disorders

The treatment plan for anxiety in the postoperative period depends on accurate diagnosis. Anxiety associated with alcohol or benzodiazepine withdrawal or withdrawal from anesthesia and pain medications generally requires tailored pharmacotherapy. Patients with adjustment disorder with anxiety or generalized anxiety disorder exacerbated by the surgical situation may respond well to psychoeducation, supportive psychotherapy, or benzodiazepines. Benzodiazepines have the advantage of rapid onset of action and relief of symptoms. However, these medications do carry significant risks including neurocognitive impairment (particularly, delirium) and increased risk of falls, which must be carefully weighed against potential benefit in the postoperative period. Generally, if benzodiazepines are used, it is advisable to use agents without active metabolites and with moderate half-lives, such as lorazepam, rather than diazepam (long half-life and active metabolites) or alprazolam (short half-life with potential for rebound anxiety and

active metabolites). In patients with panic disorder, generalized anxiety disorder, or obsessive-compulsive disorder, serotonin reuptake inhibitors are usually the preferred pharmacotherapy, but SSRIs do not have rapid onset of effect and might not sufficient for acute management in the postoperative hospital setting. There is little literature specific to the use of SSRIs for postoperative anxiety. In addition to pharmacological treatment of anxiety, behavioral techniques such as breathing exercises, visual imagery, and mindfulness-based practices can be helpful (for review, see Shapiro et al. 2008).

Delirium

Delirium is an acute medical condition characterized by a decrease in alertness with a waxing and waning level of consciousness, inattentiveness, and impaired cognition, at times including disorientation, hallucinations, and/or delusions. Typically, patients with delirium manifest either hypoactive or agitated behavior. The differential diagnosis of delirium is broad and includes direct effects of an underlying medical problem, intoxication, or withdrawal. Among cardiac surgery patients, the reported incidence of delirium ranges from 10 % to 50 %. Delirium after cardiac surgery confers significant morbidity including an increased risk of self-harm, such as interference with lines, falls, self-extubation, prolonged intensive care unit and overall hospital stays, and mortality (Shapiro et al. 2008).

Predisposing risk factors for delirium after cardiac surgery include older age, depression, history of stroke, cognitive impairment, diabetes mellitus, and atrial fibrillation (Koster et al. 2011; Lin et al. 2012). Other risk factors identified in some recent studies include peripheral vascular disease, low cardiac output, and the use of an intra-aortic balloon pump (IABP) or inotropic medication (Koster et al. 2011). Peri- and postoperative factors that increase delirium risk are extended duration of surgery, prolonged intubation, surgery type (combined valve and CABG and valve surgery alone were associated with higher rates of delirium than CABG alone), red blood cell transfusion, elevation of inflammatory markers and plasma cortisol level, and postoperative complications (Lin et al. 2012). A recent study of delirious patients in the cardiac ICU added that benzodiazepine use at the time of admission was an independent predictor of a threefold increased risk of delirium (odds ratio 3.1 [1, 9.4], $p = 0.04$) during the cardiac surgery ICU stay (McPherson et al. 2013). Off-pump surgery did not reduce the incidence of delirium (Koster et al. 2011).

Management of Delirium

Behavioral Interventions

Ultimately, treatment of delirium requires identification and treatment of the underlying medical condition responsible for the delirious state, for example, correction of hypoxia, resolution of metabolic disturbances, treatment of infection, and pain management. Reduced use of deliriogenic medications, such as opiates, anticholinergic agents, barbiturates, and benzodiazepines (while avoiding induction

of withdrawal), is essential to the resolution of delirium. Non-pharmacologic measures such as frequent verbal reorientation, family or an aide at the bedside, and exposure to light during the day and darkness at night can be helpful. In cases of severe agitation, physical restraints may become necessary, though this is typically reserved as a last resort. Management of the delirious patient may require the off-label use of antipsychotic medication to reduce agitation and treat psychosis. Although clinical trial data is lacking, in clinical practice antipsychotic agents including haloperidol, olanzapine, aripiprazole, and quetiapine are often employed to manage delirium. These medications confer significant metabolic and cardiovascular risks with long-term use, and are associated with increased mortality over follow-up periods of weeks to months, due to cardiac and infectious causes, in frail, "behaviorally disturbed" elderly populations (Wang et al. 2005). Significantly, all antipsychotics have the potential to prolong the QTc interval and thereby to induce torsade de pointes, although this is a relatively rare serious adverse event (Shapiro et al. 2008). Aripiprazole is thought to have a lesser potential for metabolic disturbances and QTc prolongation than other antipsychotic agents, suggesting an advantage for its use in cardiac patients, though no clinical trials of aripiprazole in postoperative cardiac patients exist. In patients being treated with antipsychotics for delirium, blood pressure, heart rate, QTc interval, and electrolytes should be monitored closely. In a randomized trial involving patients undergoing cardiopulmonary bypass, risperidone 1 mg given prophylactically immediately after awakening from surgery resulted in a lower incidence of delirium (risperidone group, 11.1 %; placebo group, 31.7 %; RR, 0.35, 95 % CI, 0.16–0.77, $p = 0.009$) (Prakanrattana and Prapaitrakool 2007).

Postoperative sedation with dexmedetomidine, a selective alpha-2 adrenergic agonist, rather than with benzodiazepines (lorazepam, midazolam), propofol, or narcotics (fentanyl) is associated with a lower incidence of postoperative delirium (Lin et al. 2012). In a randomized controlled trial, the incidence of delirium following valve replacement surgery was 3 % for patients receiving dexmedetomidine, 50 % for those receiving propofol, and 50 % for patients receiving midazolam. Patients who developed postoperative delirium experienced significantly longer intensive care stays and longer total hospitalization (Maldonado et al. 2009). These findings are consonant with those from the MENDS trial, which found a reduction in delirium incidence from over 30 % to about 10 % in critically ill patients treated with dexmedetomidine (Pandharipande et al. 2007). Limitations of dexmedetomidine include the risk of hypotension, necessity for ICU monitoring, and cost.

Neurocognitive Impairment

Coronary artery revascularization procedures have been associated with cognitive decline. In a study of 138 patients who at baseline had relatively low levels of cognitive impairment (2.7 %), 17.4 % had some degree of cognitive dysfunction,

largely mild cognitive impairment, 6 months after surgery. Patients with cognitive impairments also manifested impairments in general health-related quality of life (Rothenhausler 2010; Rothenhausler et al. 2005). In the immediate postoperative period, valve replacement surgery seems associated with a slightly higher risk of postoperative memory impairment and a longer time to neurocognitive recovery than CABG alone (Ebert et al. 2001).

Off-Pump Versus On-Pump

Since the development of off-pump coronary revascularization, many studies have investigated whether off-pump procedures confer improved neurocognitive outcomes compared to traditional on-pump procedures. Although some studies found that cognitive function soon after coronary surgery was superior with off-pump management (Diegeler et al. 2000), sustained beneficial effects were not observed. These studies do not demonstrate a definitive benefit of off-pump procedures with respect to cognitive outcome.

In a recent study of 280 patients randomized to percutaneous coronary intervention or off-pump CABG, follow-up at 7.5 years found neurocognitive outcomes to be similar in the two groups (Sauer et al. 2013). In a meta-analysis from 2008, off-pump surgery was found to reduce the incidence of postoperative atrial fibrillation, but the included studies were not definitive in terms of the effect of off-pump procedures on outcomes such as stroke and cardiac mortality (Møller et al. 2008; van Dijk et al. 2007). In a more recent meta-analysis of 47 randomized controlled trials, including studies between 2008 and 2012, comparing off-pump and on-pump CABG, off-pump CABG reduced postoperative stroke incidence by 20.7 % but did not affect other outcome studies, such as cardiac mortality (Sa et al. 2012).

Outcomes After Heart Transplantation

Psychiatric disorders are common after orthotopic heart transplantation. The most frequent psychiatric disorders after transplantation include major depression, adjustment disorder, and transplantation-related PTSD. Mood and anxiety disorders are most common in the first year after surgery, with declining incidence over the next several years. Notably, the risk of these disorders during the first-year posttransplant is significantly higher than patients' lifetime rates of the disorders before transplant (Dew and DiMartin 2005). Risk factors for the development of a psychiatric disorder after transplant include pre-transplant psychiatric history, lower social supports, younger age, more impaired physical functioning, and longer hospitalization (Dew et al. 2001a Dew and DiMartini 2005; Eshelman et al. 2009). Psychopathology is correlated with worse posttransplant outcomes, including graft rejection, nonadherence, recurrent hospitalization, infection, and death (Shapiro et al. 1995; Eshelman et al. 2009).

Depression

Depression is common after heart transplantation with peak incidence in the first year after surgery (Dew et al. 2001a Dew and DiMartini 2005; Favaro et al. 2011; Sirri et al. 2010). In a review of the literature, Dew et al. reported that up to 63 % of posttransplant patients reported symptoms of depressive illness (primarily MDD and dysthymia) (Dew and DiMartini 2005). Risk factors for depression after heart transplant include female gender, younger age, personal and family history of psychiatric illness, lower socioeconomic status (Dew and DiMartini 2005; Eshelman et al. 2009), worsening of physical illness (Fusar-Poli et al. 2005; Havik et al. 2007), and being unemployed or on disability (Fusar-Poli et al. 2005). Longer hospitalization and a greater number of "false alarm" calls to present for transplantation have also been associated with increased risk for depression (Pudlo et al. 2009). Furthermore, a lack of social supports (Favaro et al. 2011), avoidant coping styles, low perceived control, low levels of optimism, and poor self-esteem are psychological risk factors for posttransplant psychiatric pathology (Dew and DiMartini 2005; Eshelman et al. 2009). Not surprisingly, patients who experience medical complications and sleep disruption posttransplant are more likely to develop psychiatric complications. Notably, transplant patients tend to experience relatively severe episodes of depression, and a minority report receiving treatment (Dew et al. 2001b; Dew and DiMartini 2005). Controlled trials of antidepressants in heart transplant recipients are lacking; case series and case reports describe effective treatment with ECT and with nortriptyline (Fusar-Poli et al. 2005), but in contemporary clinical practice, serotonin reuptake inhibitors are more likely to be utilized as "first-line" therapy (Fusar-Poli et al. 2005). The differential diagnosis of depression in recent transplant patients should include the possibility of opportunistic infections, including cytomegalovirus.

Depression after transplantation has a negative impact on survival (Sirri et al. 2010; Favaro et al. 2011; Havik et al. 2007). In a prospective cross-sectional study of patients who were at a minimum 5 years posttransplant, depression was associated with an almost threefold increase in mortality (Havik et al. 2007). In a longitudinal study conducted over 8 years, Favaro et al. found that MDD was an independent risk factor for posttransplant malignancy (44 % vs. 25 %, $P < 0.05$).

Health-Related Quality of Life

Patients who undergo orthotopic heart transplant have significantly impaired health-related quality of life (HRQOL) compared to the general population, particularly in the areas of health and physical functioning. Sexual dysfunction is common after heart transplant. In a study of 39 patients (33 men and 6 women) who were at least 6 months posttransplant, sexual dysfunction was present in 78 % of men and 50 % of women. Moreover, heart transplant recipients who reported sexual dysfunction also reported significantly worse quality of life on physical health measures, though mental health was not significantly different (Phan

et al. 2010). In a long-term follow-up study of HRQOL 10 years after transplant, patients largely report being satisfied with the emotional and social aspects of their lives and did not report more bodily pain than the general population (Fusar-Poli et al. 2005).

Mania/Psychosis

In the period immediately following transplantation, patients often experience a period of euphoric mood, thought to be related to a combination of biological and psychological factors, including improved perfusion and physical functioning and the feeling of having "a new lease on life" (House and Thompson 1988). A small subset of patients develops mania or psychosis, either due to an underlying primary psychiatric disorder or secondary to steroid treatment. In a study of 49 patients assessed in the first 8 weeks after heart transplant, one developed symptoms of mania, two hypomania, and 12 slightly elevated mood. Symptoms of elevated mood were most common in the first 2 weeks after transplant (Pudlo et al. 2009). Frank psychosis is rare after transplant and has decreased in frequency with the advent of newer antirejection medications and with lower doses of corticosteroids posttransplant. However, "steroid psychosis" does still occur. The term "steroid psychosis" is quite problematic as it has been used as a catchall for the neuropsychiatric effects of corticosteroids, which in fact can include depression, mania, agitation, mood lability, anxiety, insomnia, cognitive deficits, and psychosis. High doses of steroids are more likely to result in mental status effects. The Boston Collaborative Drug Surveillance Program found that in hospitalized patients receiving prednisone (for any medical indication), the incidence of psychiatric symptoms was dose related: 1.3 % in patients taking up to 40 mg/day, 4.6 % at 41–80 mg/day, and 18.4 % at doses above 80 mg/day (Boston Collaborative Drug Surveillance Program 1972). Affective symptoms were most common, with mania or hypomanic states more likely in the short term and depressive symptoms in the long term. Other than steroid dose, there are no clearly identified risk factors as to which patients will develop neuropsychiatric complications of steroids, including a past history of psychiatric illness or a previous episode of steroid-induced psychiatric symptoms (Dubovsky et al. 2012).

Delirium

Delirium after heart transplantation is associated with many of the same predisposing and precipitating factors as that occurring after CABG and valve procedures and may require similar evaluation and management. However, a particular concern in transplant recipients is immunosuppressant toxicity. Cyclosporine and tacrolimus neurotoxicity may result in a variety of symptoms ranging from tremor and headache to encephalopathy, manifesting with cognitive dulling, obtundation, delirium, and/or seizures. Magnetic resonance imaging may

demonstrate posterior reversible leukoencephalopathy. Encephalopathy can occur even at target blood level and may require substitution of another immunosuppressant agent (Anghel et al. 2013; Dzudie et al. 2009).

Anxiety and Posttraumatic Stress

Many patients struggle with anxiety following heart transplant. In a review of the literature, Dew et al. found that up to 26 % of patients experience one or more anxiety disorders (e.g., adjustment disorder with anxiety, generalized anxiety disorder, panic disorder, or posttraumatic stress disorder related to the transplant experience). Anxiety disorders are most common in the first year after transplant (Dew and DiMartini 2005), and in a small cohort study, Pudlo et al. found that in the first 8 weeks after transplant, half of patients studied manifested anxiety symptoms. Older patients were more likely to experience anxiety symptoms; patients with longer hospitalizations or more false alarms were more likely to have severe anxiety (Pudlo et al. 2009).

PTSD

Transplantation-related posttraumatic stress disorder (PTSD-T) is characterized by hypervigilance, avoidance, nightmares, flashbacks, and insomnia and is related to an aspect of the transplant process. Triggers may include learning of the need for transplant, events during the waiting period, the surgery itself, and events during the postoperative recovery period. The reported rates of patients meeting criteria for PTSD-T range from 10 % to 17 % (Favaro et al. 2011; Dew et al. 2001a; Stukas et al. 1999). Similar to other mood and anxiety disorders, PTSD-T most commonly occurs within the first year after transplant (Dew et al. 2001a). Patients with PTSD-T were more likely to be female and to have a prior psychiatric history, lower sense of mastery (Stukas et al. 1999), or lower perceived social support (Favaro et al. 2011; Stukas et al. 1999). Most cases of PTSD-T have a chronic course (>3 months), and patients frequently do not receive treatment for their symptoms (88 %) (Dew et al. 2001a). Transplantation-related PTSD symptoms have been associated with poor adherence (82 % vs. 48 %, $P < 0.04$, OR = 4.9, 95 % CI = 1.0–23.8). Poor adherence was associated with increased mortality (adjusted OR for nonadherence=3.5, 95 % CI 1.2–9.7, $P < 0.02$) (Favaro et al. 2011).

Outcomes After Placement of a Ventricular Assist Device

Ventricular assist devices (VAD) may be implanted in patients with advanced heart failure as a "bridge to recovery," bridge to transplantation, or as destination therapy. The REMATCH trial (Rose et al. 2001) demonstrated a significant survival advantage for LVAD as destination therapy compared to optimized medical management for patients with end-stage heart failure who were not

eligible for heart transplantation. LVAD treatment was also associated with better quality of life. While potentially lifesaving, life with a VAD carries significant medical and psychiatric morbidity. VAD patients are at elevated risk for thromboembolism, infection, bleeding, and cerebrovascular events and often require extended and recurrent hospitalization (Petrucci et al. 1999). VADs demand active device management by patients and/or their caregivers. However, VADs can also significantly improve quality of life in advanced heart failure patients. In a study of patients with VAD as bridge to transplant versus medical management, VAD patients were more likely to report improved physical functioning in the first year after transplant. However, VAD patients had significantly worse cognitive functioning secondary to a higher rate of neurologic events. Social functioning improved in both groups, though VAD patients were less likely to return to work and described more social isolation (Dew et al. 2001b). VAD patients are at risk for psychiatric morbidity, most commonly delirium, anxiety, depression secondary to the medical condition, and adjustment disorder (Shapiro et al. 1996; Baba et al. 2006; Eshelman et al. 2009). Psychiatric morbidity negatively impacts cardiac outcomes and is associated with impaired cardiac rehabilitation (Shapiro et al. 1996), graft rejection, nonadherence, hospitalizations, infection, and death (Eshelman et al. 2009).

An early study found that patients with preoperative cognitive impairment were at risk to experience a postoperative organic mental syndrome following VAD placement (Shapiro et al. 1996). In the REMATCH trial of destination LVAD versus medical management (Lazar et al. 2004), 44 % of patients in the LVAD arm developed a neurological complication (TIA, toxic metabolic, or stroke). Furthermore, patients in the LVAD arm had a stroke rate of 0.19 per year as compared to a rate of 0.052 per year in the medical management arm over the course of the 2-year follow-up. The mean interval between LVAD implantation and stroke was 221.8 days (±70.4 days). A revised survival analysis indicated that LVAD therapy has significant benefit when compared to medical management when assessing combined stroke or death risk (Lazar et al. 2004).

Adjustment disorder has been reported in as many as 50 % of patients receiving VADs (Baba et al. 2006; Eshelman et al. 2009). In terms of adjustment issues, patients frequently worry about their risk of death and exhibit hypervigilance to sensations related to the device (Petrucci et al. 1999). In Petrucci et al.'s study, behavioral techniques including orientation aids, desensitization, relaxation techniques, hypnosis, music and art teleconferencing with families, computer access, and group and community interaction were found to be helpful, though these interventions were not studied in a controlled design.

Depression is also a significant problem among VAD patients. In a sample of 30 consecutive VAD patients, Shapiro and colleagues found that 20 % experienced a major depressive episode, with new onset depression occurring in 16 % (Shapiro et al. 1996). Baba et al. (2006) found depression symptoms in 14 % and major depression in 7 % among their cohort of 14 VAD patients. Depression was treated with intensive observation, supportive psychotherapy, and/or serotonin reuptake inhibitor antidepressants (Shapiro et al. 1996; Baba et al. 2006).

Conclusion

In summary, psychiatric syndromes are common after open-heart surgery, especially depression, anxiety, posttraumatic stress disorder, delirium, and neurocognitive issues. These syndromes require timely assessment and treatment to minimize adverse clinical outcomes such as increased morbidity (e.g., recurrent hospitalizations and impaired quality of life) and mortality. There is a paucity of specific literature on psychopharmacological and psychotherapeutic management after cardiac surgery, so clinical practice is largely guided by evidence from nonsurgical cardiac populations. SSRIs appear safe and effective for treating depression and primary anxiety disorders in this population. Benzodiazepines have some indication as short-term interventions for postsurgical anxiety but must be used with caution so as to not precipitate delirium. Management of delirium is complex and involves a comprehensive medical assessment to determine the etiology of the delirium and a combination of behavioral management techniques and possibly antipsychotics with careful monitoring.

Post-cardiac transplant patients are also at significantly elevated risk for psychiatric disorders. Notably, depression is most common in the first year after transplant and is associated with significant impaired in health- related quality of life. Depression in the posttransplant population is also significantly associated with mortality. Transplant-related PTSD is also most common in the first-year posttransplant and is associated with worse adherence to medical recommendations and significant morbidity. Furthermore, it is important to consider the impact of antirejection medications, particularly corticosteroids, on patients' mental health after transplant as these medications pose significant risks of affective and cognitive disturbance.

References

Anghel, D., Tanasescu, R., Campeanu, A., Lupescu, I., Podda, G., & Bajenaru, O. (2013). Neurotoxicity of immunosuppressive therapies in organ transplantation. *Maedica (Buchar), 8* (2), 170–175.

Azzopardi, S., & Lee, G. (2009). Health-related quality of life 2 years after coronary artery bypass graft surgery. *Journal of Cardiovascular Nursing, 24*(3), 232–240. doi:10.1097/JCN.0b013e31819b2125.

Baba, A., Hirata, G., Yokoyama, F., Kenmoku, K., Tsuchiya, M., Kyo, S., & Toyoshima, R. (2006). Psychiatric problems of heart transplant candidates with left ventricular assist devices. *Journal of Artificial Organs, 9*(4), 203–208. doi:10.1007/s10047-006-0353-0.

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catellier, D., Cowan, M. J., et al. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. *JAMA, 289*(23), 3106–3116. doi:10.1001/jama.289.23.3106.

Blumenthal, J. A., Lett, H. S., Babyak, M. A., White, W., Smith, P. K., Mark, D. B., et al. (2003). Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet, 362* (9384), 604–609. doi:10.1016/S0140-6736(03)14190-6.

Boston Collaborative Drug Surveillance Program. (1972). Acute adverse reactions to prednisone in relation to dosage. *Clinical Pharmacology and Therapeutics, 13*(5), 694–698.

Burg, M. M., Benedetto, M. C., Rosenberg, R., & Soufer, R. (2003). Presurgical depression predicts medical morbidity 6 months after coronary artery bypass graft surgery. *Psychosomatic Medicine, 65*(1), 111–118.

Castro, V. M., Clements, C. C., Murphy, S. N., Gainer, V. S., Fava, M., Weilburg, J. B., et al. (2013). QT interval and antidepressant use: A cross sectional study of electronic health records. *BMJ, 346*, f288. doi:10.1136/bmj.f288.

Chocran, S., Vandel, P., Durst, C., Laluc, F., Kaili, D., Chocron, M., & Etievent, J. P. (2013). Antidepressant therapy in patients undergoing coronary artery bypass grafting: The MOTIV-CABG trial. *Annals of Thoracic Surgery, 95*(5), 1609–1618. doi:0.1016/j.athoracsur.2013.02.035.

Connerney, I., Sloan, R. P., Shapiro, P. A., Bagiella, E., & Seckman, C. (2010). Depression is associated with increased mortality 10 years after coronary artery bypass surgery. *Psychosomatic Medicine, 72*(9), 874–881. doi:10.1097/PSY.0b013e3181f65fc1.

Dew, M. A., & DiMartini, A. F. (2005). Psychological disorders and distress after adult cardiothoracic transplantation. *Journal of Cardiovascular Nursing, 20*(5 Suppl), S51–S66.

Dew, M. A., Kormos, R. L., DiMartini, A. F., Switzer, G. E., Schulberg, H. C., Roth, L. H., & Griffith, B. P. (2001a). Prevalence and risk of depression and anxiety-related disorders during the first three years after heart transplantation. *Psychosomatics, 42*(4), 300–313.

Dew, M. A., Kormos, R. L., Winowich, S., Harris, R. C., Stanford, E. A., Carozza, L., & Griffith, B. P. (2001b). Quality of life outcomes after heart transplantation in individuals bridged to transplant with ventricular assist devices. *Journal of Heart and Lung Transplantation, 20*(11), 1199–1212.

Diegeler, A., Hirsch, R., Schneider, F., Schilling, L. O., Falk, V., Rauch, T., & Mohr, F. W. (2000). Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. *Annals of Thoracic Surgery, 69*(4), 1162–1166.

Dubovsky, A. N., Arvikar, S., Stern, T. A., & Axelrod, L. (2012). The neuropsychiatric complications of glucocorticoid use: Steroid psychosis revisited. *Psychosomatics, 53*(2), 103–115. doi:10.1016/j.psym.2011.12.007.

Dzudie, A., Boissonnat, P., Roussoulieres, A., Cakmak, Mosbah, K., & Bejui, F. T. (2009). Cyclosporine-related posterior reversible encephalopathy syndrome after heart transplantation: Should we withdraw or reduce cyclosporine?: Case reports. *Transplantation Proceedings, 41*(2), 716–720. doi:10.1016/j.transproceed.2009.01.041.

Ebert, A. D., Walzer, T. A., Huth, C., & Herrmann, M. (2001). Early neurobehavioral disorders after cardiac surgery: A comparative analysis of coronary artery bypass graft surgery and valve replacement. *Journal of Cardiothoracic & Vascular Anesthesia, 15*(1), 15–19. doi:10.1053/jcan.2001.20211.

Eshelman, A. K., Mason, S., Nemeh, H., & Williams, C. (2009). LVAD destination therapy: Applying what we know about psychiatric evaluation and management from cardiac failure and transplant. *Heart Failure Reviews, 14*(1), 21–28. doi:10.1007/s10741-007-9075-5.

Favaro, A., Gerosa, G., Caforio, A. L., Volpe, B., Rupolo, G., Zarneri, D., et al. (2011). Posttraumatic stress disorder and depression in heart transplantation recipients: The relationship with outcome and adherence to medical treatment. *General Hospital Psychiatry, 33*(1), 1–7. doi:10.1016/j.genhosppsych.2010.10.001.

Fusar-Poli, P., Martinelli, V., Klersy, C., Campana, C., Callegari, A., Barale, F., Politi, P., et al. (2005). Depression and quality of life in patients living 10 to 18 years beyond heart transplantation. *Journal of Heart and Lung Transplantation, 24*(12), 2269–2278. doi:10.1016/j.healun.2005.06.022.

Glassman, A. H., O'Connor, C. M., Califf, R. M., Swedberg, K., Schwartz, P., Bigger, J. T., Jr., et al. (2002). Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA, 288*(6), 701–709.

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Blaha, M. J., et al. (2014). Heart disease and stroke statistics – 2014 update: A report from the American Heart Association. *Circulation, 129*, e28–e292.

Goyal, T. M., Idler, E. L., Krause, T. J., & Contrada, R. J. (2005). Quality of life following cardiac surgery: Impact of the severity and course of depressive symptoms. *Psychosomatic Medicine, 67*(5), 759–765. doi:10.1097/01.psy.0000174046.40566.80.

Havik, O. E., Sivertsen, B., Relbo, A., Hellesvik, M., Grov, I., Geiran, O., et al. (2007). Depressive symptoms and all-cause mortality after heart transplantation. *Transplantation, 84*(1), 97–103. doi:10.1097/01.tp.0000268816.90672.a0.

Horne, D., Kehler, S., Kaoukis, G., Hiebert, B., Garcia, E., Duhamel, T. A., & Arora, R. C. (2013). Depression before and after cardiac surgery: Do all patients respond the same? *Journal of Thoracic & Cardiovascular Surgery, 145*(5), 1400–1406.

House, R. M., & Thompson, T. L., 2nd. (1988). Psychiatric aspects of organ transplantation. *JAMA, 260*(4), 535–539.

Jokinen, J. J., Hippelainen, M. J., Turpeinen, A. K., Pitkanen, O., & Hartikainen, J. E. (2010). Health-related quality of life after coronary artery bypass grafting: A review of randomized controlled trials. *Journal of Cardiac Surgery, 25*(3), 309–317. doi:10.1111/j.1540-8191.2010.01017.x.

Koster, S., Hensens, A. G., Schuurmans, M. J., & van der Palen, J. (2011). Risk factors of delirium after cardiac surgery: A systematic review. *European Journal of Cardiovascular Nursing, 10*(4), 197–204.

Ladwig, K. H., Baumert, J., Marten-Mittag, B., Kolb, C., Zrenner, B., & Schmitt, C. (2008). Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. *Archives of General Psychiatry, 65*(11), 1324–1330. doi:10.1001/archpsyc.65.11.1324.

Lazar, R. M., Shapiro, P. A., Jaski, B. E., Parides, M. K., Bourge, R. C., Watson, J. T., Naka, Y., et al. (2004). Neurological events during long-term mechanical circulatory support for heart failure: The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) experience. *Circulation, 109*(20), 2423–2427. doi:10.1161/01.cir.0000129414.95137.cd.

Lesperance, F., Frasure-Smith, N., Koszycki, D., Laliberte, M. A., van Zyl, L. T., Baker, B., et al. (2007). Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA, 297*(4), 367–379. doi:10.1001/jama.297.4.367.

Lin, Y., Chen, J., & Wang, Z. (2012). Meta-analysis of factors which influence delirium following cardiac surgery. *Journal of Cardiac Surgery, 27*(4), 481–492.

Lindau, S. T., Abramsohn, E., Gosch, K., Wroblewski, K., Spatz, E. S., Chan, P. S., Krumholz, H. M., et al. (2012). Patterns and loss of sexual activity in the year following hospitalization for acute myocardial infarction (a United States National Multisite Observational Study). *American Journal of Cardiology, 109*(10), 1439–1444. doi:10.1016/j.amjcard.2012.01.355.

Lukkarinen, H., & Lukkarinen, O. (2007). Sexual satisfaction among patients after coronary bypass surgery or percutaneous transluminal angioplasty: Eight-year follow-up. *Heart & Lung, 36*(4), 262–269. doi:10.1016/j.hrtlng.2006.12.001.

Maldonado, J. R., Wysong, A., van der Starre, P. J., Block, T., Miller, C., & Reitz, B. A. (2009). Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics, 50*(3), 206–217. doi:10.1176/appi.psy.50.3.206.

Martin, F. (2006). Recognizing depression after a coronary artery bypass graft. *British Journal of Nursing, 15*(13), 703–706.

McPherson, J. A., Wagner, C. E., Boehm, L. M., Hall, J. D., Johnson, D. C., Miller, L. R., et al. (2013). Delirium in the cardiovascular ICU: Exploring modifiable risk factors. *Critical Care Medicine, 41*(2), 405–413. doi:10.1097/CCM.0b013e31826ab49b.

Mohamed, O. A., Bennett, C. J., Roaiah, M. F., Helmy, T., Mahran, A., & Hamed, H. A. (2009). The impact of on-pump coronary artery bypass surgery vs. off-pump coronary artery bypass

surgery on sexual function. *The Journal of Sexual Medicine, 6*(4), 1081–1089. doi:10.1111/j.1743-6109.2008.01165.x.

Møller, C. H., Penninga, L., Wetterslev, J., Steinbrüchel, D. A., & Gluud, C. (2008). Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: Systematic review with meta-analyses and trial sequential analyses. *European Heart Journal, 29*(21), 2601–2616. doi:10.1093/eurheartj/ehn335.

Murray, C. J., & Lopez, A. D. (1997). Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet, 349*, 1436–1442.

Nemati, M. H., & Astaneh, B. (2011). The impact of coronary artery bypass graft surgery on depression and anxiety. *Journal of Cardiovascular Medicine (Hagerstown, Md.), 12*(6), 401–404. doi:10.2459/JCM.0b013e32834358e9.

Pae, C. U., Wang, S. M., Lee, S. J., Han, C., Patkar, A. A., & Masand, P. S. (2014). Antidepressant and QT interval prolongation, how should we look at this issue? Focus on citalopram. *Expert Opinion on Drug Safety, 13*(2), 197–205. doi:10.1517/14740338.2013.840583.

Pandharipande, P. P., Pun, B. T., Herr, D. L., Maze, M., Girard, T. D., Miller, R. R., Ely, E. W., et al. (2007). Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. *JAMA, 298*(22), 2644–2653. doi:10.1001/jama.298.22.2644.

Peterson, J. C., Charlson, M. E., Williams-Russo, P., Krieger, K. H., Pirraglia, P. A., Meyers, B. S., & Alexopoulos, G. S. (2002). New postoperative depressive symptoms and long-term cardiac outcomes after coronary artery bypass surgery. *The American Journal of Geriatric Psychiatry, 10*(2), 192–198.

Petrucci, R., Kushon, D., Inkles, R., Fitzpatrick, J., Twomey, C., & Samuels, L. (1999). Cardiac ventricular support. Considerations for psychiatry. *Psychosomatics, 40*(4), 298–303. doi:10.1016/S0033-3182(99)71222-3.

Phan, A., Ishak, W. W., Shen, B. J., Fuess, J., Philip, K., Bresee, C., et al. (2010). Persistent sexual dysfunction impairs quality of life after cardiac transplantation. *The Journal of Sexual Medicine, 7*(8), 2765–2773. doi:10.1111/j.1743-6109.2010.01854.x.

Pignay-Demaria, V., Lesperance, F., Demaria, R. G., Frasure-Smith, N., & Perrault, L. P. (2003). Depression and anxiety and outcomes of coronary artery bypass surgery. *Annals of Thoracic Surgery, 75*(1), 314–321.

Poole, L., Leigh, E., Kidd, T., Ronaldson, A., Jahangiri, M., & Steptoe, A. (2014). The combined association of depression and socioeconomic status with length of post-operative hospital stay following coronary artery bypass graft surgery: Data from a prospective cohort study. *Journal of Psychosomatic Research, 76*(1), 34–40. doi:10.1016/j.jpsychores.2013.10.019.

Prakanrattana, U., & Prapaitrakool, S. (2007). Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesthesia and Intensive Care, 35*(5), 714–719.

Pudlo, R., Piegza, M., Zakliczynski, M., & Zembala, M. (2009). The occurrence of mood and anxiety disorders in heart transplant recipients. *Transplantation Proceedings, 41*(8), 3214–3218. doi:10.1016/j.transproceed.2009.09.031.

Rollman, B. L., Belnap, B. H., LeMenager, M. S., Mazumdar, S., Houck, P. R., Counihan, P. J., et al. (2009). Telephone-delivered collaborative care for treating post-CABG depression: A randomized controlled trial. *JAMA, 302*(19), 2095–2103. doi:10.1001/jama.2009.1670.

Rose, E. A., Gelijns, A. C., Moskowitz, A. J., Heitjan, D. F., Stevenson, L. W., Dembitsky, W., et al. (2001). Long-term use of a left ventricular assist device for end-stage heart failure. *New England Journal of Medicine, 345*(20), 1435–1443. doi:10.1056/NEJMoa012175.

Rothenhausler, H. B. (2010). The effects of cardiac surgical procedures on health – Related quality of life, cognitive performance, and emotional status outcomes: A prospective 6 – Month follow – Up study. *Psychiatria Danubina, 22*(1), 135–136.

Rothenhausler, H. B., Grieser, B., Nollert, G., Reichart, B., Schelling, G., & Kapfhammer, H. P. (2005). Psychiatric and psychosocial outcome of cardiac surgery with cardiopulmonary bypass: A prospective 12-month follow-up study. *General Hospital Psychiatry, 27*(1), 18–28. doi:10.1016/j.genhosppsych.2004.09.001.

Sa, M. P., Ferraz, P. E., Escobar, R. R., Martins, W. N., Lustosa, P. C., Nunes Ede, O., et al. (2012). Off-pump versus on-pump coronary artery bypass surgery: Meta-analysis and meta-regression of 13,524 patients from randomized trials. *Revista Brasileira de Cirurgia Cardiovascular, 27* (4), 631–641.

Sauer, A. M., Nathoe, H. M., Hendrikse, J., Peelen, L. M., Regieli, J., Veldhuijzen, D. S., et al. (2013). Cognitive outcomes 7.5 years after angioplasty compared with off-pump coronary bypass surgery. *Annals of Thoracic Surgery, 96*(4), 1294–1300. doi:10.1016/j.athoracsur.2013.05.001.

Schelling, G., Richter, M., Roozendaal, B., Rothenhausler, H. B., Krauseneck, T., Stoll, C., et al. (2003). Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. *Critical Care Medicine, 31*(7), 1971–1980. doi:10.1097/01.ccm.0000069512.10544.40.

Shapiro, P. A. (2008). Depression in coronary artery disease: Does treatment help? *Cleveland Clinic Journal of Medicine, 75*(Suppl 2), S5–S9.

Shapiro, P. A. (2009). Treatment of depression in patients with congestive heart failure. *Heart Failure Reviews, 14*(1), 7–12. doi:10.1007/s10741-007-9058-6.

Shapiro, P. A., Williams, D. L., Foray, A. T., Gelman, I. S., Wukich, N., & Sciacca, R. (1995). Psychosocial evaluation and prediction of compliance problems and morbidity after heart transplantation. *Transplantation, 60*(12), 1462–1466.

Shapiro, P. A., Levin, H. R., & Oz, M. C. (1996). Left ventricular assist devices. Psychosocial burden and implications for heart transplant programs. *General Hospital Psychiatry, 18* (6 Suppl), 30S–35S.

Shapiro, P. A., Fedoronko, D. A., Epstein, L. A., Mirasol, E. G., & Desai, C. V. (2008). Psychiatric aspects of heart and lung disease in critical care. *Critical Care Clinics, 24*(4), 921–947. doi:10.1016/j.ccc.2008.05.003. x.

Sirri, L., Potena, L., Masetti, M., Tossani, E., Magelli, C., & Grandi, S. (2010). Psychological predictors of mortality in heart transplanted patients: A prospective, 6-year follow-up study. *Transplantation, 89*(7), 879–886. doi:10.1097/TP.0b013e3181ca9078.

Stukas, A. A., Jr., Dew, M. A., Switzer, G. E., DiMartini, A., Kormos, R. L., & Griffith, B. P. (1999). PTSD in heart transplant recipients and their primary family caregivers. *Psychosomatics, 40*(3), 212–221.

Tarsitani, L., De Santis, V., Mistretta, M., Parmigiani, G., Zampetti, G., Roselli, V., Picardi, A., et al. (2012). Treatment with beta-blockers and incidence of post-traumatic stress disorder after cardiac surgery: A prospective observational study. *Journal of Cardiothoracic & Vascular Anesthesia, 26*(2), 265–269. doi:10.1053/j.jvca.2011.09.011.

Tully, P. J., Baker, R. A., Turnbull, D. A., Winefield, H. R., & Knight, J. L. (2009). Negative emotions and quality of life six months after cardiac surgery: The dominant role of depression not anxiety symptoms. *Journal of Behavioral Medicine, 32*(6), 510–522. doi:10.1007/s10865-009-9225-4.

van Dijk, D., Spoor, M., Hijman, R., Nathoe, H. M., Borst, C., Jansen, E. W., et al. (2007). Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA, 297*(7), 701–708. doi:10.1001/jama.297.7.701.

Wang, P. S., Schneeweiss, S., Avorn, J., Fischer, M. A., Mogun, H., Solomon, D. H., & Brookhart, M. A. (2005). Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *New England Journal of Medicine, 353*(22), 2335–2341. doi:10.1056/NEJMoa052827.

Xiong, G. L., Jiang, W., Clare, R. M., Shaw, L. K., Smith, P. K., O'Connor, C. M., et al. (2010). Safety of selective serotonin reuptake inhibitor use prior to coronary artery bypass grafting. *Clinical Cardiology, 33*(6), E94–E98. doi:10.1002/clc.20621.

Zivin, K., Pfeiffer, P. N., Bohnert, A. S., Ganoczy, D., Blow, F. C., Nallamothu, B. K., & Kales, H. C. (2013). Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. *The American Journal of Psychiatry, 170*(6), 642–650. doi:10.1176/appi.ajp.2013.12030408

Cognitive Impairment After Cardiac Surgery: Confounding Factors and Recommendations for Improved Practice

Kathryn M. Bruce, Gregory W. Yelland, Julian A. Smith, and Stephen R. Robinson

Contents

Abstract

Impaired cognition following cardiac surgery is a common complication. Estimates of the incidence of postoperative cognitive decline/dysfunction (POCD) vary from 20 % to 70 % of patients in the week after cardiac surgery to 10–40 %

K.M. Bruce • J.A. Smith (✉)
Department of Surgery, Monash University, Monash Medical Centre, Clayton, VIC, Australia
e-mail: julian.smith@monash.edu

G.W. Yelland • S.R. Robinson
School of Health Sciences, RMIT University, Bundoora, VIC, Australia

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_4

by 6 weeks. It has become evident that differences in research design have contributed significantly to these differing estimates of POCD and that greater consistency will be achieved if future studies utilize appropriate control groups. Recent studies have shown that many patients have cognitive impairment prior to undergoing cardiac surgery and furthermore that some of the POCD is associated with surgical procedures in general, rather than with cardiac surgery in particular. The domains of language, concentration, and motor control are commonly affected during the first week after cardiac surgery, and memory and executive function can also be affected. Some individuals are more vulnerable than others. In the future it might be possible to identify these individuals prior to surgery with computer-based cognitive tests and measures of emotional state, so that the factors involved can be managed and the risk of POCD can be reduced.

Keywords

Cardiopulmonary bypass (CPB) machine • Cognitive impairment • Post-cardiac surgery (*see* postoperative cognitive decline/dysfunction (POCD)) • Median sternotomy • Neuropsychological testing • POCD • Postoperative cognitive decline/dysfunction (POCD) • Anesthesia • CABG vs. valve surgery • Cardiac surgical factors • Cardiopulmonary bypass machine • Clinical implications • Emotional state effects • On cognitive performance • Median sternotomy • Neuropsychological testing • Preoperative cognitive performance • Statistical approaches for

Introduction

Advances in surgical technique, anesthetic management, and postoperative care of patients undergoing cardiac surgery have reduced the rates of morbidity and mortality, despite an increase in the risk profiles of patients now undergoing surgery (Likosky et al. 2005). A complication frequently associated with cardiac surgery is impaired cognitive function that manifests immediately after surgery and can persist indefinitely (Rudolph et al. 2010). Estimates of the incidence of postoperative cognitive decline/dysfunction (POCD) vary from 20 % to 70 % of patients in the week after cardiac surgery to 10–40 % by 6 weeks (Bruce et al. 2008). This incidence is considerably higher than that reported for other postsurgical neurological events such as stroke (1–5.2 %) and encephalopathy (~10 %) (Lombard and Mathew 2010). POCD can involve impairments in intellectual function, attention, concentration, fine motor skills, memory, and increased levels of confusion, agitation, and disorientation (Roach et al. 1996; Zamvar et al. 2002).

The presence of POCD can be detected by comparing a patient's performance on a battery of neuropsychological tests that are administered before and after surgery (Silbert et al. 2011). Since it is difficult to quantify the impact of cognitive impairment on the health-care system, reliable figures regarding the extent of this cost are not yet available. Nonetheless, it is evident that POCD imposes a burden on the economy because it slows recovery from surgery, increases length of stay in

intensive care units, delays discharge from hospital, and reduces compliance with postoperative cardiac rehabilitation programs, with some patients requiring readmission (Lewis et al. 2004). As POCD is also associated with a decreased quality of life and early withdrawal from the workforce, it represents a considerable burden to society (Van Harten et al. 2012).

The intention of this chapter is to provide an overview of the substantial obstacles surrounding the determination of cognitive change following cardiac surgery and to discuss risk factors associated with cognitive change during cardiac surgery. Subsequently, the assessment of cognitive change and the methods used to define this change will be discussed. The chapter will conclude with an overview of the current estimates of cognitive impairment following coronary artery bypass graft (CABG) surgery, conventional valve surgery, and robotically assisted valve surgery.

Cognitive Impairment Following Cardiac Surgery

Surgical Factors Implicated in POCD

Much of the literature dealing with POCD has been concerned with the extent to which surgical factors influence cognitive outcome. The surgical factors implicated in POCD following CABG and valve surgery include the use of the cardiopulmonary bypass (CPB) machine, the role of anesthesia, and the use of a median sternotomy to access the surgical field.

Cardiopulmonary Bypass Machine

The CPB machine has enabled the development of all types of heart surgery and has made CABG and valve surgery common practices throughout the world. Despite the unquestionable value of the CPB machine, it has been regarded as a major contributor to POCD (Anastasiadis et al. 2011). The CPB machine introduces particles (e.g., damaged platelets) and gaseous microemboli into the bloodstream. In addition, after restoration of the normal blood supply following CPB, clots formed during cannulation and by clamping of the aorta may be freed into the bloodstream. These thrombi and emboli can lodge in the small arteries of the brain and cause transient ischemic attacks or "micro-strokes" that can temporarily or permanently impair function in the region of the brain supplied by that vessel. The CPB machine can also cause fluctuations in blood pressure, blood pH, and body temperature and can induce a systemic inflammatory response (Arrowsmith et al. 2000; Ho et al. 2004; Kapetanakis et al. 2004). All of these effects have the potential to impair brain function. Identification of these possible areas of concern has led to advances in the surgical equipment and procedures used for CPB. For example, studies with alternate oxygenators and use of arterial filters have shown that the number of microemboli released during CPB can be reduced (Blauth et al. 1990).

A breakthrough advance in CABG surgery came with the introduction of an off-pump technique. This innovation permitted a more thorough investigation of the effect of the CPB machine on cognition, because the same surgical procedure could

be performed with or without the CPB. In off-pump CABG surgery, the heart is chemically slowed to 40 beats per minute and is mechanically stabilized, so that the operation can be performed on the beating heart without the need for a CPB machine (Rankin et al. 2003). However, despite the strong a priori reasons for expecting CPB machines to contribute to postoperative cognitive impairment, the data from comparative studies of CABG with or without CPB are equivocal. While some studies found that off-pump CABG produced better cognitive outcomes immediately following surgery and just prior to discharge (Motallebzadeh et al. 2007; Ngaage 2003; Zamvar et al. 2002), these results were not supported by other studies that found no difference in cognitive performance between groups immediately after surgery or up to 6 months following surgery (Ernest et al. 2006; Farhoudi et al. 2010; Jensen et al. 2006; Lund et al. 2005). Conversely, another study reported no change immediately following surgery but reported better function at 6 months in the off-pump CABG surgery group (Stroobant et al. 2002). Further to this, other studies that assessed cognitive function 12 months following surgery reported no significant differences between patients who underwent CABG with or without CPB (Rankin et al. 2003; Van Dijk et al. 2002). This variation in outcomes is likely to be due to methodological differences in study design, such as a lack of consistency between studies in (i) the cognitive tests used, (ii) the time points used for reassessments, (iii) the criteria used to define POCD, and (iv) the statistical methods used to correct for bias in the data (Farhoudi et al. 2010). There is a lack of consensus regarding which tests to include, which cognitive domains to examine, what postoperative intervals to use when testing patients, and even what constitutes a significant degree of cognitive impairment (Arrowsmith et al. 2000; Lewis et al. 2004).

While it is possible that CPB machines do contribute to cognitive impairment, on-pump CABG is associated with a similar incidence of POCD to that found after other forms of major surgery which do not use a CPB machine (Moller et al. 1998). The conflicting results from the comparison between off-pump and on-pump CABG, and the results showing that similar rates of POCD occur from noncardiac surgery, raise the possibility that factors other than CPB, such as general anesthesia, may be responsible for the POCD seen following on-pump CABG surgery (Browne et al. 2003).

Anesthesia

Anesthetic agents allow surgery to occur by immobilizing the body, inducing amnesia, and providing an absence of awareness. While the exact mechanisms by which this occurs are unknown, it is evident that anesthetic agents act on the central nervous system and influence mental functioning on recovery from anesthesia (Bruce and Bach 1976; Istaphanous et al. 2010). Evidence suggests that anesthetic agents affect the blood-brain barrier, which exists to provide physical and metabolic protection from neurotoxic substances circulating in the blood (Correale and Villa 2009). There is also evidence that neuroinflammation occurs in response to circulating cytokines that are released in response to the surgical trauma (Minagar et al. 2002; Wilson et al. 2002). Neuroinflammation can cause cognitive impairment, and when coupled with the disruption of the blood-brain barrier caused by anesthetic

agents, the combined effects may promote POCD (Ben-Nathan et al. 2000; Wu et al. 2012).

Research into the impact of anesthesia on cognitive function began with cardiac surgery about 25 years ago and now includes other major forms of surgery, especially orthopedic and abdominal surgery (Silbert et al. 2011). While recovery from anesthesia does affect cognition postoperatively (Farag et al. 2006; Steinmetz et al. 2010), the duration of this effect has been difficult to assess due to variable outcomes (Sutton 2007). Estimates of the duration of POCD resulting from anesthesia range between 1 h and 1 week after surgery (Papaioannou et al. 2005; Rasmussen et al. 2003).

Median Sternotomy

A median sternotomy provides excellent exposure of the surgical field, yet it can cause significant pain and distress to the patient in the weeks after surgery (Stahle et al. 1997). There is clear evidence that pain can disrupt attention and memory and reduce mental flexibility (Dick and Rashiq 2007; Karp et al. 2006). Further, since performance on most neuropsychological tests is suboptimal if the subject is distracted or is lacking in motivation (e.g., due to pain and discomfort), there is a high probability that some of the "cognitive impairment" reported after cardiac surgery is due to an inability to fully concentrate on the cognitive tests. Furthermore, a number of cognitive tests (e.g., Rey Osterrieth Complex Figure Test, Grooved Pegboard) involve drawing or fine movement control, which may be impaired if the patient is in physical discomfort. Thus, if performance on these tests is worse than it was prior to surgery, it may be due to physical restriction rather than to cognitive impairment.

It is possible that pain and physical restriction following cardiac surgery has contributed to overestimates of the extent of cognitive impairment that exists immediately after surgery. In addition, the majority of patients receive analgesics postoperatively (generally opiates), which may also have adverse effects on cognitive performance (Wang et al. 2007). It is possible, therefore, that much of the "recovery" in cognitive performance seen in the weeks and months after surgery is due to a reduction in pain and physical restriction and to the withdrawal of analgesics.

Differences Between CABG and Valve Surgery

Comparing of the POCD outcomes of CABG and valve procedures is challenging, due to the abundance of research assessing POCD following CABG surgery compared to the scarcity of studies that have assessed POCD following conventional valve repair and replacement surgery. In a sample of 79 research articles that had assessed POCD following cardiac surgery (Appendix A), 41 studies consisted of on-pump CABG patients only, 19 studies had on-pump CABG and off-pump CABG groups, 13 studies had a combination of both CABG and conventional valve surgery patients, and only six studies consisted of a conventional valve surgery group only (see Appendix A for more details). Only three research papers compared the incidence of POCD by in CABG and conventional valve patients.

The obvious difference between these two forms of surgery include the more invasive nature of valve surgery, requiring incision of the chambers inside the heart, rather than having vessels bypassed on the surface of the heart, as occurs in CABG surgery. Studies that have assessed POCD following valve surgery have concluded that valve patients exhibit higher levels of POCD than CABG patients, which is thought to be due to the introduction of air and tissue debris into the heart during the open-chamber procedure (Braekken et al. 1998; Ebert et al. 2001; Hong et al. 2008; Nussmeier 1996).

Summary of Cardiac Surgical Factors Associated with POCD

There are several surgical factors common to both CABG and conventional valve surgery that may contribute to POCD. Both procedures involve the trauma of a median sternotomy. The physical trauma of having the chest wall incised and opened is severe, and compounding this is the invasiveness of the actual cardiac procedure and the acute postoperative pain. The development of robotically assisted valve repair surgery eliminates the need for a median sternotomy, and studies have found it to improve the rate of physical recovery following surgery. To date, only a study by the present authors has assessed POCD following this type of surgery (Bruce et al. 2014), and the results are discussed later in the chapter.

In summary, the main cardiac surgical factors that have been implicated in POCD are the CPB machine, accessing the surgical field via median sternotomy, the use of general anesthesia, and whether the surgery is intracardiac or extracardiac. Due to the numerous surgical factors that can influence cognitive function after surgery, it is essential that studies which aim to ascertain the unique contribution of cardiac surgery use a comparator group that have undergone another form of major surgery. While the need for a surgical control group might seem to be self-evident, the vast majority of studies of POCD following cardiac surgery have not included such a group (Bruce et al. 2008; Selnes et al. 2006; Silbert et al. 2011). Thus, it is unclear what proportion of the POCD reported by these studies was due to factors associated with surgical procedures in general, rather than to cardiac surgery in particular (Bruce et al. 2008, 2013a, b; Selnes 2013).

Nonsurgical Factors Implicated in POCD

Nonsurgical factors that have been implicated in POCD include age (Bishop et al. 2010; Cargin et al. 2006; Li et al. 2001; McDaniel and Einstein 2011; Resnick et al. 2003) and education level (e.g., dos Santos et al. 2011; Meng and D'Arcy 2012; Sachdev and Valenzuela 2009; Satz et al. 2011). These two factors have been extensively reviewed elsewhere and will not be discussed here. Other factors include the pre- and postsurgical emotional state of patients and their pre-existing disease state.

Effect of Emotional State on Cognitive Performance

The requirement to undergo cardiac surgery is a major life-altering event for most patients, and understandably it affects their emotional state. While much of the research into emotional disturbances has focused on depression, a number of studies have found increased levels of anxiety before and after CABG surgery. Depression and anxiety are associated with deficits in working memory, processing speed, verbal and visual memory, and various aspects of executive function (Andersson et al. 2010). Both appear to be associated with a significant risk of readmission following CABG, and preoperative levels of depression and anxiety are associated with an increased incidence of cardiac morbidity following CABG surgery (Bankier et al. 2004; McKenzie et al. 2010; Pignay-Demaria et al. 2003; Tully et al. 2008). Given that both depression and anxiety affect cognitive function, their impact on cognitive performance before and after cardiac surgery needs to be considered when investigating POCD (Tsushima et al. 2005). Andrew and colleagues (2001) found that preoperative depression, anxiety, and stress were not related to preoperative neuropsychological performance, but they additionally found that high levels of preoperative depression and anxiety predicted deficits on attention and verbal memory tasks following CABG. Stroobant and Vingerhoets (2008) also showed that while preoperative depression was not associated with preoperative neuropsychological performance, it was associated with postoperative impairments in visuomotor tasks. Conversely, in 2009, Tully and colleagues found that levels of postoperative depression and anxiety had minimal effects on cognitive function after CABG. Freiheit and colleagues (2012) found that preoperatively, the average cognitive domain scores in attention/executive function, learning/memory, verbal fluency, and global cognition were lower in patients with depressive symptoms, and this difference persisted for up to 30 months postoperatively.

Most studies that have assessed emotional state following cardiac surgery have only included measures of depression and anxiety; they have not investigated the impact of pre- or postoperative levels of stress. As a major traumatic event, cardiac surgery will induce significant amounts of stress. Stress increases cortisol levels, which can impair cognitive performance (Peavy et al. 2009; Sandi and Pinelo-Nava 2007). Initial research (Andrew et al. 2001) found that while preoperative mood state is a critical predictor of postoperative mood state, stress was not associated with a reduction in cognitive performance in these patients. However, more recent studies have shown that CABG patients are significantly more stressed, anxious, and depressed than valve and nonsurgical control groups prior to surgery, and this stress influences the degree of cognitive impairment that is present after surgery (Bruce et al. 2013a, b, 2014).

Many CABG patients are required to wait for surgery for months, with some patients even being prepared and placed on the gurney waiting for surgery, only to be informed that the surgical procedure has been canceled due to the need to operate on another patient with a condition requiring more urgent attention. For example, the OECD reported that in 2010, 25 % of patients in Canada, 22 % in Sweden, 21 % in Norway and the United Kingdom, 18 % in Australia, and 7 % in France,

Switzerland, and the USA waited for 4 or more months before their surgery (Siciliani 2013). The uncertainty and false starts associated with the elective surgery process are likely to contribute to the heightened levels of stress, anxiety, and depression detected in CABG patients prior to surgery. The possibilities of permanent deterioration and myocardial infarction are another source of psychological distress for CABG patients (Koivula et al. 2002; Lamarche et al. 1998). While waiting for surgery, CABG patients suffer from impaired functional status, chest pain, shortness of breath, and fear of death. The situation also has a negative impact on the patient's family and their social interactions (Koivula et al. 2002). Most cardiac patients who reported elevated levels of depression, anxiety, or stress postoperatively also had these symptoms preoperatively, and these states were associated with slower physical recovery, more persistent symptoms, and longer time before resuming former activities (Gallo et al. 2005).

The preceding findings indicate that many cardiac surgery patients experience depression, anxiety, and stress prior to and after surgery and that these emotional states do affect cognitive performance. In view of this, we suggest that an emotional state measure ought to be routinely included in every preoperative and postoperative neuropsychological assessment.

Preoperative Cognitive Performance

The estimated levels of POCD may be inflated by a failure to assess the preoperative cognitive performance (Bruce et al. 2013a, 2014; Selnes et al. 2012; Sweet et al. 2008). CABG patients with atherosclerosis or coronary artery disease/cardiovascular disease have a high risk of developing hypertension, diabetes mellitus, hyperlipidemia, peripheral arterial disease, and cerebrovascular changes, all of which negatively affect cognitive function (Maekawa et al. 2011; McKhann et al. 2005; Selnes and Zeger 2007). The restriction of blood flow through the heart will decrease cerebral perfusion, potentially causing cerebral ischemic damage and cognitive dysfunction (Hoth et al. 2008).

Neuropsychological Testing Following Cardiac Surgery

Assessment of cognitive function usually involves a battery of neuropsychological tests that measure performance across a range of cognitive domains that can include intelligence, learning, memory, attention, receptive and expressive language, visuospatial ability, sensory processing, motor ability, reasoning, and higher-order executive functions (Daliento et al. 2006). Neuropsychological assessment is difficult to perform after cardiac surgery, in part because the patients are not well but also because the availability of neuropsychologists in hospitals is limited. Consequently, surgeons without expertise in neuropsychological assessment frequently make judgments regarding the choice of tests and the manner of scoring (Smith 1995). These tests are often basic tests of global cognitive function (such as the Mini-Mental State

Exam) that are primarily designed to detect substantial decrements in cognition. In general, surgeons are concerned with whether the patient has acquired a major disability or if the family has noticed a disability that interferes with performance of their daily activities (Selnes and McKhann 2001). Surgeons are constrained in their choice due to the need for tests that are brief and easy to conduct at the bedside, that display minimal practice effects (i.e., availability of alternate forms for repeat testing or choice of tests with no inherent learning), and that have no linguistic or cultural bias.

Neuropsychological Tests for Measuring POCD

In 1995, a "Statement of Consensus" made recommendations about the design of neuropsychological test batteries that should be used to assess cognitive impairment after cardiac surgery (Murkin et al. 1995). The consensus was drafted by researchers with expertise in a range of relevant disciplines, recommended tests that should be conducted, and issues to be considered. The issues included the need for a baseline and control group for comparison postoperatively, the optimal time to perform postoperative assessment, the importance of including a mood state assessment, and advice regarding practice effects (which occur when the patient improves their outcome on a measure because of learning through practice).

After addressing the points mentioned above, the authors of the consensus recommended a core battery of four tests: the Rey Auditory Verbal Learning Test (verbal learning and memory), the Grooved Pegboard (motor skills), and the Trail Making Tests A and B (attention and concentration and executive function, respectively). They were chosen because they can be standardized against normative data, are easy to administer, have alternative forms available for repeat testing sessions, and are sensitive to cognitive changes following cardiac surgery (Murkin et al. 1995). The consensus recommendations have not been widely adopted (Rudolph et al. 2010). For instance, in a selection of 79 research studies that assessed cognitive change following cardiac surgery (Appendix A), only 30 studies (38 %) chose their neuropsychological assessment battery on the basis of recommendations in the consensus.

The consensus stated the need for a control group, but there was no recommendation regarding what parameters to control for (e.g., age, gender, coronary artery disease, or surgical procedure) (Newman et al. 2006). Furthermore, it has been suggested that a measure of mood state be included in assessment batteries (Murkin et al. 1995). However, a review of published manuscripts by Rudolph and colleagues (2010) revealed that only half of the studies assessed anxiety or depression. As stated earlier in this chapter, the potential for mood state to influence cognitive performance is large, and the present authors strongly recommend that future studies include a mood state assessment tool such as the Depression, Anxiety, and Stress Scale (DASS).

Despite the lack of a consistent approach, some trends have emerged (Appendix A). For instance, tests that have most commonly detected POCD include the Boston

naming test, visual naming test, verbal fluency test (e.g., COWAT), and verbal learning test (e.g., RAVLT). Since all of these tests measure some aspect of language proficiency, it appears that language is a domain that is frequently affected by cardiac surgery. Other tests that often detect POCD are the Trail Making Test, digit symbol, and the Grooved Pegboard. These tests are sensitive to impairments in several domains, but their area of commonality is concentration, making it likely that this domain is affected. The data summarized in Appendix A indicate that language, concentration, and motor control are commonly affected during the recovery period following cardiac surgery. Memory, attention, and executive function may also be impaired, but it is difficult to conclude whether these impairments are as common, due to the lower proportion of studies that have investigated these domains and a lack of consistency in the choice of tests used to assess these domains.

Computerized Cognitive Tests

The growing availability of personal computers from the 1980s has led to an increase in the use of computers for cognitive testing (Butcher et al. 2000; Schlegel and Gilliland 2007). Existing pen and paper tests were translated into a computerized format, and new cognitive tests were developed, taking advantage of the automated timing of stimulus presentation and data collection (Wild et al. 2008). Computerized cognitive tests are now widely employed because, if developed correctly, they can overcome many of the limitations associated with conventional tests. Computer-based tests are generally quick and easy to use, results can be analyzed automatically, and they may be able to overcome cultural and language barriers (Collie et al. 2003; Silbert et al. 2004). Some computerized tests can be conducted at the bedside by nurses or other hospital personnel because they do not need to be administered or scored by neuropsychologists. This facility makes it possible to screen patients, both before and after surgery, in order to track a patient's recovery from POCD. Computerized tests that have been used to assess POCD following cardiac surgery include CogState (Silbert et al. 2004), MicroCog (Raymond et al. 2007), the CANTAB (Kidher et al. 2014), and the SCIT (Bruce et al. 2013a, 2014).

Statistical Approaches for Defining Postoperative Cognitive Change

The statistical approach used to define postoperative cognitive change can have a substantial effect on the estimated incidence of POCD. Some approaches depend on the availability of presurgical test results, whereas others compare performance against population norms or the performance of a control group. Definitions of impairment have included:

1. One standard deviation decline from the preoperative test score on each test (Vingerhoets et al. 1997; Ebert et al. 2001; Rosengart et al. 2006).

2. One standard deviation from the preoperative group mean on a specified number of measures (i.e., usually ≥20 % or ≥2 tests) (Silbert et al. 2001; Zamvar et al. 2002; Hogue et al. 2003; Ho et al. 2004).
3. Twenty percent decline from preoperative test results on 20 % or more tests (Van Dijk et al. 2002; Ho et al. 2004; Keizer et al. 2005).
4. One standard deviation below published normative means for each test (Rosengart et al. 2006).
5. Z-score: the mean difference between patient and control group is calculated, and the z-score is determined by subtracting from it the mean learning effect in the control group and then dividing by the standard deviation measured in the control group. Z-scores can be calculated for each test or each cognitive domain being assessed. Decline is defined by a cut-off value (e.g., $Z \geq 1.96$) that can differ between studies (Rasmussen et al. 2004; Selnes et al. 2005).
6. Composite score: a combined score containing results from all or only some of the tests in the battery (Motallebzadeh et al. 2007).
7. Reliable Change Index (RCI): specifies the degree of change from pre- to postoperative test results that is required to achieve a decline in performance that is statistically reliable after the practice effects have been removed (Kneebone et al. 1998; Keith et al. 2002; Keizer et al. 2005; Raymond et al. 2006; Rosengart et al. 2006). The RCI method tends to produce more conservative estimates of POCD because it eliminates the distorting effects of patient familiarity with the testing procedure.
8. Standardized regression-based technique, a modified z-score procedure that takes into account the change from baseline, and the influence of any demographic variables chosen (Raymond et al. 2006).

This lack of concordance regarding how to define POCD has itself contributed to the large variance in estimates of the incidence of cognitive impairment following cardiac surgery. Of the methods detailed above, the RCI and the standardized regression-based techniques are the most rigorous (Rosengart et al. 2006), as they account for the measurement error and practice effects that are a feature of repeated-measure tests (Jacobson and Truax 1991).

Cognitive Impairment Following CABG

Studies are beginning to show that the 20 % or 2SD definition can lead to over-estimates of cognitive decline after CABG surgery (Raymond et al. 2006; Selnes and Zeger 2007; Selnes et al. 2006; Stroobant et al. 2010). Several studies have reported that the prevalence of POCD differs according to the definition of impairment used. For example, Keizer et al. (2005) assessed cognitive decline following CABG surgery at 3 months using three different definitions of decline: a one standard deviation decrease in test performance on 20 % of the tests, a 20 % decrease in test performance on 20 % of tests, and the RCI. The incidence of decline was 10.5 % using the standard deviation method, 31 % using the 20 % method, and 7.7 % using

the RCI. The same group reanalyzed results from a previous study that had reported that 28 % of patients showed POCD 3 months after surgery (using the 20 % definition of decline) and found that this proportion decreased to 9.9 % using the RCI method (Van Dijk et al. 2000). These analyses indicate that the RCI method is a more conservative measure. Together, these results suggest that the RCI has greater external validity than other measures for determining the incidence of POCD following cardiac surgery. The present authors recommend that the RCI method be regarded as the method of first choice in future studies of POCD.

In a study by the present authors (Bruce et al. 2013a), the RCI was used in combination with a more tightly controlled study design. It was found that the majority of CABG patients recovered to baseline cognitive performance or better within 8 weeks of surgery. Furthermore, when the RCI was used to assess cognitive performance on an individual patient basis, only a small proportion of patients exhibited cognitive impairment. These impaired patients strongly influenced the overall results at a group level (Bruce et al. 2013a).

Cognitive Impairment Following Conventional and Robotically Assisted Valve Surgery

Robotically assisted valve surgery offers the opportunity to investigate whether the pain and physical restriction caused by the median sternotomy during conventional valve surgery contribute to overestimates of cognitive impairment in the weeks immediately after surgery.

In the only study that has assessed cognitive performance following robotically assisted surgery, the present authors found that the patients performed worse than conventional valve patients in the first testing session after surgery (Bruce et al. 2014). While this result was unexpected, it should be noted that the average interval between surgery and cognitive testing was 6.6 days for robotically assisted patients and 10 days for conventional valve patients. The reason for this difference is that the robotically assisted patients experienced less pain and discomfort and were discharged more quickly from hospital. This difference in re-testing time provided the conventional valve group with more time to recover from the effects of anesthesia and on-pump surgery. In both groups, any cognitive change that was present in the week after surgery had resolved within 8 weeks (Bruce et al. 2014).

Clinical Implications

Some computer-based tests of global cognition can be conducted at the bedside by hospital personnel. This availability makes it possible to routinely screen patients before and after surgery in order to assess the effects of surgery on cognition and to monitor patient recovery. Such results will help to inform best surgical practice and will also provide an additional indication of when patients are fit for discharge from hospital.

The data reviewed in the present chapter indicate that the domains of language, concentration, and motor control are commonly affected during the first week after cardiac surgery and that memory and executive function can also be affected. There is considerable variability between patients in the degree of POCD, and some of this variability seems to be associated with emotional state. Importantly, most cardiac patients improve to their presurgical levels of cognition (or better) within 8 weeks of surgery. Awareness of these patterns may help clinicians to prepare their patients for the surgical outcomes and to allay patient fears of the risk of permanent impairments.

The current data indicate that a proportion of CABG patients exhibit cognitive impairment prior to undergoing surgery; typically, this impairment does not improve after surgery (Bruce et al. 2013a). While the cause of this permanent impairment is not yet known, it seems likely to be due to hypoxic brain injury resulting from cerebrovascular or cardiovascular disease. It is suggested that earlier interventions are needed in order to avoid permanent brain damage. This would require at-risk patients to be screened for the presence of cognitive impairment and for priority to be given to CABG patients who have cognitive impairment and are on surgical waiting lists.

Conclusion

There is a need to identify the risk factors and surgical techniques that influence POCD, yet it is difficult to reach definitive conclusions from the present data, due to the heterogeneity in experimental design and methods of data analysis. As these factors can greatly affect the estimated magnitude of cognitive impairment following cardiac surgery, it is imperative to develop a consistent research methodology in order to obtain more reliable results. We suggest that future studies should include both nonsurgical and surgical control groups. Nonsurgical control groups help to address changes that occur in cognitive performance as the result of repeated testing, often due to a learning effect. They also control for any impairments that are a function of normal, healthy aging. Surgical control groups address factors related to the surgical procedure that can influence cognitive performance, such as stress and anxiety, duration of anesthesia, and surgical trauma. The present authors also recommend that the cognitive function and emotional state of patients be assessed prior to and after surgery. The DASS is a useful tool for assessing the levels of depression, anxiety, and stress. Computer-based tests are convenient ways to screen for global changes in cognition, and they can be complemented (if needed) by pencil-and-paper tests of specific cognitive domains.

Appendix A

See Table 1.

Table 1 An illustrative sample of studies reviewing the neuropsychological tests used, the methods used to define cognitive impairment and the cognitive impairment found in their studies

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
O'Brien et al. (1992)	On-pump CABG valve	10 days	24–40 days	Other[a]	Digit span, CPT, CVLT, visual reproduction and logical memory subtests of WMS, PERT	No	**TI**: CVLT↓, CPT↓, **T2**: CVLT↓	**TI**: ↓ **T2**: ↔
Vingerhoets et al. (1997)	On-pump CABG valve	7–8 days	6 months	1	RCFT, RAVLT, TMT A and B, Purdue Pegboard, digits test and TAPS test, Stroop color-word test, dot cancellation test, line bisection test, COWAT, token test	Yes	**TI**: line bisection↓, RAVLT↓, TAPS test↑; COWAT↑, TMT A↑, token test↑ **T2**: CFT↑, TMT A↑, COWAT↑, Stroop Test↑	**TI**: 45 % **T2**: **12 %**
Andrew et al. (1998)	On-pump CABG MIDCAB, 9 SGC, 27 MGC	7 days	Nil	7	CVLT, Purdue Pegboard, COWAT, TMT A and B, digit symbol, Boston naming test, NART, DASS	Yes	**MIDCAB**: no tests declined over 30 % **SGC**: Purdue Pegboard 55.6 %; **MGC**: Purdue Pegboard 44.4 %↓., TMT B 40.7 %↓., digit symbol 40.7 %↓	**TI**: decline on four or more measures: 14.3 %↓ **MIDCAB**; 11.1 %↓ **SGC**; 44.4 %↓ **MGC**

Braekken et al. (1998)	On-pump CABG valve	3–5 days	2 months	1	COWAT, CVLT, Grooved Pegboard, TMT A and B, WMS, serial digit learning, letter cancellation test, digit symbol, computerized reaction time test, State-trait anxiety inventory	No	**TI**: valve only: Grooved Pegboard↓, letter cancellation test↓, digit symbol↓, **T2**: valve: CVLT↑, state-trait anxiety inventory↑ CABG: CVLT↑, WMS↑, digit symbol↑	**TI**: valve 67 % **T2**: valve 23 %; CABG 14 %
Kneebone et al. (1998)	On-pump CABG	7 days	Nil	1,7	CVLT, Purdue Pegboard, COWAT, TMT A and B, digit symbol, Boston naming test	Yes	**TI**: RCI method: Purdue Pegboard↓, TMT B↓, digit symbol↓, Boston naming test↓,	**TI**: RCI 36 %, SD 0 %
Selnes et al. (1999)	On-pump CABG	1 month	1 year	5	RAVLT, RCFT, symbol digit, Boston naming test, digit span, written alphabet task, Grooved Pegboard, Stroop, NART, MMSE	No	No individual test stats given	Study looking at association between cognitive decrease and medical and intraoperative variables. No overall stats given on performance
Andrew et al. (2000)	On-pump CABG valve combined	6.5 days	Nil	5,7	CVLT, Purdue Pegboard, COPWAT, TMT A and B, digit symbol, Boston naming test, NART	Yes	Digit symbol 28.8 %↓., TMT B 24 %↓.	**TI**: 70 %↓. on one or more test, 42 %↓ on two or more tests

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Diegeler et al. (2000)	On-pump CABG off-pump CABG	7 days	Nil	4	Syndrom Kurztest (cognition)	No	**TI**: Syndrom Kurztest; 90 %↓. on-pump CABG; 0 %↓ off-pump CABG	**TI**: 90 %↓.on-pump CABG; 0 %↓. Off-pump CABG
Andrew et al. (2001)	On-pump CABG valve	7 days	6 m	7,2	CVLT, Purdue Pegboard, COWAT, TMT A and B, digit symbol, Boston naming test	Yes	**TI**: digit symbol↓. (valve and CABG), TMT B↓ (valve and CABG), CVLT↓ (valve only)	**TI**: CABG 50 %, valve 50 %
							T2: TMT A↓ (valve and CABG), TMT B↓ (valve and CABG), digit symbol↓ (valve only)	**T2**: CABG 27 %, valve 40 %
Baker et al. (2001)	On-pump CABG off-pump CABG	7 days	6 months	7	CVLT, Purdue Pegboard, TMT A and B, digit symbol	Yes	Tests most susceptible to deficits: on-pump CABG-Purdue Pegboard, TMT B, digit symbol. OPCAB-CVLT, digit symbol (not identified as significant deficit)	No difference between groups at **TI** or **T2**

Basile et al. (2001)	On-pump CABG	6 months	Nil	2	MMSE, Randt memory test, judgment of similarities and differences, interpretation of proverbs, nonsense stories, token test, naming of pictures and definitions	No	**TI**: MMSE↑; Randt paired words (acquisition and recall)↓	**TI**: 37.5 %↓, 62.5 %↑
Di Carlo et al. (2001)	On-pump CABG valve	6 months	Nil	1	MMSE, Randt memory test, token test, confrontation and definitional naming, similarities and differences	No	**T2**: MMSE↓, Randt memory test↓, token test↓, confrontation naming↓	**TI**: 29 %
Ebert et al. (2001)	On-pump CABG valve	2 days	7 days	2	MMSE, COWAT, picture naming, 12 arithmetic tasks, verbal memory, clock reading tasks	No	**TI**: CABG and valve: ↓ on all tests except naming but valve had significantly greater decline than CABG on COWART, verbal memory, and arithmetic tasks. **T2**: CABG: verbal fluency↓, clock reading↓, arithmetic↓. Valve: verbal fluency↓, arithmetic↓, verbal learning↓	**TI**: CABG 57 %, valve 71 % **T2**: CABG 19 %, valve 36 %

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Grigore et al. (2001)	On-pump CABG	Nil	6 week	1	Randt memory test, digit span, digit symbol, modified visual reproduction test, TMT B	No	**T2**:Means and SD given only, no significant changes identified in individual tests	**T2**: 39.3 %↓
Kilo et al. (2001)	On-pump CABG off-pump CABG	7 days	4 months	1	MMSE, TMT A	No	No significant changes on tests	**TI**:↔ **T2**:↔
Millar et al. (2001)	On-pump CABG	6 days	6 months	1	Stroop test, beck depression inventory	No	Pre-existing cognitive impairment and depression significant factors in decline	**TI**: 14 %[b] **T2**: 2 %[b] independent of depression and existing impairment
Newman et al. (2001)	On-pump CABG	7 days	6 weeks, 6 months, 5 year	2	Randt memory test, digit span, Benton revised visual retention, digit symbol substitution, TMT B	No	**T2**: TMT B↓	**TI**: lwk: 53 % **T2**: 6 weeks, 36 %; 6 months, 24 %; 5 years, 42.5 %
Selnes et al. (2001)	On-pump CABG	1 year	5 year	6	RAVLT, RCFT, symbol digit, Boston naming test, digit span, written alphabet task, Grooved Pegboard, Stroop test, MMSE	No	**TI (ly)**: ↑RAVLT, ↑RCFT, ↑Stroop, ↑Grooved Pegboard, ↑symbol digit. T2 (5 years): ↓RCFT, ↑Stroop, ↓symbol digit and↓, written alphabet	No percentage impairment given

Silbert et al. (2001)	On-pump CABG	18 h	5 days	2	WMS, TMT A&B, digit span, COWAT	Yes	No individual test scores given	**TI**: 30 % T2: 10 %
Abildstrom et al. (2002)	On-pump CABG	5–7 days	3 months	5	ISPOCD test battery: visual verbal learning test, Concept shifting test, Stroop test, letter-digit coding test	No	No individual test stats given. Study looked at comparing patients with and without POCD to cerebral blood flow. No significant difference in cerebral blood flow between groups with POCD and without POCD	**TI**: 26.7 %↓ T2: 20 %↓
Ahlgren et al. (2003)	On-pump CABG, PCI	4–6 weeks	Nil	2	TMT A, RCT, RAVLT, computerized driving test: K-test (focused attention), simple reaction time, complex reaction time, simultaneous capacity, reaction time on two choice visual stimuli	No	Decline most frequently seen in TMT A&B, RAVLT, K-test, simple reaction time, and reaction time on two choice visual stimuli, but no numerical stats given to state that they were significantly declined	**TI**: CABG 48 %↓, PCI 10 %↓

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Rasmussen et al. (2002)	On-pump CABG	7 days	3 months	5	ISPOCD test battery: visual verbal learning test, Concept Shifting Test, Stroop Test, Letter-Digit Coding Test	No	No individual test scores given	**TI**: 46.7 %↓ T2: 6.7 %↓
Van Dijk et al. (2002)	On-pump CABG Off-pump CABG	3 m	12 months	5	RAVLT, Grooved Pegboard, TMT A a ndB, Sternberg memory comparison, Line Orientation Test, Stroop Test, CPT, self-ordering tasks, visuospatial working memory test, digit symbol	Yes	No individual test scores given	**TI**: on-pump 29.2 % Off-pump 21.1 % **T2**: on-pump 33.6 % Off-pump 30.8 %
Zamvar et al. (2002)	On-pump CABG off-pump CABG	7 days	10 weeks	2	RAVLT, TMT A&B, digit symbol, digit span, Grooved Pegboard, COWART	Yes	**TI**: on-pump, Grooved Pegboard↓, digit symbol↓, **T2**: on-pump, TMT B↓, Grooved Pegboard↓, digit symbol↓,	**TI**: on-pump 66 %, off-pump 27 % **T2**: on-pump 40 %, off-pump 10 %

Zimpfer et al. (2002)	On-pump CABG valve	7 days	4 months	1	TMT A, MMSE	No	No individual test scores given	**TI**: ↔ **T2**: ↔
Browne et al. (2003)	On-pump CABG	2 days	5 days, 3 months	6	Adult Memory Information Processing Battery Battery, TMT B, RAVLT, COWAT	No	No individual test scores given	**TI**: 5 days, ↓ **T2**: 3 months, ↑ (increased beyond baseline)
Grimm et al. (2003)	Valve	7 days	4 months	1	MMSE, TMT A	No	Replace vs. repair: 7 days and 4 months, ↓TMT A. MMSE ↔ at either time point	No change in valve repair group at 7 days or 4 m. ↓decline in replace group at 7 days and 4 m
Hogue et al. (2003)	On-pump CABG	4–6 weeks	Nil	2	TMT A&B, digit symbol, digit span, Grooved Pegboard, WMS, Benton Visual Form Discrimination, RAVLT	Yes	TMT A&B↓, Benton Visual Form Discrimination↓, Grooved Pegboard↓	**TI**: ↔
Lee et al. (2003)	On-pump CABG off-pump CABG	2 weeks	1 year	3	Vocabulary of WAIS, RAVLT, Benton Visual Retention Test, TMT A&B, Grooved Pegboard, finger-tapping test, digit symbol, state anxiety, beck depression	Yes	On-pump: no significant difference on any test at 2 weeks or 1 year. Off-pump: significant ↑ on RAVLT at 2 weeks and 1 year. Both groups ↑improvement on state anxiety at both times	**TI**: on-pump 15.4 %↓. vs. off-pump 16.1 %↓ **T2**: on-pump 14.8 %↓ vs. 18.5 %↓ off-pump

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Lund et al. (2003)	On-pump CABG off-pump CABG	3 months	Nil	3	Grooved Pegboard, digit symbol, TMT A&B, digit span, Stroop Test, RAVLT, similarities and vocabulary from WAIS, COWAT, visuoconstructive abilities from WAIS	No	No individual test scores given	**TI**: on-pump 35 %↓, off-pump 29 %↓, no significant difference between groups
Rankin et al. (2003)	On-pump CABG off-pump CABG	10 week	Nil	5,6	Boston naming test, COWAT, Rey and Taylor Complex Figure Tests, Judgment of Line Orientation, digit span, TMT A&B, Stroop Test, CVLT, Grooved Pegboard, Ruff Figurai Fluency, MMSE	Yes	CFT↑ (both on- and off-pump)	No significant decline in off- or on-pump CABG
Selnes et al. (2003)	On-pump CABG	3 months	12 months	5	RAVLT, RCFT, Boston naming test, MMSE, TMT A, written alphabet, Grooved Pegboard, TMT B	No	CABG ↑ in verbal memory and global summary measure. Overall ↑ in CABG group on RAVLT, BNT, pegboard compared to nonsurgical controls	**TI**: ↔ **T2**: ↔

Stygallet al (2003)	On-pump CABG	6 days	8 weeks, 5 years	6	RAVLT, nonverbal recognition memory task, TMT A&B, block design, finger-tapping test, letter cancellation test, symbol digit replacement test, choice reaction time, displaced reaction time test	No	5 years: RAVLT + TMT A↑, all other tests decline	Most tests decline at 6 days, improve at 8 weeks, then decline at 5 years
Ho et al. (2004)	On-pump CABG	6 months	Nil	2,3,6	Blessed Orientation-Memory-Concentration Test, Behavioral Dyscontrol Scale, TMT A	No	Behavioral Dyscontrol Scale↓, Blessed Orientation-Memory-Concentration Test↓,	**TI**: >0.5SD = 4.7 %, >1SD = 8.2 % >20 % = 36.6 %
Kanbaket al. (2004)	On-pump CABG	3 days	6 days	1	MMSE, visual aural digit span		3 days: VADST↓, MMSE ↔ 6 days: VADST return to baseline level, MMSE ↔	No overall percentage change given. Two clinical groups are ofluorane vs. propofol, no difference between groups
Silbert et al. (2004)	On-pump CABG	6 days	Nil	7	CERAD, Symbol Digit Modalities Test, TMT A&B, semantic fluency test, Grooved Pegboard, CogState	Yes	Conventional tests: Grooved Pegboard↓, only significant one. Computerized test: four variable significance ↓ – three types of reaction time, and accuracy	**TI**: conventional tests 32 %↓, computerized tests 42 %↓

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Askar et al. (2005)	On-pump CABG:	7 days	3 months	3	COGNISTAT (10 subtests assessing orientation, attention, comprehension, repetition, naming, constructions, memory, calculations, similarities, judgment	No	No individual test scores given	**TI**: group 1 48.2 %↓; group 2 58.8 %↓ **T2**: group 1 37.5 %↓, group 2 29.4 %↓
Carrascal et al. (2005)	On-pump CABG	7 days	Nil	1	PASAT (Paced Auditory Serial Addition Test)	No	**TI**: 45.5 %7↓ PASAT	**TI**: 45.5 %↓
Kadoi et al. (2005)	On-pump CABG	7 days	6 months	2	MMSE, RAVLT, TMT A&B, digit span, Grooved Pegboard	Yes	TMT A↓, TMT B↓ (7 days), RAVLT↓	**TI**: 68 %↓ **T2**: 28 %↓
Keizer et al. (2005)	On-pump CABG off-pump CABG	3 m	12 months	2,3,7	RAVLT, Sternberg letter test, TMT A&B, Grooved Pegboard, Stroop Test, Symbol Digit Modalities Test, self-ordering tasks	No	Data on statistically different changes in performance on individual tests was not provided	T1:>SD = 10.5 %, >20 % = 31 %, RCI = 7.7 % **T2**:RCI = 12.3 %
Kneebone et al. (2005)	On-pump CABG	6 months	Nil	6,8	CVLT, Purdue Pegboard, COWAT, TMT, Boston naming test, digits symbol, NART, DASS	Yes	TMT↓, digit symbol↓	**TI**: 43.5 %↓ on 1 test, 18.8 %↓ on 2 tests, 7.1 %↓ on3 tests

Knipp et al. (2005)	Valve	4–7 days	4 months	No definition given	TMT A&B, digit span, Corsi block-tapping test, Horn's performance test, Zimmerman's divided attention test, verbal learning test, von Zircon test (mood), general depression scale	No	Discharge:↓TMT A&B, digit span, Corsi block-tapping test. 4 months: ↑digit span, Horn's performance, depression and mood scales	**TI**: discharge: ↓on 5 of 13 tests/ subtests **T2**: 4 months ↔ from baseline
McKhann et al. (2005)	On-pump CABG off-pump CABG	3 months	12 months	5	RAVLT, RCFT, Boston naming test, digit span, symbol digit, written alphabet, Grooved Pegboard, Stroop Test, MMSE	No	**T2**: (3 months and 12 months) no significant cognitive decline in any cardiac surgical group	**TI** and **T2**: on-pump CABG ↔; Off-pump CABG ↔
Rothenhausler et al. (2005)	On-pump CABG combined	6–7 days	1 year	2	Syndrom Kurztest (SKT), German version of the ten-item Montgomery-Asberg Depression Rating Scale, PTSS-10 (stress scale)	No	No significant correlation between cognitive dysfunction and MADRS or PTSS-10 scales (i.e., depression or stress levels)	**TI**: 38.2 %↓ (17.6 % minimal, 11.8 % mild, 2.9 % severe) **T2**: 20 %↓ (13.3 % minimal, 6.7 % moderate)
Selnes et al. (2005)	On-pump CABG	12 months	36 months	5	RAVLT, RCFT, Boston naming test, MMSE, TMT A&B, written alphabet, Grooved Pegboard	No	Boston naming test↓, RAVLT↓, Grooved Pegboard↓	**TI**: ↔ **T2**: ↔

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Stroobant et al. (2005)	On-pump CABG off-pump CABG	6 days	6 months	3	RAVLT, TMT B, Grooved Pegboard, block taps test, line bisection test, COW AT, Judgment of Line Orientation	No	**TI**: block taps test↓, line bisection test↓ **T2**: (on-pump) line bisection test↓ (on- and off-pump) TMT B↓, block taps test↓	**TI**: 60 %↓. (59.4 % on-pump CABG, 61.2 % off- pump CABG) **T2**: 24.2 % ↓ (31.8 % on-pump CABG, 9.1 % off-pump CABG)
Boodhwani et al. (2006)	On-pump CABG	6–7 days	Nil	2	Verbal list learning procedure, digit span, Grooved Pegboard, symbol digit, TMT A&B, RAVLT, WMS Memory Scale	Yes	61 %↓ in 1 domain, 30 %↓, in 2 domains, 9 %↓ in 3 domains. No individual test data given	**TI**: 59 %↓
Dupuis et al. (2006)	On-pump CABG	5–12 months	Nil	1	Boston naming test, COWAT, digit symbol, Logical Memory Scale, Visual Reproduction Scale, facial recognition test	No	No individual test scores given	No overall percentage change given

Emest et al. (2006)	On-pump CABG off-pump CABG	2 months	6 months	4	RAVLT, Grooved Pegboard, TMT A&B, digit span, digit symbol, letter cancellation test, COWAT, Boston naming test, WMS-R Visual Reproduction, Judgment of Line Orientation, Stroop color-word test	Yes	**TI**: no difference between tests and groups in tests	**TI**: ↔
							T2: ↑COWAT score in off-pump vs. on-pump at 6 months	**T2**:↔between on- and off-pump group or baseline
Hammon et al. (2006)	On-pump CABG off-pump CABG	3–5 days	6 weeks, 6 months	3	Not defined: stated in text "Patients underwent an 11-part neuropsychological examination, which was administered by a psychologist. The elements of the test and its results in large numbers of patients in this institution and others have previously been published" referred to Murkin et al. (1995)-statement of consensus	Yes	No individual test scores given	**TI**: MC 59.5 %↓; SC 59.5 %↓; OPCAB; 70.2 %↓,
								T2: MC 51 %↓; SC 31.8 %↓; OPCAB 39.2 %↓, T3: MC 57.1 %↓; SC 29.7 %↓; OPCAB 31.7 %↓
Jensen et al. (2006)	On-pump CABG off-pump CABG	3 months	Nil	2,3	MMSE, visual verbal learning test, Concept Shifting Test, Stroop Color-Word Interference Test, Letter-Digit Coding Test	Yes	No individual test scores given	**TI**: 1. OPCAB 7.4 %↓, CCAB 9.8 %↓; 2. OPCAB 20.4 %↓, CCAB 23.5 %↓ 3. OPCAB 26.0 %↓ CCAB 21.6 %↓

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Lewis et al. (2006)	On-pump CABG	1 week	Nil	2	WLT, TMT A&B, digit symbol, COWAT, Grooved Pegboard	No	T1:CERAD↓, TMT A&B↓, COWAT↓, Grooved Pegboard↓	**TI**: two tests = 13.3 %↓; seven tests = 49.4 %↓; adjusted for controls = 8–17.5 %↓
Raymond et al. (2006)	On-pump CABG	2 weeks	Nil	2, 3, 7, 8	MicroCog: assessment of cognitive function	No	**TI**: SRB: information processing speed↓, general cognitive functioning↓ all methods: attention/mental control↓	**TI**: >1SD = 3.6 %↓, 65.5 %↑ >20 % = 5.5 %↓, 9.1 %t RCI = 16.4 %↓,<7 %↑ SRB = 32.7 %↓, <7 %↑
Rosengart et al. (2006)	On-pump CABG	3 weeks	4 months	1, 4, 7	Digit span, Grooved Pegboard, digit symbol, TMT A&B, Stroop Test, COWAT, visual naming of the Multilingual Aphasia Exam, Hopkins verbal learning test	No	T1:RCI, visual naming of the multilingual aphasia exam↓	**TI**:↔ **T2**:↔
Szalma et al. (2006)	On-pump CABG	6 weeks	Nil	1	Word fluency test, digit symbol, digit span, block design subtest of WAIS, TMT (Hungarian), RAVLT (Hungarian), Pieron test,	No	No significant changes found on any tests in placebo group	**TI**: ↔

					Simple Reaction Time, Choice Reaction Time, serial reaction time, Spielberger State-Trait Anxiety Inventory, Beck Depression Inventory			
Cook et al. (2007)	On-pump CABG, valve combined	7 days	4–6 weeks	3	RAVLT, nonverbal memory test, symbol digit, letter cancellation, TMT A&B, Grooved Pegboard, finger-tapping test	Yes	No individual test scores given	**TI**: 88 %↓ **T2**: 30 %↓
Hammon et al. (2007)	On-pump CABG	3–7 days	3–6 weeks, 6 months	3	WAIS, RAVLT, TMT A&B, Grooved Pegboard, finger-tapping test, digit symbol, letter cancellation task, visual reaction time test	No	Data on statistically different changes in performance on individual tests was not provided	**T2** (6 months only given): on-pump: 26.0–44.4 %↓, off-pump: 11.5–38.4 %↓
Hernandez et al. (2007)	On-pump CABG off-pump CABG	Day of discharge	6 months	3	Digit span, VIGIL, Grooved Pegboard, RCF, COWAT, Hopkins verbal learning test, WRAT-3, Brixton Spatial Anticipation Test, Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory	No	4 days: TMT A, and state anxiety↓ in OPCAB compared to CABG. 6 months: ↔ in all tests	**TI**:↔between groups **T2**:↔ between groups

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Ille et al. (2007)	Combined	7 days	Nil	1	Test zur Fruherkennung der Demenz mit Depressionsabgrenzung (TFDD)	No	Only one test used	**TI**: 43.2 %↓, 38.6 %↑
Motallebzadeh et al. (2007)	On-pump CABG off-pump CABG	7 days	6 weeks, 6 months	6	MCG complex figure test, Grooved Pegboard, RAVLT, letter cancellation test, Symbol Digit Modalities Test, verbal fluency test	Yes	Data on statistically different changes in performance on individual tests was not provided	**TI**: on-pump↓ vs. off-pump **T2**: ↔ T3: ↔
Nathan et al. (2007)	On-pump CABG	1 week	5 years	6	Buschke Selective Reminding, digit span, TMT A&B, Grooved Pegboard, Symbol Digit Modalities Test	No	Significant changes only identified between groups	**TI**: 45 %↓ **T2**: 44 %↓
Puskas et al. (2007)	On-pump CABG	6 weeks	Nil	6	Randt memory test, digit span, digit symbol, TMT B, modified visual reproduction test from WMS	No	No individual test scores given	**TI**: diabetic patients, 38 %↓. With hyper, 41 %↓. Without hyper. Nondiabetic: 40 %↓. With hyper, 29 %↓ without hyper
Rubens et al. (2007)	On-pump CABG	5 days	3 months	6	TMT A&B, RAVLT, digit span, COWAT	Yes	Significant changes only identified between groups	**TI**: 39 %↓ **T2**: 15.9 %↓

Selnes et al. (2007)	On-pump CABG off-pump CABG	3 months	12 months, 36 months	5	RAVLT, RCF, block design, Boston naming test, Grooved Pegboard, TMT A, written alphabet, MMSE, TMT B	No	36 months: attention domain MMSE, ↑to above baseline levels	**T2** (36 months only stats given):↔ relative to baseline across all tests
Tagarakis et al. (2007)	On-pump CABG	1 month	1 year	1	MMSE, Wechsler Memory Scale Revised, Brief Psychiatric Rating Scale, Delirium Rating Scale	No	**TI**: all test significant↓	No overall percentage change given
Van Dijk et al (2007)	On-pump CABG off-pump CABG	5 years	Nil	3,7	RAVLT, Grooved Pegboard, TMT A&B, Sternberg memory comparison, Line Orientation Test, Stroop Test, CPT, self-ordering tasks, visuospatial working memory test, Symbol Digit Modalities Test	Yes	**TI**: individual test stats do not indicate if significant change occurred within groups	**T2**: **20 % method**, 50.4 %↓ off-pump CABG, 50.4 %↓. On-pump CABG. RCI method: 33.3 %↓ off-pump CABG, 35.0 %↓ on-pump CABG
Yin et al. (2007)	On-pump CABG off-pump CABG	7–10 days	Nil	2	MMSE, digit span, digit symbol, TMT A, Stroop Test, self-rating depression scale, Spielberger State-Trait Anxiety Inventory	Yes	**TI**: **Off-pump CABG**: self-rating depression↓., MMSE ↓, Stroop Test↓.: **On- pump CABG**: self-rating depression↓, digit span↓, Stroop Test↓	**TI (decline on 2 or more tests)**: off-pump CABG – 32.5 %↓, on-pump CABG ∼52.5 %↓

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Mathew et al. (2007)	On-pump CABG	6 weeks	Nil	2	Randt memory test (short story), digit span, modified visual reproduction test, digit symbol, TMT B	No	No individual test scores given	**TI**: MH 37.5 %↓, PH 42.5 %↓
Ropacki et al. (2007)	On-pump CABG	1 week	Nil	2	Digit span, digit symbol coding, letter-number sequencing, vocabulary, FAS test, category fluency, Hopkins verbal learning test (HVLT), mental control subtest of WMS, Randt memory test (short story), RCFT, TMT A&B	Yes	**TI**: 47.6 %↓ on psychomotor speed (TMT A and digit symbol), 45.2 %↓. On working memory and executive function (FAS test, digit span, TMT B, letter-number sequencing), 57.1 %↓. Verbal memory (short story of Randt memory test, HVLT), 16.7 %↓ visual memory (RCFT)	**TI**: 66.7 %↓

Cicekcioglu et al. (2008)	Off-pump CABG valve	6 days	2 months	1	Raven's standard progressive matrices (RSPM), RAVLT, Stroop Test, Line Orientation Test (LOT)	Yes	**TI**: RSPM↔, LOT↓., RAVLT↑, Stroop↑ **T2**: RSPM↔, LOT↔, RAVLT↑, Stroop↑	No overall percentage decline stated
Hong et al. (2008)	Valve	7 days	Nil	1	MMSE, TMT A, Grooved Pegboard	No	**TI**: MMSE ↔, TMT A↓, Grooved Pegboard↓	**TI**: 23 %↓
Sweet et al. (2008)	On-pump CABG PCI	3 weeks	4 months, 12 months	5,7	Digit span; GP; digit symbol; TMT A; Stroop color-word test; COWAT; visual naming of the multilingual aphasia examination (MAE); TMT B; HVLT-R	Yes	No clear pattern of change found	**TI**: ↔ **T2**: ↔ T3: ↔
Slater et al. (2009)	On-pump CABG	1 week	3 months	2	MMSE; TMT A; TMT B; HVLT; GP; Stroop color and word test; saccadic/antisaccadic eye movement; hospital anxiety and depression scale (HADS)	Yes	No individual test scores given	**TI**: 60 %↓ **T2**: 29 %↓
Kozora et al. (2010)	On-pump CABG off-pump CABG	12 months	Nil	2	Logical memory and faces subtest from Wechsler Memory Scale; digit span; digit symbol; TMT A; TMT B; clock drawing; BDI	No	No individual test scores given	**TI**: 12 % in-pump and 13.2 % off-pump decline; 37.9 % on-pump and 41.6 % off-pump improve

(*continued*)

Table 1 (continued)

Study	Surgery type	Time point 1	Time point 2	Definition of decline	Psychological assessment measures	Core battery used[b]	Decline in individual NP tests	Overall prevalence of cognitive impairment (%)
Anastasiadis et al. (2011)	On-pump CABG	1 week	3 months	3	Judgment of Line Orientation Test; Stroop color-word test; Symbol Digit Modalities Test; digit span – forward; digit span –backward; Fuld Object Memory Evaluation; Positive and Negative Affect Schedule; Spielberger State-Trait Anxiety Inventory; Geriatric Depression Scale	Yes	No significant changes reported (reported as % change instead)	**T1**: 53 %↓ **T2**: 41 %↓
Maekawa et al. (2011)	On-pump CABG off-pump CABG valve combined	1 week	Nil	3	Hasegawa dementia scale; digit span; digit symbol; Kana Pick-out Test	No	No individual test scores given	**T1**: off-pump CABG 18 %↓; on-pump CABG 23 %↓; CABG/ Valve 11 %↓; valve 48 %↓

Hudetz et al. (2011)	On-pump CABG valve combined	1 week	Nil	5	Memory and work list memory from Repeatable Battery for the Assessment of Neuropsychological status, brief visual memory test revised, backward digit span, semantic memory, phonemic memory, geriatric depression scale	No	No individual test scores given	**TI**: 50 %↓
Djaiani et al. (2012)	On-pump CABG	12 months	Nil	5	RAVLT; Rey visual design learning test; TMT A&B; GP; forward digit span; backward digit span; spatial span forward; spatial span backward; choice and simple reaction time tests; verbal fluency test	No	Significant decline on; Rey visual design learning test↓; GP↓; verbal fluency test↓	**TI**: 17.4 %↓
Meybohm et al. (2013)	On-pump CABG valve combined	5–7 days	Nil	1,5	Core battery of ten tests including the following four main domains: memory, motor skills, attention, and executive function (no test names given)	Yes	Summary statistics given for SD method and no individual test differences were shown using z-score measure	**TI**: SD method, 52 %↓ and 23 %↑; z-score ↔ **T2**: SD method, 21 %↓ and 36 %↑; z-score ↔

[a]Definitions of decline: see section "Statistical Approaches for Defining Postoperative Cognitive Change"
[b]Core battery-based consensus statement from Murkin et al. (1995) paper

References

Abildstrom, H., Hogh, P., Sperling, B., Moller, J. T., Yndgaard, S., & Rasmussen, L. S. (2002). Cerebral blood flow and cognitive dysfunction after coronary surgery. *The Annals of Thoracic Surgery, 73*(4), 1174–1178. discussion 1178–1179.

Ahlgren, E., Lundqvist, A., Nordlund, A., Aren, C., & Rutberg, H. (2003). Neurocognitive impairment and driving performance after coronary artery bypass surgery. *European Journal of Cardio-Thoracic Surgery, 23*(3), 334–340.

Anastasiadis, K., Argiriadou, H., Kosmidis, M. H., Megari, K., Antonitsis, P., Thomaidou, E., . . . Papakonstantinou, C. (2011). Neurocognitive outcome after coronary artery bypass surgery using minimal versus conventional extracorporeal circulation: A randomised controlled pilot study. *Heart, 97*(13), 1082–1088. doi: 10.1136/hrt.2010.218610.

Andersson, S., Lövdahl, H., & Malt, U. F. (2010). Neuropsychological function in unmedicated recurrent brief depression. *Journal of Affective Disorders, 125*, 155–164.

Andrew, M. J., Baker, R. A., Kneebone, A. C., & Knight, J. L. (1998). Neuropsychological dysfunction after minimally invasive direct coronary artery bypass grafting. *Annals of Thoracic Surgery, 66*(5), 1611–1617.

Andrew, M. J., Baker, R. A., Kneebone, A. C., & Knight, J. L. (2000). Mood state as a predictor of neuropsychological deficits following cardiac surgery. *Journal of Psychosomatic Research, 48*, 537–546.

Andrew, M. J., Baker, R. A., Bennetts, J., Kneebone, A. C., & Knight, J. L. (2001). A comparison of neuropsychologic deficits after extracardiac and intracardiac surgery [see comment]. *Journal of Cardiothoracic & Vascular Anesthesia, 15*(1), 9–14.

Arrowsmith, J. E., Grocott, H. P., Reves, J. G., & Newman, M. F. (2000). Central nervous system complications of cardiac surgery. *British Journal of Anaesthesia, 84*(3), 378–393.

Askar, F. Z., Cetin, H. Y., Kumral, E., Cetin, O., Acarer, A., Kosova, B., & Yagdi, T. (2005). Apolipoprotein E4 allele and neurobehavioral status after on-pump coronary artery bypass grafting. *Journal of Cardiac Surgery, 20*, 501–505.

Baker, R. A., Andrew, M. J., Ross, I. K., & Knight, J. L. (2001). The octopus II stabilizing system: Biochemical and neuropsychological outcomes in coronary artery bypass surgery. *The Heart Surgery Forum, 1*(4 Suppl 1), S19–S23.

Bankier, B., Januzzi, J. L., & Littman, A. B. (2004). The high prevalence of multiple psychiatric disorders in stable outpatients with coronary heart disease. *Psychosomatic Medicine, 66*, 645–650.

Basile, A. M., Fusi, C., Conti, A. A., Paniccia, R., Trefoloni, G., Pracucci, G., . . . Inzitari, D. (2001). S-100 protein and neuron-specific enolase as markers of subclinical cerebral damage after cardiac surgery: Preliminary observation of a 6-month follow-up study. *European Neurology, 45*, 151–159.

Ben-Nathan, D., Kobiler, D., Rzotkiewicz, S., Lustig, S., & Katz, Y. (2000). CNS penetration by noninvasive viruses following inhalation anesthetics. *Annals of the New York Academy of Sciences, 917*(1), 944–950.

Bishop, N. A., Lu, T., & Yankner, B. A. (2010). Neural mechanisms of ageing and cognitive decline. *Nature, 464*(7288), 529–535.

Blauth, C. I., Smith, P. L., Arnold, J. V., Jagoe, J. R., & Wootton, R. (1990). Influence of oxygenator type on the prevalence and extent of microemboli retinal ischemia during cardiopulmonary bypass: Assessment by digital image analysis. *The Journal of Thoracic and Cardiovascular Surgery, 99*, 61–69.

Boodhwani, M., Rubens, F. D., Wozny, D., Rodriguez, R., Alsefaou, A., Hendry, P. J., & Nathan, H. J. (2006). Predictors of early neurocognitive deficits in low-risk patients undergoing on-pump coronary artery bypass surgery. *Circulation, 114*(1 Suppl), I461–I466. doi:10.1161/CIRCULATIONAHA.105.001354.

Braekken, S. K., Reivang, I., Russell, D., Brucher, R., & Svennevig, J. L. (1998). Association between intraoperative cerebral microembolic signals and postoperative neuropsychological

deficit: Comparison between patients with cardiac valve replacement and patients with coronary artery bypass grafting. *Journal of Neurology, Neurosurgery, and Psychiatry, 63*, 573–576.

Browne, S. M., Halligan, P. W., Wade, D. T., & Taggart, D. P. (2003). Postoperative hypoxia is a contributory factor to cognitive impairment after cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery, 126*, 1061–1064.

Bruce, D. L., & Bach, M. J. (1976). Effects of trace anaesthetic gases on behavioural performance of volunteers. *British Journal of Anaesthesia, 48*(9), 871–876.

Bruce, K. M., Smith, J. A., Yelland, G. W., & Robinson, S. R. (2008). The impact of cardiac surgery on cognition. *Stress and Health, 24*, 249–266.

Bruce, K. M., Yelland, G. W., Smith, J. A., & Robinson, S. R. (2013a). Recovery of cognitive function after coronary artery bypass graft operations. *Annals of Thoracic Surgery, 95*, 1306–1313. in press.

Bruce, K. M., Yelland, G. W., Smith, J. A., & Robinson, S. R. (2013b). The reliable change index for assessment of cognitive dysfunction after coronary artery bypass graft surgery. Reply to the editor. *Annals of Thoracic Surgery, 96*, 1529–1530.

Bruce, K. M., Yelland, G. W., Almeida, A. A., Smith, J. A., & Robinson, S. R. (2014). Effects on cognition of conventional and robotically assisted cardiac valve operation. *The Annals of Thoracic Surgery, 97*(1), 48–55. doi:10.1016/j.athoracsur.2013.07.018.

Butcher, J. N., Perry, J. N., & Atlis, M. M. (2000). Validity and utility of computer-based test interpretation. *Psychological Assessment, 12*(1), 6–18.

Cargin, J. W., Maruff, P., Collie, A., & Masters, C. (2006). Mild impairment in healthy older adults is distinct from normal aging. *Brain and Cognition, 60*, 146–155.

Carrascal, Y., Casquero, E., Gualis, J., Di Stefano, S., Florez, S., Fulquet, E., . . . Fiz, L. (2005). Cognitive decline after cardiac surgery: Proposal for easy measurement with a new test. *Interactive CardioVascular and Thoracic Surgery, 4*(3), 216–221. doi: 10.1510/icvts.2004.092528.

Cicekcioglu, F., Ozen, A., Tuluce, H., Tutun, U., Parlar, A.I., Kervan, U., . . . Katircioglu, S. F. (2008). Neurocognitive functions after beating heart mitral valve reaplcement without cross-clamping the aorta. *Journal of Cardiac Surgery, 23*, 114–119.

Collie, A., Maruff, P., Darby, D. G., & McStephen, M. (2003). The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. *Journal of the International Neuropsychological Society, 9*(3), 419–428.

Cook, D. J., Huston, J., III, Trenerry, M. R., Brown, R. D., Zehr, K. J., & Sundt, T. M., III. (2007). Postcardiac surgical cognitive impairment in the aged using diffusion-weighted magnetic resonance imaging. *The Annals of Thoracic Surgery, 83*, 1389–1395.

Correale, J., & Villa, A. (2009). Cellular elements of the blood-brain barrier. *Neurochemical Research, 34*(12), 2067–2077. doi:10.1007/s11064-009-0081-y.

Daliento, L., Mapelli, D., & Volpe, B. (2006). Measurement of cognitive outcome and quality of life in congenital heart disease. *Heart, 92*, 569–574.

Di Carlo, A., Perna, A. M., Pantoni, L., Basile, A. M., Bonacchi, M., Pracucci, G., . . . Inzitari, D. (2001). Clinically relevant cognitive impairment after cardiac surgery: A 6-month follow-up study. *Journal of the Neurological Sciences, 188*(1–2), 85–93.

Dick, B. D., & Rashiq, S. (2007). Disruption of attention and working memory traces in individuals with chronic pain. *Anesthesia and Analgesia, 104*(5), 1223–1229.

Diegeler, A., Hirsch, R., Schneider, F., Schilling, L. O., Falk, V., Rauch, T., & Mohr, F. W. (2000). Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. *Annals of Thoracic Surgery, 69*, 1162–1166.

Djaiani, G., Katznelson, R., Fedorko, L., Rao, V., Green, R., Carroll, J., & Karski, J. (2012). Early benefit of preserved cognitive function is not sustained at one-year after cardiac surgery: A longitudinal follow-up of the randomized controlled trial. *Canadian Journal of Anesthesia, 59*, 449–455.

Dos Santos, E. B., Tudesco, I. S., Caboclo, L. O., & Yacubian, E. M. (2011). Low educational level effects on the performance of healthy adults on a neuropsychological protocol suggested by the commission on neuropsychology of the liga brasileira de epilepsia.

Dupuis, G., Kennedy, E., Lindquist, R., Barton, F. B., Terrin, M. L., Hoogwerf, B. J., . . . Post, Cabg Biobehavioral Study Investigators. (2006). Coronary artery bypass graft surgery and cognitive performance. *American Journal of Critical Care, 15*(5), 471–478; quiz 479.

Ebert, A. D., Walzer, T. A., Huth, C., & Herrmann, M. (2001). Early neurobehavioral disorders after cardiac surgery: A comparative analysis of coronary artery bypass graft surgery and valve replacement. *Journal of Cardiothoracic and Vascular Anesthesia, 15*(1), 15–19.

Ernest, C. S., Worcester, M. U., Tatoulis, J., Elliot, P. C., Murphy, B. M., Higgins, R. O., . . . Goble, A. J. (2006). Neurocognitive outcomes in off-pump versus on-pump bypass surgery: A randomized controlled trial. *The Annals of Thoracic Surgery, 81*, 2105–2114.

Farag, E., Chelune, G. J., Schubert, A., & Mascha, E. J. (2006). Is depth of anesthesia, as assessed by the bispectral index, related to postoperative cognitive dysfunction and recovery? *Anesthesia and Analgesia, 103*, 633–640.

Farhoudi, M., Mehrvar, K., Afrasiabi, A., Parvizi, R., Khalili, A. A., Nasiri, B., . . . Ghabili, K. (2010). Neurocognitive impairment after off-pump and on-pump coronary artery bypass graft surgery – An Iranian experience. *Neuropsychiatric Disease and Treatment, 6*, 775–778. doi: 10.2147/NDT.S14348.

Freiheit, E. A., Hogan, D. B., Eliasziw, M., Patten, S. B., Demchuk, A. M., Faris, P., . . . Maxwell, C. J. (2012). A dynamic view of depressive symptoms and neurocognitive change among patients with coronary artery disease. *Archives of General Psychiatry, 69*(3), 244–255.

Gallo, L. C., Malek, M. J., Gilbertson, A. D., & Moore, J. L. (2005). Perceived cognitive function and emotional distress following coronary artery bypass surgery. *Journal of Behavioral Medicine, 28*(5), 433–442.

Grigore, A. M., Mathew, J., Grocott, H. P., Reves, J. G., Blumenthal, J. A., White, W. D., . . . Endeavors, Care Investigators of the Duke Heart Center. Cardiothoracic Anesthesia Research. (2001). Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery. *Anesthesiology, 95*(5), 1110–1119.

Grimm, M., Zimpfer, D., Czerny, M., Kilo, J., Kasimir, M.T., Kramer, L., . . . Wolner, E. (2003). Neurocognitive deficit following mitral valve surgery. *European Journal Cardio-Thoracic Surgery*, *23*(3), 265–271.

Hammon, J. W., Stump, D. A., Butterworth, J.F., Moody, D.M., Rorie, K., Deal, D.D., . . . Kon, N.D. (2006). Single crossclamp improves 6-month cognitive outcome in high-risk coronary bypass patients: The effect of reduced aortic manipulation. *The Journal of Thoracic and Cardiovascular Surgery, 131*, 114–121.

Hammon, J. W, Stump, D. A., Butterworth, J.F., Moody, D.M., Rorie, K., Deal, D.D., . . . Kon, N.D. (2007). Coronary artery bypass grafting with single cross-clamp results in fewer persistent neuropsychological deficits than multiple clamp or off-pump coronary artery bypass grafting. *The Annals of Thoracic Surgery, 84*, 1174–1179.

Hernandez, F., Jr., Brown, J. R., Likosky, D. S., Clough, R. A., Hess, A. L., Roth, R. M., . . . Klemperer, J. D. (2007). Neurocognitive outcomes of off-pump versus on-pump coronary artery bypass: A prospective randomized controlled trial. *The Annals of Thoracic Surgery, 84*(6), 1897–1903. doi: 10.1016/j.athoracsur.2007.07.036.

Ho, P. M., Arciniegas, D. B., Grigsby, J., McCarthy, M., Jr., McDonald, G. O., Moritz, T. E., . . . Hammermeister, K. E. (2004). Predictors of cognitive decline following coronary artery bypass graft surgery. *Annals of Thoracic Surgery, 77*(2), 597–603; discussion 603.

Hogue, C. W., Lillie, R., Hershey, T., Birge, S., Nassief, A. M., Thomas, B., & Freedland, K. E. (2003). Gender influence on cognitive function after cardiac operation. *Annals of Thoracic Surgery, 76*(4), 1119–1125.

Hong, S. W., Shim, J. K., Choi, Y. S., Kim, D. H., Chang, B. C., & Kwak, Y. L. (2008). Prediction of cognitive dysfunction and patients' outcome following valvular heart surgery and the role of cerebral oximetry. *European Journal of Cardio-Thoracic Surgery, 33*(4), 560–565. doi:10.1016/j.ejcts.2008.01.012.

Hoth, K. F., Poppas, A., Moser, D. J., Paul, R. H., & Cohen, R. A. (2008). Cardiac dysfunction and cognition in older adults with heart failure. *Cognitive and Behavioral Neurology, 21*(2), 65–72. doi:10.1097/WNN.0b013e3181799dc8.

Hudetz, J. A., Iqbal, Z., Gandhi, S. D., Patterson, K. M., Byrne, A. J., & Pagel, P. S. (2011). Postoperative delirium and short-term cognitive dysfunction occur more frequently in patients undergoing valve surgery with or without coronary artery bypass graft surgery compared with coronary artery bypass graft surgery alone: Results of a pilot study. *Journal of Cardiothoracic and Vascular Anesthesia, 25*(5), 811–816. doi:10.1053/j.jvca.2010.05.003.

Ille, R., Lahousen, T., Schweiger, S., Hofmann, P., & Kapfhammer, H. P. (2007). Influence of patient-related and surgery-related risk factors on cognitive performance, emotional state, and convalescence after cardiac surgery. *Cardiovascular Revascularization Medicine, 8*(3), 166–169. doi:10.1016/j.carrev.2006.12.001.

Istaphanous, G. K., Ward, C. G., & Loepke, A. W. (2010). The impact of the perioperative period of neurocognitive development, with a focus on pharmacological concerns. *Best Pratice & Research Clinical Anaesthesiology, 24*, 433–449.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting & Clinical Psychology, 59*(1), 12–19 [see comment].

Jensen, B. O., Hughes, P., Rasmussen, L. S., Pederson, P. U., & Steinbruchel, D. A. (2006). Cognitive outcomes in elderly high-risk patients after off-pump versus conventional coronary artery bypass grafting: A randomized trial. *Circulation, 113*, 2790–2795.

Kadoi, Y., Saito, S., Fujita, N., & Goto, F. (2005). Risk factors for cognitive dysfunction after coronary artery bypass graft surgery in patients with type 2 diabetes. *The Journal of Thoracic and Cardiovascular Surgery, 129*(3), 576–583. doi:10.1016/j.jtcvs.2004.07.012.

Kanbak, M., Saricaoglu, F., Avci, A., Ocal, T., Koray, Z., & Aypar, U. (2004). Propofol offers no advantage over isoflurane anesthesia for cerebral protection during cardiopulmonary bypass: A preliminary study of S-100beta protein levels. *Canadian Journal of Anaesthesia, 51*(7), 712–717.

Kapetanakis, E. I., Stamou, S. C., Dullum, M. K., Hill, P. C., Haile, E., Boyce, S. W., . . . Corso, P. J. (2004). The impact of aortic manipulation on neurologic outcomes after coronary artery bypass surgery: A risk-adjusted study. *The Annals of Thoracic Surgery, 78*, 1564–1571.

Karp, J. F., Reynolds, C. F., Butters, M. A., Dew, M. A., Mazumdar, S., Begley, A. E., . . . Weiner, D. K. (2006). The relationship between pain and mental flexibility in older adult pain clinic patients. *Pain Medicine, 7*(5), 444–452.

Keith, J. R., Puente, A. E., Malcolmson, K. L., Tartt, S., & Coleman, A. E. (2002). Assessing postoperative cognitive change after cardiopulmonary bypass surgery. *Neuropsychology, 16*(3), 411–421.

Keizer, A. M. A., Hijman, R., Kalkman, C. J., Kahn, R. S., & van Dijk, D. (2005). The incidence of cognitive decline after (not) undergoing coronary artery bypass grafting: The impact of a controlled definition. *Acta Anaesthesiol Scand, 49*, 1232–1235.

Kidher, E., Harling, L., Sugden, C., Ashrafian, H., Casula, R., Evans, P., . . . Athanasiou, T. (2014). Aortic stiffness is an indicator of cognitive dysfunction before and after aortic valve replacement for aortic stenosis. *Interactive CardioVascular and Thoracic Surgery*, 1–10. doi: 10.1093/icvts/ivu194.

Kilo, J., Czerny, M., Gorlitzer, M., Zimpfer, D., Baumer, H., Wolner, E., & Grimm, M. (2001). Cardiopulmonary bypass affects cognitive brain function after coronary artery bypass grafting. *Annals of Thoracic Surgery, 72*, 1926–1932.

Kneebone, A. C., Andrew, M. J., Baker, R. A., & Knight, J. L. (1998). Neuropsychologic changes after coronary artery bypass grafting: Use of reliable change indices. *Annals of Thoracic Surgery, 65*(5), 1320–1325 [see comment].

Kneebone, A. C., Luszcz, M. A., Baker, R. A., & Knight, J. L. (2005). A syndromal analysis of neuropsychological outcome following coronary artery bypass graft surgery. *Journal of Neurology, Neurosurgery, and Psychiatry, 76*, 1121–1127.

Knipp, S. C., Matatko, N., Schlamann, M., Wilhelm, H., Thielman, M., Forsting, M., . . . Jakob, H. (2005). Small ischemic brain lesions after cardiac valve replacement detected by diffusion-weighted magnetic resonance imaging: Relation to neurocognitive function. *European Journal of Cardio-thoracic Surgery, 28*(1), 88–96. doi: 10.1016/j.ejcts.2005.02.043

Koivula, M., Tarkka, M., Tarkka, M., Laippala, P., & Paunonen-Ilmonen, M. (2002). Fear and anxiety in patients at different time-points in the coronary artery bypass process. *International Journal of Nursing Studies, 39*, 811–822.

Kozora, E., Kongs, S., Collins, J. F., Hattler, B., Baltz, J., Hampton, M., . . . Shroyer, A. L. (2010). Cognitive outcomes after on- versus off-pump coronary artery bypass surgery. *Annals of Thoracic Surgery, 90*, 1134–1141.

Lamarche, D., Taddeo, R., & Pepler, C. (1998). The preparation of patients for cardiac surgery. *Clinical Nursing Research, 7*(4), 390–405.

Lee, J. D., Lee, S. J., Tsushima, W. T., Yamauchi, H., Lau, W. T., Popper, J., . . . Dang, C. R. (2003). Benefits of off-pump bypass on neurologic and clinical morbidity: A prospective randomized trial. *Annals of Thoracic Surgery, 76*(1), 18–25; discussion 25–16.

Lewis, M., Maruff, P., & Silbert, B. (2004). Statistical and conceptual issues in defining post-operative cognitive dysfunction. *Neuroscience and Biobehavioral Reviews, 28*, 433–440.

Lewis, M., Maruff, P., Silbert, B., Evered, L., & Scott, D. (2006). Detection of postoperative cognitive decline after coronary artery bypass graft surgery is affected by the number of neuropsychological tests in the assessment battery. *The Annals of Thoracic Surgery, 81*, 2097–2104.

Li, S., Lindenberger, U., & Sikström, S. (2001). Aging cognition: From neuromodulation to representation. *TRENDS in Cognitive Sciences, 5*(11), 479–486.

Likosky, D. S., Nugent, W. C., & Ross, C. S. (2005). Improving outcomes of cardiac surgery through cooperative efforts: The northern New England experience. *Seminars in Cardiothoracic and Vascular Anesthesia, 9*(2), 119–121.

Lombard, F. W., & Mathew, J. P. (2010). Neurocognitive dysfunction following cardiac surgery. *Seminars in Cardiothoracic and Vascular Anesthesia, 14*(2), 102–110. doi:10.1177/1089253210371519.

Lund, C., Hol, P. K., Lundblad, R., Fosse, E., Sundet, K., Tennoe, B., . . . Russell, D. (2003). Comparison of cerebral embolization during off-pump and on-pump coronary artery bypass surgery. *Annals of Thoracic Surgery, 76*(3), 765–770; discussion 770.

Lund, C., Sundet, K., TennØe, M. D., Hol, P. K., Rein, K. A., Fosse, E., & Russell, D. (2005). Cerebral ischemic injury and cognitive impairment after off-pump and on-pump coronary artery bypass grafting surgery. *Annals of Thoracic Surgery, 80*, 2126–2131.

Maekawa, K., Goto, T., Baba, T., Yoshitake, A., Katahira, K., & Yamamoto, T. (2011). Impaired cognition preceding cardiac surgery is related to cerebral ischemic lesions. *Journal of Anesthesia, 25*, 330–336.

Mathew, J. P., Mackensen, G. B., Phillips-Bute, B., Stafford-Smith, M., Podgoreanu, M. V., Grocott, H. P., . . . Neurologic Outcome Research Group of the Duke Heart, Center. (2007). Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. *Anesthesiology, 107*(4), 577–584. doi: 10.1097/01.anes.0000281896.07256.71.

McDaniel, M. A., & Einstein, G. O. (2011). The neuropsychology of prospective memory in normal aging: A componential approach. *Neurospsychologica, 49*, 2147–2155.

McKenzie, L. H., Simpson, J., & Stewart, M. (2010). A systematic review of pre-operative predictors of post-operative depression and anxiety in individuals who have undergone coronary artery bypass graft surgery. *Psychology, Health & Medicine, 15*(1), 74–93.

McKhann, G. M., Grega, M. A., Borowicz, L. M., Bailey, M. M., Barry, S. J. E., Zeger, S. L., . . . Selnes, O. A. (2005). Is there cognitive decline 1 year after CABG? *Neurology, 65*, 991–999.

Meng, X., & D'Arcy, C. (2012). Education and dementia in the context of the cognitive reserve hypothesis: A systematic review with meta-analyses and qualitative analyses. *PloS One, 7*(6), e38268. doi:10.1371/journal.pone.0038268.

Meybohm, P., Jochen, R., Broch, O., Caliebe, D., Albrecht, M., Cremer, J., . . . Bein, B. (2013). Postoperative neurocognitive dysfunction in patients undergoing cardiac surgery after remote ischemic preconditioning: A double-blind randomized controlled pilot study. *PLoS ONE, 8*(5), e64743.

Millar, K., Asbury, A. J., & Murray, G. D. (2001). Pre-existing cognitive impairment as a factor influencing outcome after cardiac surgery. *British Journal of Anaesthesia, 86*(1), 63–67 [see comment].

Minagar, A., Shapshak, P., Fujimura, R., Ownby, R., Heyes, M., & Eisdorfer, C. (2002). The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. *Journal of Neurological Sciences, 202*(1), 13–23.

Moller, J. T., Cluitmans, P., Rasmussen, L. S., Houx, P., Rasmussen, H., Canet, J, . . . Gravenstein, J.S. (1998). Long-term postoperative cognitive dysfunction in the elderley ISPOCD1 study. *Lancet, 351*, 857–861.

Motallebzadeh, R., Bland, M. B., Markus, H. S., Kaski, J. C., & Jahangiri, M. (2007). Neurocognitive function and cerebral emboli: Randomized study of on-pump versus off-pump coronary artery bypass surgery. *The Annals of Thoracic Surgery, 83*, 475–482.

Murkin, J. M., Newman, S. P., Stump, D. A., & Blumenthal, J. A. (1995). Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. *Annals of Thoracic Surgery, 59*(5), 1289–1295.

Nathan, H. J., Rodriguez, R., Wozny, D., Dupuis, J. Y., Rubens, F. D., Bryson, G. L., & Wells, G. (2007). Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: Five-year follow-up of a randomized trial. *The Journal of Thoracic and Cardiovascular Surgery, 133*(5), 1206–1211. doi:10.1016/j.jtcvs.2006.09.112.

Newman, M. F., Kirchner, J. L., Phillips-Bute, B., Gaver, V., Grocott, H., Jones, R. H., . . . Blumenthal, J. A. (2001). Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *The New England Journal of Medicine, 344*(6), 395–402.

Newman, M., Mathew, J. P., Grocott, H., Mackensen, G., Monk, T., Welsh-Bohmer, K., . . . Mark, D. B. (2006). Central nervous system injury associated with cardiac surgery. *The Lancet, 368*, 694–703.

Ngaage, D. L. (2003). Off-pump coronary artery bypass grafting: The myth, the logic and the science. *European Journal of Cardio-Thoracic Surgery, 24*, 557–570.

Nussmeier, N. A. (1996). Adverse neurologic events: Risks of intracardiac versus extracardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia, 10*(1), 31–37.

O'Brien, D. J., Bauer, R. M., Yarandi, H., Knauf, D. G., Bramblett, P., & Alexander, J. A. (1992). Patient memory before and after cardiac operations. *Journal of Thoracic & Cardiovascular Surgery, 104*, 1116–1124.

Papaioannou, A., Fraidakis, O., Michaloudis, D., Balalis, C., & Askitopoulou, H. (2005). The impact of the type of anaesthesia on cognitive status and delirium during the first postoperative days in elderly patients. *European Journal of Anaesthesiology, 22*, 492–499.

Peavy, G. M., Salmon, D. P., Jacobson, M. W., Hervey, A., Gamst, A. C., Wolfson, T., . . . Galasko, D. (2009). Effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. *American Journal of Psychiatry, 166*(12), 1384–1391. doi: 10.1176/appi.ajp.2009.09040461.

Pignay-Demaria, V., Lespérance, F., Demaria, R. G., Frasure-Smith, N., & Perrault, L. P. (2003). Depression and anxiety and outcomes of coronary artery bypass surgery. *Annals of Thoracic Surgery, 75*(1), 314–321.

Puskas, F., Grocott, H. P., White, W. D., Mathew, J. P., Newman, M. F., & Bar-Yosef, S. (2007). Intraoperative hyperglycemia and cognitive decline after CABG. *The Annals of Thoracic Surgery, 84*(5), 1467–1473. doi:10.1016/j.athoracsur.2007.06.023.

Rankin, K. P., Kochamba, G. S., Boone, K. B., Petitti, D. B., & Buckwalter, J. G. (2003). Presurgical cognitive deficits in patients receiving coronary artery bypass graft surgery. *Journal of the International Neuropsychological Society, 9*(6), 913–924.

Rasmussen, L. S., Christiansen, M., Eliasen, K., Sander-Jensen, K., & Moller, J. T. (2002). Biochemical markers for brain damage after cardiac surgery – Time profile and correlation with cognitive dysfunction. *Acta Anaesthesiologica Scandinavica, 46*, 547–551.

Rasmussen, L. S., Johnson, T., Kuipers, H.M., Kristensen, D., Siersma, V. D., Vila, P., . . . Moller, J. T. (2003). Does anaesthesia cause postoperative cognitive dysfunction? A randomized study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiologica Scandinavica, 2003*, 260–266.

Rasmussen, L. S., Siersma, V. D., & Ispocd, Group. (2004). Postoperative cognitive dysfunction: True deterioration versus random variation. *Acta Anaesthesiologica Scandinavica, 48*, 1137–1143.

Raymond, P. D., Hinton-Bayre, A. D., Radel, M., Ray, M. J., & Marsh, N. A. (2006). Assessment of statistical change criteria used to define significant change in neuropsychological test performance following cardiac surgery. *European Journal of Cardio-Thoracic Surgery, 29*, 82–88.

Raymond, P. D., Radel, M., Ray, M. J., Hinton-Bayre, A. D., & Marsh, N. A. (2007). Investigation of factors relating to neuropsychological change following cardiac surgery. *Perfusion, 22*(1), 27–33.

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. *The Journal of Neuroscience, 23*(8), 3295–3301.

Roach, G. W., Kanchuger, M., Mangano, C. M., Newman, M., Nussmeier, N., Wolman, R., . . . Ley, C. (1996). Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators.[see comment]. *New England Journal of Medicine., 335*(25), 1857–1863.

Ropacki, S. A., Bert, A. A., Ropacki, M. T., Rogers, B. L., & Stern, R. A. (2007). The influence of cognitive reserve on neuropsychological functioning following coronary artery bypass grafting (CABG). *Archives of Clinical Neuropsychology, 22*(1), 73–85. doi:10.1016/j.acn.2006.11.001.

Rosengart, T. K., Sweet, J. J., Finnin, E., Wolfe, P, Cashy, J., Hahn, E., . . . Sanborn, T. (2006). Stable cognition after coronary artery bypass grafting: Comparisons with percutaneous intervention and normal controls. *The Annals of Thoracic Surgery, 82*, 597–607.

Rothenhausler, H. B., Grieser, B., Nollert, G., Reichart, B., Schelling, G., & Kapfhammer, H. P. (2005). Psychiatric and psychosocial outcome of cardiac surgery with cardiopulmonary bypass: A prospective 12-month follow-up study. *General Hospital Psychiatry, 27*(1), 18–28. doi:10.1016/j.genhosppsych.2004.09.001.

Rubens, F. D., Boodhwani, M., Mesana, T., Wozny, D., Wells, G., Nathan, H. J., & Investigators Cardiotomy. (2007). The cardiotomy trial: A randomized, double-blind study to assess the effect of processing of shed blood during cardiopulmonary bypass on transfusion and neurocognitive function. *Circulation, 116*(11 Suppl), I89–I97. doi:10.1161/CIRCULATIONAHA.106.678987.

Rudolph, J. L., Schreiber, K. A., Culley, D. J., McGlinchey, R. E., Crosby, G., Levitsky, S., & Marcantonio, E. R. (2010). Measurement of post-operative cognitive dysfunction after cardiac surgery: A systematic review. *Acta Anaesthesiologica Scandinavica, 54*(6), 663–677. doi:10.1111/j.1399-6576.2010.02236.x.

Sachdev, P. S., & Valenzuela, M. (2009). Brain and cognitive reserve. *The American Journal of Geriatric Psychiatry, 17*(3), 175–178.

Sandi, C., & Pinelo-Nava, M. T. (2007). Stress and memory: Behavioral effects and neurobiological mechanisms. *Neural Plasticity, 2007*, 78970. doi:10.1155/2007/78970.

Satz, P., Cole, M. A., Hardy, D. J., & Rassovsky, Y. (2011). Brain and cognitive reserve: Mediator (s) and construct validity, a critique. *Journal of Clinical and Experimental Neuropsychology, 33* (1), 121–130. doi:10.1080/13803395.2010.493151.

Schlegel, R. E., & Gilliland, K. (2007). Development and quality assurance of computer-based assessment batteries. *Archives of Clinical Neuropsychology, 22S*, S49–S61. doi:10.1016/j.acn.2006.10.005.

Selnes, O. A. (2013). Recovery of cognitive function after coronary artery bypass graft operations. Invited commentary. *Annals of Thoracic Surgery, 95*, 1313–1314.

Selnes, O. A., Royall, R. M., Grega, M. A., Borowicz, L. M., Quaskey, S., & McKhann, G. M. (2001). Cognitive Changes 5 Years After Coronary Artery Bypass Grafting: Is There Evidence of Late Decline? *Archives of Neurology.* 58(4):598-604. doi:10.1001/archneur.58.4.598.

Selnes, O. A., & Zeger, S. L. (2007). Coronary artery bypass grafting baseline cognitive assessment: Essential not optional. *Annals of Thoracic Surgery, 73*, 374–376.

Selnes, O. A., Goldsborough, M. A., Borowicz, L. M., Enger, C., Quaskey, S. A., & McKhann, G. M. (1999). Determinants of cognitive change after coronary artery bypass surgery: A multifactorial problem. *Annals of Thoracic Surgery, 67*(6), 1669–1676.

Selnes, O. A., Grega, M. A., Borowicz, L. M., Jr., Royall, R. M., McKhann, G. M., & Baumgartner, W. A. (2003). Cognitive changes with coronary artery disease: A prospective study of coronary artery bypass graft patients and nonsurgical controls. *The Annals of Thoracic Surgery, 75*(5), 1377–1384.

Selnes, O. A., Grega, M. A., Borowicz, L. M., Jr., Barry, S., Zeger, S., Baumgartner, W. A., & McKhann, G. M. (2005). Cognitive outcomes three years after coronary artery bypass surgery: A comparison of on-pump coronary artery bypass graft surgery and nonsurgical controls. *The Annals of Thoracic Surgery, 79*(4), 1201–1209. doi:10.1016/j.athoracsur.2004.10.011.

Selnes, O., Pham, P., Zeger, S., & McKhann, G. (2006). Defining cognitive change after CABG: Decline versus normal variability. *The Annals of Thoracic Surgery, 82*, 388–390.

Selnes, O. A., Gottesman, R. F., Grega, M. A., Baumgartner, W. A., Zeger, S. L., & McKhann, G. M. (2012). Cognitive and neurologic outcomes after coronary-artery bypass surgery. *The New England Journal of Medicine, 366*, 250–257.

Siciliani, L. (2013). *Waiting time policies in the health sector: What works?* Paris: OECD Publishing.

Silbert, B. S., Scott, D. A., Doyle, T. J., Blyth, C., Borton, M. C., O'Brien, J. L., & De L Horne, D. J. (2001). Neuropsychologic testing within 18 hours after cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia, 15*(1), 20–24 [see comment].

Silbert, B. S., Maruff, P., Evered, L. A., Scott, D. A., Kalpokas, M., Martin, K. J., . . . Myles, P. S. (2004). Detection of cognitive decline after coronary surgery: A comparison of computerized and conventional tests. *British Journal of Anaesthesia., 92*(6), 814–820.

Silbert, B., Evered, L., & Scott, D. A. (2011). Cognitive decline in the elderly: Is anaesthesia implicated? *Best Pratice & Research Clinical Anaesthesiology, 25*, 379–393.

Slater, J. P., Guarino, T., Stack, J., Vinod, K., Bustami, R. T., Brown, J. M., 3rd, . . . Parr, G. V. (2009). Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *The Annals of Thoracic Surgery, 87*(1), 36–44; discussion 44–35. doi: 10.1016/j.athoracsur.2008.08.070.

Smith, P. L. (1995). Cerebral dysfunction after cardiac surgery: Closing address. *Annals of Thoracic Surgery, 59*(5), 1359–1362.

Stahle, E., Tammelin, A., Bergstrom, R., Hambreus, A., Nystrom, S. O., & Hansson, H. E. (1997). Sternal wound complications – Incidence, microbiology and risk factors. *European Journal of Cardio-Thoracic Surgery, 11*, 1146–1153.

Steinmetz, J., Funder, K. S., Dahl, B. T., & Rasmussen, L. S. (2010). Depth of anaesthesia and postoperative cognitive dysfunction. *Acta Anaesthesiologica Scandinavica, 54*(2), 162–168. doi:10.1111/j.1399-6576.2009.02098.x.

Stroobant, N., & Vingerhoets, G. (2008). Depression, anxiety, and neuropsychological performance in coronary artery bypass graft patients: A follow-up study. *Psychosomatics, 49*(4), 326–331. doi:10.1176/appi.psy.49.4.326.

Stroobant, N., Van Nooten, G., Van Belleghem, Y., & Vingerhoets, G. (2002). Short-term and long-term neurocognitive outcome in on-pump versus off-pump CABG. *European Journal of Cardio-Thoracic Surgery, 22*(4), 559–564.

Stroobant, N., Van Nooten, G., Van Belleghem, Y., & Vingerhoets, G. (2005). Relation between neurocognitive impairment, embolic load, and cerebrovascular reactivity following on- and off-pump coronary artery bypass grafting. *Chest, 127*, 1967–1976.

Stroobant, N., Van Nooten, G., Van Belleghem, Y., & Vingerhoets, G. (2010). The effect of CABG on neurocognitive functioning. *Acta Cardiologica, 65*(5), 557–564.

Stygall, J., Newman, S. P., Fitgerald, G., Steed, L., & Mulligan, K. (2003). Cognitive change 5 years after coronary artery bypass surgery. *Health Psychology, 22*(6), 579–586.

Sutton, R. (2007). *The effects of general anaesthesia on post-surgical cognitive performance* (Honours Degree Unpublished honours thesis). Melbourne: Monash University.

Sweet, J. J., Finnin, E. F., Wolfe, P. L., Beaumont, J. L., Hahn, E., Marymont, J., . . . Rosengart, T. K. (2008). Absence of cognitive decline one year after coronary bypass surgery: Comparison to nonsurgical and healthy controls. *Annals of Thoracic Surgery, 85*, 1571–1578.

Szalma, I., Kiss, A., Kardos, L., Horvath, G., Nyitrai, E., Tordai, Z., & Csiba, L. (2006). Piracetam prevents cognitive decline in coronary artery bypass: A randomized trial versus placebo. *The Annals of Thoracic Surgery, 82*(4), 1430–1435. doi:10.1016/j.athoracsur.2006.05.005.

Tagarakis, G. I., Tsolaki-Tagaraki, F., Tsolaki, M., Diegeler, A., Tsilimingas, N. B., & Papassotiropoulos, A. (2007). The role of apolipoprotein E in cognitive decline and delirium after bypass heart operations. *American Journal of Alzheimer's Disease and Other Dementias, 22*, 223–228. doi:10.1177/1533317507299415.

Tsushima, W. T., Johnson, D. B., Lee, J. D., Matsukawa, J. M., & Fast, K. M. (2005). Depression, anxiety and neuropsychological test scores of candidates for coronary artery bypass graft surgery. *Archives of Clinical Neuropsychology, 20*(5), 667–673. doi:10.1016/j.acn.2005.04.003.

Tully, P. J., Baker, R. A., & Knight, J. L. (2008). Anxiety and depression as risk factors for mortality after coronary artery bypass surgery. *Journal of Psychosomatic Research, 64*, 285–290.

van Dijk, D., Keizer, A. M., Diephuis, J. C., Durand, C., Vos, L. J., & Hijman, R. (2000). Neurocognitive dysfunction after coronary artery bypass surgery: A systematic review. *Journal of Thoracic and Cardiovascular Surgery, 120*(4), 632–639 [see comment].

Van Dijk, D., Jansen, E. W., Hijman, R., Nierich, A. P., Diephuis, J. C., Moons, K. G., . . . Kalkman, C. J. (2002). Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: A randomized trial.[see comment]. *JAMA, 287*(11), 1405–1412.

van Dijk, D., Spoor, M., Hijman, R., Nathoe, H. M., Borst, C., Jansen, E. W., . . . Octopus Study, Group. (2007). Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA, 297*(7), 701–708. doi: 10.1001/jama.297.7.701.

van Harten, A. E., Scheeren, T. W., & Absalom, A. R. (2012). A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. *Anaesthesia, 67*(3), 280–293. doi:10.1111/j.1365-2044.2011.07008.x.

Vingerhoets, G., Van Nooten, G., Vermassen, F., De Soete, G., & Jannes, C. (1997). Short-term and long-term neuropsychological consequences of cardiac surgery with extracorporeal circulation. *European Journal of Cardio-Thoracic Surgery, 11*(3), 424–431.

Wang, Y., Sands, L. P., Vaurio, L., Mullen, E. A., & Leung, J. M. (2007). The effects of postoperative pain and its management on postoperative cognitive dysfunction. *The American Journal of Geriatric Psychiatry, 15*(1), 50–59.

Wild, K., Howieson, D., Webbe, F., Seelye, A., & Kaye, J. (2008). Status of computerized cognitive testing in aging: A systematic review. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 4*(6), 428–437. doi:10.1016/j.jalz.2008.07.003.

Wilson, C. J., Finch, E., & Cohen, H. J. (2002). Cytokines and cognition – The case for a head-to-toe inflammatory paradigm. *Journal of American Geriatrics Society, 50*(12), 2041.

Wu, X., Lu, Y., Dong, Y., Zhang, G., Zhang, Y., & Xu, Z. (2012). The inhalation anesthetic isoflurane increases levels of proinflammatory TNF-α, IL-6 and IL-1β. *Neurobiology of Aging, 33*(7), 1364–1378. doi:10.1016/j.neurobiolaging.2010.11.002.

Yin, Y., Luo, A., Guo, X., Li, L., & Huang, Y. (2007). Postoperative neuropsychological change and its underlying mechanisms in patients undergoing coronary artery bypass grafting. *Chinese Medical Journal, 120*(22), 1951–1957.

Zamvar, V., Williams, D., Hall, J., Payne, N., Cann, C., Young, K., . . . Dunne, J. (2002). Assessment of neurocognitive impairment after off-pump and on-pump techniques for coronary artery bypass graft surgery: Prospective randomised controlled trial. *BMJ, 325*(7375), 1268–1272.

Zimpfer, D., Czerny, M., Kilo, J., Kasimir, M., Madl, C., Kramer, L., . . . Grimm, M. (2002). Cognitive deficit after aortic valve replacement. *The Annals of Thoracic Surgery, 74*, 407–412.

Part III

Personality, the Social Environment, and Cardiovascular Disease

Personality and Cardiovascular Disease: Overview

George D. Bishop

Contents

Abstract

This chapter provides an overview of major attempts to relate personality in the form of stable traits to the development and progression of coronary heart disease (CHD). Among the first attempts to relate personality to CHD was the Type A behavior pattern, a complex of emotion and action tendencies including aggressive competitiveness, free-floating hostility, and time urgency. Although evidence supported the relationship of the Type A pattern to CHD, questions arose concerning the aspects of the Type A pattern that were the active ingredients. Analysis of components of the Type A pattern suggested hostility as the primary active ingredient. This has led to a large number of studies of the relationship of hostility and anger to CHD, mostly with positive results. In addition to this work, there is also a body of literature suggesting that a combination of negative affectivity and social inhibition, a pattern known as the Type D (distressed) personality, is associated with heightened CHD risk.

G.D. Bishop (✉)
Division of Social Science, Yale-NUS College, Singapore, Singapore

Department of Psychology, National University of Singapore, Singapore, Singapore
e-mail: george.bishop@yale-nus.edu.sg

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_28

Although some studies have supported this idea, a number of studies have obtained negative findings, and there are concerns about the way in which the Type D personality is conceptualized and measured. Recently, an integrative review has suggested that the personality trait of interpersonal sensitivity, a concern with negative social evaluation, is associated with CHD. This review concludes by considering possible mechanisms by which personality traits are associated with CHD.

Keywords
CHD risk • Coronary-prone personality • Type A personality • Type D personality • Hostility • Anger • Interpersonally sensitive disposition

Introduction

Attempts to relate personality in terms of enduring dispositions to coronary heart disease (CHD) go back more than half a century. Over the years a number of attempts have been made to specify which personality traits are associated with CHD and to lay out the biological processes by which this association occurs. This chapter reviews the major attempts to relate personality to CHD and will consider the potential mechanisms involved.

Type A Behavior Pattern

Among the first major attempts to relate personality to CHD derives from work by two cardiologists Friedman and Rosenman (1959, 1974) who observed that individuals at risk for CHD tended to be individuals who were highly competitive, aggressive, and hostile and had a sense of time urgency. This clinical observation became enshrined as the Type A behavior pattern. Different methods have been used to measure Type A with the most common instruments being the structured interview (SI; Chesney et al. 1980) and the Jenkins Activity Survey (Jenkins et al. 1971). The two measures appear to actually measure slightly different things, and of the two, the SI has the strongest relationship with CHD (Matthews 1988). Since chapter "► Anger, Hostility, and Cardiovascular Disease in the Context of Interpersonal Relationships" covers the Type A pattern in detail, this chapter will only mention Type A briefly as part of the historical development of research on personality and CHD.

Early evidence for the relationship of Type A to CHD came from the Western Collaborative Group Study (WCGS; Rosenman et al. 1975) and the Framingham Heart Study (Haynes et al. 1980), both prospective studies that showed a significant relationship between the Type A pattern and CHD over periods of 8–9 years. By the late 1970s, there was enough evidence that a review panel of the National Heart, Lung, and Blood Institute (Cooper et al. 1981) issued a report declaring the Type A

pattern to be a significant risk factor for CHD. This conclusion has been reinforced over the years by meta-analyses that have shown a strong relationship between Type A and CHD in a variety of both cross-sectional and prospective studies (Booth Kewley and Friedman 1987; Matthews 1988).

Despite the generally positive results for the Type A pattern, a number of questions remained including the composition of the pattern and which of its ingredients were the most responsible for its relationship to CHD. Type A started out as a clinical observation and contains several components including high achievement striving, hostility, aggressiveness, and a sense of time urgency, among others. These components are seen as forming an overall syndrome that together elevate the person's risk of developing CHD. However, it is not clear whether all of these components are equally important or whether there are some components that are more toxic than others. Initial evidence on this question came from studies of the relationship of the components of Type A to CHD. For example, Dembroski et al. (1985) found evidence for the primacy of hostility and anger as key elements of the Type A pattern. Findings such as these have led to a focus on hostility and anger as important predictors of CHD.

Hostility and Anger

The hypothesis that hostility and anger play a role in heart disease goes back at least to the nineteenth century (Smith et al. 2004). Empirical work on this topic, however, began in earnest after analyses of the key components of the Type A pattern. For example, Barefoot and his colleagues (Barefoot et al. 1983) in a 25-year follow-up of 255 physicians found a nearly fivefold difference in CHD incidence between those high and low in hostility as measured by the Cook and Medley (1954) Hostility (Ho) Scale. Numerous other studies have since been done with findings consistently showing an increased rate of CHD among those high in hostility (Smith et al. 2004).

Although hostility and anger are conceptually separate, in practice, it is often difficult to distinguish between them. Hostility is generally conceptualized in cognitive terms as being "a negative attitude towards others consisting of enmity, denigration, and ill will" (Smith 1994, p. 26). Among the measures of hostility that have been related to CHD are the Cook and Medley (1954) Ho Scale and the Interpersonal Hostility Assessment Technique (IHAT; Haney et al. 1996). Anger, by contrast, is generally defined as an affect. Specifically, anger is defined as being an unpleasant emotion that varies in intensity from mild irritation to rage. From a personality point of view, trait anger is the enduring tendency to experience frequent episodes of anger. Among the measures used to assess anger in relation to CHD is the State-Trait Anger Expression Inventory (STAXI; Spielberger et al. 1983).

Studies of the association of hostility and anger to CHD have generally supported this relationship. Although there have been studies with negative findings, a meta-analysis of studies examining the relationship of hostility to CHD

found a significant relationship that seemed to vary by the measure of hostility used (Miller et al. 1996). Since that review, a number of further studies have also found supporting evidence. For example, the Multiple Risk Factor Intervention Trial (MRFIT) found that hostility above the sample median, as measured by the IHAT, was associated with a 60 % increase in risk of cardiovascular death over a 16-year follow-up period as compared with individuals low on the IHAT (Matthews et al. 2004). Further, a study of 1,000 men over a 30-year period found that high scores on a three-item measure of trait anger were associated with a three- to sixfold increase in cardiovascular disease, CHD, and myocardial infarction, after controlling for traditional medical, demographic, and behavioral risk factors (Chang et al. 2002). For further discussion of the relationship between hostility, anger, and CHD, please see chapter "▶ Gender Differences in Psychological Risk Factors for Development of Heart Disease".

Type D Personality

More recently Denollet and colleagues (Denollet and Pederson 2011; Denollet et al. 2010) have proposed that a general propensity for psychological distress is a significant risk factor for CHD. Known as the Type D (distressed) personality, this psychological configuration includes high negative affectivity (NA) combined with high levels of social inhibition (SI). Assessment of the Type D personality is done through the Type D Scale (DS14; Denollet 2005) which contains subscales for both NA and SI. A person is considered to have a Type D personality when scoring high on both scales. In most studies such individuals are then compared with individuals scoring low on one or both scales.

Initial evidence for the association of Type D with CHD came from a prospective study of 303 coronary artery disease (CAD) patients who were assessed for Type D at baseline and then followed for 6–10 years. At follow-up, 14 % of the participants had died with those assessed as Type D being 3.8 times as likely to die as those who were non-Type D (Denollet et al. 1996). Further studies replicated this result, and a meta-analysis of studies of Type D by Denollet and his colleagues in various populations showed that individuals assessed as Type D showed a relative risk of poor prognosis of roughly three times that of non-Type D individuals (Denollet et al. 2010). Evidence was also obtained that Type D was predictive of prognosis in patients with heart failure although not all studies showed this effect (Denollet and Pederson 2011).

Denollet and Pederson (2011) estimate that the prevalence of Type D among CHD patients ranges from 20 % to 40 % with the prevalence in the general population ranging between 13 % and 27 %. In addition to poor prognosis in CHD patients, Type D has also been related to increased risk of emotional distress among cardiovascular patients including depression, anxiety, mental distress, vital exhaustion, and negative affect (Denollet and Pederson 2011). It is further argued that Type D is a distinct construct from depression with Type D being an enduring trait, whereas depression is episodic. In one study of 1,205 myocardial infarction

(MI) patients, it was noted that 17 % met the criteria for depression, and 19 % were assessed to have a Type D personality. However, only one in four of the patients showing distress had both depression and Type D (Denollet et al. 2009).

Not all studies of Type D have produced positive results, however. For example, a recent study by Meyer and colleagues (2014) did a 5-year follow-up of 465 patients who had undergone percutaneous coronary intervention (PCI). No evidence was found for an association between Type D personality and major adverse cardiovascular events (MACE). Negative results have also been obtained with cardiac patients by Grande et al. (2011). In their study 1,040 cardiac patients were followed for an average of 6 years. At follow-up there were no differences in mortality rates between patients classified as Type D and non-Type D. Also Coyne and colleagues (2011) found no prognostic value for Type D in a sample of 958 heart failure patients.

One key methodological issue concerns the way in which Type D is defined in most studies. By comparing patients high on both NA and SI with all other patients, a great deal of information is lost, and no account is taken of the independent effects of each of these variables in their association with CHD. Further, the power of statistical tests is reduced, and it is quite possible that the outcome of the study then depends on "lucky cuts" (Smith 2011). It is of interest to note that four of the studies obtaining negative results analyzed NA and SI as continuous variables (Coyne et al. 2011; Grande et al. 2011; Meyer et al. 2014; Pelle et al. 2010). This strongly argues that future studies of Type D should avoid dichotomization of NA and SI and analyze these as continuous variables.

Currently available evidence indicates that Type D, while it is a theoretically based and rigorously defined construct, may or may not be predictive of prognosis in CHD. Most of the positive evidence for the validity of Type D comes from one research group, and of late several studies have reported negative findings. As such it is too early to draw firm conclusions about the role of Type D in CHD.

Interpersonally Sensitive Disposition

Recently, Marin and Miller (2013) have proposed the interpersonally sensitive (IS) disposition as a potential risk factor for ill health including CHD. IS is defined as "a stable trait characterized by ongoing concerns about negative social evaluation" (Marin and Miller 2013, p. 942). As yet there is no psychometric instrument specifically designed to measure IS, but Marin and Miller argue that evidence for IS can be found in studies examining such concepts as rejection sensitivity, social anxiety and avoidance, social and psychological inhibition, shyness, submissiveness, introversion, and Type D. All of these constructs overlap with the general definition of IS although none of them entirely embody the concept. Marin and Miller argue that research done on the relationship of these constructs to health can be used as evidence for the role of IS in health outcomes and that IS provides a common rubric for interpreting these results. IS is further conceptualized as being broken down into a cognitive/affective component that represents vigilance for and

sensitivity to negative social evaluation and a behavioral component that entails defensive postures like submission and inhibition. These two components of IS are helpful with respect to determining if there are certain aspects of the IS construct that are particularly important in health outcomes and also as a way to potentially shed light on possible mechanisms.

Marin and Miller evaluate the evidence for the relationship of IS to health using four different health outcomes: infectious disease, CHD, cancer, and all-cause mortality. With respect to CHD, they identified 19 studies of constructs such as social anxiety, social avoidance, submissiveness, introversion, shyness, and Type D that examined relationships with CHD. Of these 15 showed positive associations with individuals higher in IS showing greater morbidity or mortality. Five prospective studies examined whether variables reflecting IS were associated with increased morbidity and mortality among initially healthy individuals. Three studies examined the association of social avoidance/anxiety to CHD outcome. Räikkönen et al. (2001) found a positive relationship between social anxiety and the development of hypertension among middle-aged women. Shen et al. (2008) reported a significant positive relationship between social anxiety and MI among older men who were originally disease free, and Berry et al. (2007) in the Western Electric Study found a significant and positive relationship between social avoidance and CHD and CVD mortality. One study examined the association between submissiveness and cardiovascular risk (Whiteman et al. 1997) finding, contrary to the prediction of the IS concept, that higher levels of submissiveness were associated with lower risk of MI. This suggests that submissiveness is a protective factor against CHD. Finally, Nakaya et al. (2005) tested the association between introversion and CVD among 29,767 residents of Miyagi Prefecture in northern Japan and found no relationship between introversion and either ischemic heart disease or stroke.

Stronger evidence is found among the 14 studies that examined the association between IS and clinical outcomes in patient populations. Most of these studies were done by Denollet and his group on the Type D personality. As noted above, there is some evidence that Type D is associated with clinical outcomes in CHD and heart failure patients although there have recently been some negative findings.

At this stage IS is best conceptualized as an integrative heuristic for organizing studies of the association of various personality characteristics to health outcomes (Smith 2013). To date there is no agreed upon measure of IS, and there have been no studies that have set out specifically to test the association of IS to CHD. Only time will tell whether IS is eventually recognized as a risk factor for either the development or progression of CHD.

Mechanisms Linking Personality to CHD

A critical question in the association of personality to CHD concerns the mechanisms by which this occurs. Along these lines, several possible mechanisms have been hypothesized and have gained support from research studies. Overall, five general models have been proposed for linking personality to CHD. These are described by

Smith et al. (2004) as being the psychophysiological reactivity model, the psychosocial vulnerability model, the transactional model, the health behavior model, and the constitutional vulnerability model. Each of these will now be discussed in turn.

Psychophysiological reactivity model. Originally formulated by Williams and his colleagues (Williams et al. 1985) to explain the relationship of hostility to CHD, this model hypothesizes that personality confers risk through exaggerated physiological reactivity on the part of certain individuals. Specifically, as generalized to the personality characteristics reviewed here, it is hypothesized that individuals high in anger or hostility or having a Type D personality or being high in IS show large increases in blood pressure and heart rate as well as neuroendocrine responses to various stressors. These exaggerated physiological responses are then hypothesized to promote the development of atherosclerosis. Since its proposal this hypothesis has gained strong research support. For example, Suarez and Williams (1989) randomly assigned young men with high or low hostility, as measured by the Cook and Medley (1954) Ho Scale, to either doing a set of anagrams while harassed by a rude research technician or doing those same anagrams without harassment. Measurements of blood pressure during this procedure revealed that those high on the Ho Scale showed significantly larger increases in blood pressure when harassed than when not harassed, whereas those low on the Ho Scale did not show this pattern. Similar results have been obtained for Type D. In an experiment relating NA and SI to cardiovascular reactivity, Habra et al. (2003) found that higher levels of SI were related to blood pressure reactivity while doing a mental arithmetic task while being harassed, whereas higher levels of NA were related to dampened heart rate change.

Additional evidence for the reactivity model has been obtained by Smith and colleagues in studies of interactions of married couples (Smith et al. 2004). In several studies it has been noted that husbands high in hostility show exaggerated cardiovascular reactivity during stressful marital interactions as compared with husbands low in hostility. Further, a similar pattern has been found for wives of high hostile husbands. Evidence linking cardiovascular reactivity to the development of atherosclerosis has been obtained by Kamarck et al. (1997) who found that blood pressure reactivity was related to the development of atherosclerosis over a 4-year period as determined by ultrasound measurements of carotid artery wall thickness in a sample of Finnish men.

More recently, the psychophysiological reactivity model has been extended to include both baseline and stress-related increases in triglycerides and both total and low-density cholesterol. For example, Siegman et al. (2002) found that a measure of outwardly directed anger was significantly related a negative lipid profile (high levels of total serum cholesterol, low-density lipoproteins, and triglycerides) among health women who were physically unfit. Interestingly, this finding was not found among physically fit women which suggests that physical fitness has a protective effect in this situation. Also Finney et al. (2002) found high triglyceride reactivity to a stressful speech task among men who either always expressed or always inhibited their expression of anger.

Another possible set of mechanisms relates to the role of inflammatory processes in the development of CHD. Along these lines Suarez et al. (2002) report that

measures of hostility and aggressiveness were positively associated with increased levels of tumor necrosis factor (TNF)-α in response to lipopolysaccharide stimulation in a sample of healthy men. Since TNF-α is associated with atherogenesis, this suggests another route by which psychophysiological reactivity may mediate the relationship between personality and CHD.

Psychosocial vulnerability model. This model posits that personality is associated with CHD through the effect of personality on interpersonal relationships and the experience of stress. Most of the evidence for this model comes from work on the association of hostility and anger to CHD, but similar arguments can be made for the Type D personality and IS disposition. Studies of psychosocial vulnerabilities have consistently found that individuals high in hostility and anger experience higher degrees of stress and conflict and report lower levels of social support. For example, Smith et al. (1988) found that individuals scoring high on the Cook and Medley (1954) Ho Scale reported more hassles and negative life events; reported lower social support, higher conflict within the family, lower marital satisfaction, and higher marital conflict; and also reported more job stress and less job satisfaction. In a similar vein, Miller et al. (1995) found among a sample of Mexican-Americans that a measure of hostility from the Buss and Durkee (1957) Hostility Inventory was associated with several measures of interpersonal conflict over an 11-year follow-up period. These are just two studies out of a large number that have shown these relationships (cf. Smith et al. 2004). Although fewer studies have been done with Type D personality, there is evidence that Type D individuals experience significantly more suppressed anger than non-Type D individuals and that this suppressed anger is associated with adverse clinical events among patients with CAD (Denollet et al. 2010).

These psychosocial vulnerabilities may well operate through psychophysiological mechanisms in increasing the risk of CHD. The higher levels of stress and interpersonal conflict experienced by individuals high in hostility as well as lowered social support would tend to lead to more episodes of high psychophysiological reactivity which would then increase risk for CHD. Further, it has been demonstrated that individuals high in hostility tend to benefit less from the social support that they do have. For example, Lapore (1995) found that whereas having a supportive confederate present during a stressful speech task reduced cardiovascular reactivity for individuals low in cynicism, this was not the case for those high in cynicism.

Transactional model. This model incorporates both the psychophysiological reactivity and psychosocial vulnerability models and takes the analysis a step further in viewing these vulnerabilities as being part of a transaction between person and environment. Individuals high in hostility do not just react to situations with greater reactivity and tend to have lower social support and higher interpersonal conflict. They also tend to create situations of higher conflict. Although this is a logical next step after the psychophysiological and psychosocial vulnerability models, the transactional model is, in many respects, more of a heuristic for integrating related concepts and guiding future research than it is a model to be tested empirically. One line of research that tends to emphasize the transactional nature of the association of personality to CHD is work done by Smith and his colleagues on stressful

marital interactions in which the cardiovascular reactivity and martial satisfaction of one spouse is often influenced by the level of hostility in the other spouse (Smith et al. 2004). Another potential avenue for exploring the transactional nature of psychosocial risk for CHD is through the use of ambulatory monitoring in which simultaneous measurements are taken of relevant stressor and physiological responses and then related to personality traits such as hostility. For example, Benotsch et al. (1997) found that individuals high in hostility showed higher ambulatory blood pressure than did those low in hostility, a relationship that was partially explained by higher levels of stress among high hostiles. Also another study done in Singapore found that Indians showed a positive relationship between anger and ambulatory mean arterial pressure, whereas this was not the case for Chinese and Malays. Further, irrespective of ethnicity, individuals high in hostility showed a positive relationship between momentary negative affect and SBP, whereas this was not the case for individuals low in hostility (Enkelmann et al. 2005).

Health behavior model. Another possible pathway by which personality may influence CHD is through differential health behaviors. There is evidence that individuals high in hostility or having a Type D personality engage in less healthy behaviors than do those without these traits. For example, Miller et al. (1995) found hostility to be associated with heavy drinking and current smoking among Mexican-Americans in an 11-year longitudinal study. Similar results were obtained by Siegler et al. (2003) who also found that changes in hostility from college to midlife predicted avoidance of exercise and a high-fat diet. Similar results have been obtained for Type D personality in which individuals with a Type D personality have been found to be less likely to eat sensibly, avoid letting things get them down, and get a regular medical checkup (Williams et al. 2008). Given the relationship between health behaviors and health outcomes, results such as these are strongly supportive of the health behavior model linking personality to CHD.

Constitutional vulnerability model. This model hypothesizes that both personality and disease vulnerability are a result of the person's constitutional makeup which is likely to be genetically determined. This implies that the relationship between personality and CHD may not be a causal one but rather the result of the person's overall genetic constitution. Evidence for this model has come from work on genes associated with the serotonergic system. For example, Manuck et al. (1999) found that the gene coding for tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin biosynthesis, showed elevated levels of aggression and the tendency to experience anger. Similarly, Williams and his colleagues (2010) have reported a relationship between alleles of the MAOA-uVNTR gene and a cluster of psychosocial risk factors including hostility. Further, serotonergic genes have been associated with cardiovascular responses to stress (Williams et al. 2001, (2003) and fasting glucose (Boyle et al. 2015) as well as to CHD morbidity and mortality (Brummett et al. 2013).

Although these results are promising with respect to support of the constitutional vulnerability model, it is important to keep in mind that the genes identified do not operate in isolation but rather in conjunction with the environment in the form of gene-environment interactions (Moffitt et al. 2006). This argues that far from being

a stand-alone model, the constitutional vulnerability model needs to be understood in the context of the transactional model with the transactions being not only between the person and the social environment but also between the person's genetics and the social environment.

Conclusion

Since the inception of systematic research on the relationship of personality to CHD more than half a century ago, there has been considerable progress in understanding the personality traits that predispose people to CHD and also the mechanisms involved in that relationship. Although the Type A construct has been the only personality construct to date that has been endorsed as a risk factor by an expert panel, research has moved on to the identification of the toxic ingredients in that syndrome. In particular, there is now a strong body of evidence demonstrating a significant association between anger/hostility and the occurrence and progression of CHD. Further there has been significant progress in illuminating the pathways through which this association takes place. There is strong evidence that physiological reactivity plays an important role as well as evidence that certain personality traits raise one's psychosocial risk and lead to poorer health behaviors. Recent evidence for the constitutional vulnerability model argues that a person's genetic makeup can predispose a person to high-risk personality traits as well as higher disease risk.

Of the different personality traits reviewed, anger/hostility has received the strongest support as a CHD risk factor. There is some evidence for the Type D personality in the prognosis of CHD, but the jury is still out as to whether it is a significant risk factor. IS has been proposed as an integrating framework for the role of certain negative personality traits in the development and progression of CHD, but there is as yet no agreed upon measure for IS, and no studies to date have specifically tested the relationship of IS to the development or progression of CHD.

With respect to the mechanisms involved, there is evidence for all of the models reviewed, and it seems most likely that, being a multifaceted phenomenon, all of the models can contribute to our understanding of the personality-CHD link. Future research needs to replicate the findings obtained to date and also further explore the links involved. The research on genetic aspects of psychosocial risk and CHD is particularly exciting, and future studies should further explore the role of gene-environment interactions when relating personality to CHD risk.

References

Barefoot, J. C., Dahlstrom, W. G., & Williams, R. B. (1983). Hostility, CHD incidence and total mortality: A 25-year follow-up study of 255 physicians. *Psychosomatic Medicine, 45*, 59–64.

Benotsch, E. G., Christensen, A. J., & McKelvey, L. (1997). Hostility, social support, and ambulatory cardiovascular activity. *Journal of Behavioral Medicine, 20*, 163–176.

Berry, J. D., Lloyd-Jones, D. M., Garside, D. B., Wang, R., & Greenland, P. (2007). Social avoidance and long-term risk for cardiovascular disease death in health men: The Western Electric Study. *Annals of Epidemiology, 17*, 591–596.

Booth Kewley, S., & Friedman, H. S. (1987). Psychological predictors of heart disease: A quantitative review. *Psychological Bulletin, 101*, 343–362.

Boyle, S. H., Georgiades, A., Brummett, B. H., Barefoot, J. C., Siegler, I. C., Matson, W. R., ... Surwit, R. D. (2015). Associations between central nervous system serotonin, fasting glucose, and hostility in African American females. *Annals of Behavioral Medicine, 49,* 49–57.

Brummett, B. H., Babyak, M. A., Jiang, R., Shah, S. H., Becker, R. C., Haynes, C., . . .,Williams, R. B. (2013). A functional polymorphism in the 5HTR2C gene associated with stress responses also predicts incident cardiovascular events. *PLoS One, 8*(12), e82781.

Buss, A. H., & Durkee, A. (1957). An inventory for assessing different kinds of hostility. *Journal of Consulting Psychology, 21*, 343–349.

Chang, P. P., Ford, D. E., Meoni, L. A., Want, N. Y., & Klag, M. J. (2002). Anger in young men and subsequent premature cardiovascular disease: The precursors study. *Archives of Internal Medicine, 162*, 901–906.

Chesney, M. A., Eagleston, J. R., & Rosenman, R. H. (1980). The Type A structured interview: A behavioral assessment in the rough. *Journal of Behavioral Assessment, 2*(4), 255–272.

Cook, W. W., & Medley, D. M. (1954). Proposed hostility and pharisaic virtue scales for the MMPI. *Journal of Applied Psychology, 38*, 414–418.

Cooper, T., Detre, T., Weiss, S. T., Bristow, J. D., Carlton, R., Dustan, H. P., . . . Stallones, R. A. (1981). Coronary-prone behavior and coronary heart disease: A critical review. *Circulation, 63*, 1199–1215.

Coyne, J. C., Jaarsma, T., Luttik, M.-L., van Sonderen, E., van Velhuisen, D. J., & Sanderman, R. (2011). Lack of prognostic value of Type D personality for mortality in a large sample of heart failure patients. *Psychosomatic Medicine, 73*, 557–562.

Dembroski, T. M., MacDougall, J. M., Williams, R. B., Haney, T. L., & Blumenthal, J. A. (1985). Components of Type A, hostility and anger in: Relationship to angiographic findings. *Psychosomatic Medicine, 47*, 219–231.

Denollet, J. (2005). DS14: Standard assessment of negative affectivity, social inhibition and the Type D personality. *Psychosomatic Medicine, 67*, 89–97.

Denollet, J., & Pederson, S. (2011). Type D personality in patients with cardiovascular disorders. In R. Allan & J. Fisher (Eds.), *Heart and mind: The practice of cardiac psychology* (2nd ed., pp. 219–247). Washington, DC: American Psychological Association.

Denollet, J., Vaes, J., Stoobant, N., Rombouts, H., Gillebert, T. C., & Brutseart, D. L. (1996). Personality as independent predictor of long-term mortality in patients with coronary heart disease. *Lancet, 347*, 417–421.

Denollet, J., deJonge, P., Kuyper, A., Schene, A. H., van Melle, J. P., Ormel, J., & Honig, A. (2009). Depression and Type D personality represent different forms of distress in Myocardial INfarction and Depression – Intervention Trial (MIND-IT). *Psychological Medicine, 39*, 749–756.

Denollet, J., Gidron, Y., Vrints, C. J., & Conraads, V. M. (2010a). Anger, suppressed anger, and risk of adverse events in patients with coronary artery disease. *American Journal of Cardiology, 105*, 1555–1560.

Denollet, J., Schiffer, A. A., & Spek, V. (2010b). A general propensity to psychological distress affects cardiovascular outcomes: Evidence from research on the Type D (Distressed) personality profile. *Circulation Cardiovascular Quality Outcomes, 3*, 546–557.

Enkelmann, H. C., Bishop, G. D., Tong, E. M. W., Diong, S. M., Why, Y. P., Khader, M., & Ang, J. (2005). The roles of hostility, affect and ethnicity in cardiovascular responses: An ambulatory study in Singapore. *International Journal of Psychophysiology, 56*, 185–197.

Finney, M. L., Stoney, C. M., & Engebretson, T. O. (2002). Hostility and anger expression in African American and European American men is associated with cardiovascular and lipid reactivity. *Psychophysiology, 39*, 340–349.

Friedman, M., & Rosenman, R. H. (1959). Association of specific overt behavior pattern with blood and cardiovascular findings: Blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease. *Journal of the American Medical Association, 169*, 1286–1296.

Friedman, M., & Rosenman, R. H. (1974). *Type A behavior and your heart*. New York: Knopf.

Grande, G., Romppel, J., Vesper, J.-M., Schubmann, R., Glaesmer, H., & Hermann-Lingen, C. (2011). Type D personality and all-cause mortality in cardiac patients – Data from a German cohort study. *Psychosomatic Medicine, 73*, 548–556.

Habra, M. E., Linden, W., Angerson, J. C., & Weinberg, J. (2003). Type D personality is related to cardiovascular and neuroendocrine reactivity to acute stress. *Journal of Psychosomatic Research, 55*, 235–245.

Haney, T. L., Maynard, K. E., Houseworth, S. J., Scherwitz, L. W., Williams, R. B., & Barefoot, J. C. (1996). Interpersonal hostility assessment technique: Description and validation against the criterion of coronary artery disease. *Journal of Personality Assessment, 66*, 386–401.

Haynes, S. G., Feinleib, M., & Kannel, W. B. (1980). The relationship of psychosocial factors to coronary heart disease in the Framingham study. III. Eight-year incidence or coronary heart disease. *American Journal of Epidemiology, 111*(1), 37–58.

Jenkins, C. D., Zyzanski, S. J., & Rosenman, R. H. (1971). Progress toward validation of a computer-scored test for the type A coronary-prone behavior pattern. *Psychosomatic Medicine, 33*, 193–202.

Kamarck, T. W., Everson, S. A., Kaplan, G. A., Manuck, S. B., Jennings, J. R., Salonen, R., . . ., Jukka, T. (1997). Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish man: Findings from the Kuopio Ischemic Heart Disease Study. *Circulation, 96*, 3842–3848.

Lapore, S. J. (1995). Cynicism, social support, and cardiovascular reactivity. *Health Psychology, 14*, 210–216.

Manuck, S. B., Flory, J. D., Ferrell, R. E., Kent, K. M., Mann, J. J., & Muldoon, M. F. (1999). Aggression and anger-related traits associated with a polymorphism of the tryptophan hydroxylase gene. *Biological Psychiatry, 45*, 603–614.

Marin, T. J., & Miller, G. E. (2013). The interpersonally sensitive disposition and health: An integrative review. *Psychological Bulletin, 139*, 941–984.

Matthews, K. A. (1988). Coronary heart disease and Type A behaviors: Update on and alternative to the Booth-Kewley and Friedman (1987) quantitative review. *Psychological Bulletin, 104*, 373–380.

Matthews, K. A., Gump, B. B., Harris, K. F., Haney, T. L., & Barefoot, J. C. (2004). Hostile behaviors predict cardiovascular mortality in men from the Multiple Risk Factor Intervention Trial. *Circulation, 10*, 66–70.

Meyer, T., Hussein, S., Lange, H. W., & Hermann-Lingen, C. (2014). Type D personality is unrelated to major adverse cardiovascular events in patients with coronary artery disease treated by intracoronary stenting. *Annals of Behavioral Medicine, 48*, 156–162.

Miller, T. Q., Karkides, K. S., Chiriboga, D. A., & Ray, L. A. (1995). A test of the psychosocial vulnerability and health behavior models of hostility: Results from an 11-year follow-up study of Mexican Americans. *Psychosomatic Medicine, 57*, 572–581.

Miller, T. Q., Smith, T. W., Turner, C. W., Guijarro, M. L., & Hallet, A. J. (1996). A meta-analytic review of research on hostility and physical health. *Psychological Bulletin, 119*, 322–348.

Moffitt, T. E., Caspi, A., & Rutter, M. (2006). Measured gene-environment interactions in psychopathology: Concepts, research strategies, and implications for research, intervention, and public understanding of genetics. *Perspectives on Psychological Science, 1*, 5–27.

Nakaya, N., Tsubono, Y., Hosokawa, T., Hozawa, A., Kuriyama, S., Fukudo, S., & Tsuji, I. (2005). Personality and mortality from ischemic heart disease and stroke. *Clinical and Experimental Hypertension, 27*, 297–305.

Pelle, A. J., Pederson, S. S., Schiffer, A. A., Szabo, B., Widdershoven, J. W., & Denollet, J. (2010). Psychological distress and mortality in systolic heart failure. *Circulation. Heart Failure, 3*, 261–267.

Raikkonen, K., Matthews, K. A., & Kuller, L. H. (2001). Trajectory of psychological risk and incident hypertension in middle-aged women. *Hypertension, 38*, 798–802.

Rosenman, R. H., Brand, R. J., Jenkins, C. D., Friedman, M., Straus, R., & Wurm, M. (1975). Coronary heart disease in the Western Collaborative Group Study: Final follow-up experience of 8 1/2 years. *Journal of the American Medical Association, 233*, 872–877.

Shen, B. J., Avivi, Y. E., Todar, J. F., Spiro, A., Laurenceau, J. P., Ward, K. D., & Niaura, R. (2008). Anxiety characteristics independently and prospectively predict myocardial infarction in men: The unique contribution of anxiety among psychologic factors. *Journal of the American College of Cardiology, 51*, 113–119.

Siegler, I. C., Costa, P. T., Brummett, B. H., Helms, M. J., Barefoot, J. C., Williams, R. B., . . . Rimer, B. K. (2003). Patterns of change in hostility from college to midlife in the UNC Alumni Heart Study predict high-risk status. *Psychosomatic Medicine, 65*, 738–745.

Siegman, A. W., Malkin, A. R., Boyle, S., Vaitkus, M., Barko, W., & Franco, E. (2002). Anger, plasma lipid, lipoprotein, and glucose levels in healthy women: The mediating role of physical fitness. *Journal of Behavioral Medicine, 25*, 1–16.

Smith, T. W. (1994). Concepts and methods in the study of anger, hostility, and health. In A. W. Siegman & T. W. Smith (Eds.), *Anger, hostility, and the heart* (pp. 23–42). Hillsdale: Erlbaum.

Smith, T. W. (2011). Towards a more systematic, cumulative, and applicable science of personality and health: Lessons from Type D personality. *Psychosomatic Medicine, 73*, 528–532.

Smith, T. W. (2013). Does the interpersonally sensitive disposition advance research on personality and health? Comment on Marin and Miller (2013). *Psychological Bulletin, 139*, 985–990.

Smith, T. W., Pope, M. K., Sanders, J. D., Allred, K. D., & O'Keeffe, J. L. (1988). Cynical hostility at home and work: Psychosocial vulnerability across domains. *Journal of Research in Personality, 22*, 525–548.

Smith, T. W., Glazer, K., Ruiz, J. M., & Gallo, L. C. (2004). Hostility, anger, aggressiveness and coronary heart disease: An interpersonal perspective on personality, emotion and health. *Journal of Personality, 72*, 1217–1270.

Spielberger, C. D., Jacobs, G., Russell, S., & Crane, R. S. (1983). Assessment of anger: The State-Trait Anger Scale. In J. N. Buttcher & C. D. Spielberger (Eds.), *Advances in personality assessment* (Vol. 2, pp. 159–187). Hillsdale: Erlbaum.

Suarez, E. C., & Williams, R. B. (1989). Situational determinants of cardiovascular and emotional reactivity in high and low hostile men. *Psychosomatic Medicine, 51*, 404–418.

Suarez, E. C., Lewis, J. G., & Kuhn, C. (2002). The relation of aggression, hostility, and anger to lipopolysaccharide-stimulated tumor necrosis factor (TNF)-a by blood monocytes from normal men. *Brain, Behavior, and Immunity, 16*, 675–684.

Whiteman, M. C., Deary, I. J., Lee, A. J., & Fowkes, F. G. (1997). Submissiveness and protection from coronary heart disease in the general population: Edinburgh Artery Study. *Lancet, 350*, 541–545.

Williams, R. B., Barefoot, J. C., & Shekelle, R. (1985). The health consequences of hostility. In M. A. Chesney & R. H. Rosenman (Eds.), *Anger and hostility in cardiovascular and behavioral disorders* (pp. 173–185). New York: Hemisphere.

Williams, R. B., Marchuk, D. A., Gadde, K. M., Barefoot, J. C., Grichnick, K., Helms, M. J., . . . Siegler, I. C. (2001). Central nervous system serotonin function and cardiovascular responses to stress. *Psychosomatic Medicine, 63*, 300–305.

Williams, R. B., Marchuk, D. A., Gadde, K. M., Barefoot, J. C., Grichnik, K., Helms, M. J., . . . Siegler, I. C. (2003). Serotonin-related gene polymorphisms and central nervous system serotonin function. *Neuropsychopharmacology, 28*, 533–541.

Williams, L., O'Connor, R. C., Howard, S., Hughes, B. M., Johnston, D. W., Hay, J. L., . . ., O'Carroll, R. E. (2008). Type-D personality mechanisms of effect: The role of health-related behavior and social support. *Journal of Psychosomatic Research, 64*, 63–69.

Williams, R. B., Surwit, R. D., Siegler, I. C., Ashely-Koch, A. E., Collins, A. L., Helms, M. J., . . . Kuhn, C. M. (2010). Central nervous system serotonin and clustering of hostility, psychosocial, metabolic, and cardiovascular endophenotypes in men. *Psychosomatic Medicine, 72*, 601–607.

Type A Behavior and Cardiovascular Disease

Geir Arild Espnes and Don Byrne

Contents

Abstract

The type A behavior pattern (TABP) showed immense success in predicting coronary heart disease (CHD) incidence for three decades, from the 1960s onward, and was considered a strong and independent risk factor for CHD development. The TABP, or behavior classifications closely related to this pattern, are still used both in practice and in research settings, for this purpose. But due to a number of

G.A. Espnes (✉)
Center for Health Promotion Research, Department of Social Work and Health Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Australian National University, Canberra, ACT, Australia
e-mail: geirae@svt.ntnu.no; geir.arild.espnes@svt.ntnu.no

D. Byrne
ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia

ANU Medical School, Research School of Psychology, Australian National University, Acton, Canberra, ACT, Australia
e-mail: don.byrne@anu.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_30

negative findings and critical commentaries on the relation between type A behavior pattern and CHD from the middle of the 1980s and few positive findings in the same period of time, researchers and practitioners have questioned whether the TABP's predictability of future CHD development was really quite so well established. This chapter describes the early history of TABP and also scrutinizes the related concept of type A personality, which became the concept to describe what was the underlying personality of TABP. It sums up the research history for the TABP construct by starting with a number of reviews and meta-analyses on the concept from the late 1980s and until now. The chapter is based on a close examination of the research on TABP involving extensive literature searches conducted in 2003, 2010, and 2013 using PubMed, MEDLINE and PsycINFO, and the search term "type behavior and CVD." While the volume of evidence has declined over time, recent work suggests a continuing utility for the construct.

Keywords
Type A behaviour • Coronary prone behaviour • Cardiovascular risk • Myocardial infarction • Epidemiology

The Early History of the Type A Behavior Pattern and Its Relation to Coronary Heart Disease (CHD) Development

One day in the early 1950s, an upholsterer repairing chairs in the waiting room of two successful cardiologists in San Francisco, Dr. Ray Rosenman and Dr. Meyer Friedman, mentioned to the doctors, after again having redone the chairs of their waiting room, that they had to have a rather special patient group since only the front edge on the chairs was worn down. That made the two insightful cardiologists curious about the behaviors of their patients and instigated both a discussion to conceptualize the nature of the behaviors and, eventually, a program of research to determine whether the speculation – for that is what it initially was – held any validity. And from small beginnings, it was the motivation for the iconic Western Collaborative Group Study (WCGS), a large study to reveal if there was a common behavioral pattern among persons in danger of suffering a clinical event of coronary heart diseases (CHD). The study concluded, on the basis of incontestable evidence, that there were indeed similarities in the behavior of those at risk of CHD and the behavioral pattern that emerged was named type A behavior pattern (TABP). The WCGS was the first study to investigate behavior patterns as risk for heart attacks. Three thousand five hundred twenty-four men aged 39–59 and employed in the San Francisco Bay or Los Angeles areas were enrolled in 1960 and 1961. In addition to determinations of behavior pattern, the initial examination included the person's medical and family history and a row of medical, biochemical, and biomedical tests. The WCGS concluded that type A behavior pattern was a very significant risk factor for the development of CHD.

The TABP became well known and drew enormous attention through the 1950s and 1960s and was for a long time recognized as *the* "coronary-prone behavior" pattern (Friedman and Rosenman 1974). The overall hypothesis that a distinct

pattern of behavioral characteristics could be an independent risk factor for CHD development (Rosenman et al. 1964; Friedman and Rosenman 1974; Rosenman et al. 1975) was based partly on their intellectual curiosity (seen in the story of the upholsterer) and partly on much earlier observations of psychological factors in CHD development (e.g., Osler 1892, 1910; Menninger and Menninger 1936; Kemple 1945; Gildea 1949).

The concept became even more important and widely known, after the Framingham Heart Study, where people with the TABP showed a relative risk on 2.9 among white-collar workers and 2.1 in women working outside the home, for developing a CHD, with other risk factors having been taken into account (Haynes et al. 1980). So both WCGS and the Framingham supported the hypothesis that there was a cluster of behaviors which increased the probability of CHD onset. These studies concluded that the pattern of characteristics (the TABP) was an independent risk factor for CHD development and also that it was as strong a predictor of CHD as the rest of the known risk factors combined. This led the American National Heart, Lung, and Blood Institute review panel, in a rather momentous step, to conclude without equivocation that the TABP is associated with increased risk of clinically apparent CHD in employed, middle-aged US citizens (Review Panel 1981), with TABP broadly defined as referring to any person who "... is involved in an aggressive and incessant struggle to achieve more and more in less and less time" (Friedman and Rosenman 1974).

Both practitioners and researchers worldwide rapidly expressed great confidence in the behavior pattern and its ability to predict future cardiac problems. And, by extension, these modifications to this behavior pattern through psychological interventions would have the capacity to prevent the development of CHD in men along the same lines that the modification of smoking behavior, elevated cholesterol, or high blood pressure would be expected to achieve.

Assessment of the TABP: Measures and Their Relative Usefulness

The utility of any psychosocial construct in predicting illness events is only as good as the availability of sound psychometric instruments to measure it. The TABP has been assessed in many ways over the years, some being demonstrably better than others – instruments derived from, or part of, existing personality measures have been used, along with a plethora of short, ad hoc, and usually not well-validated self-report inventories of behaviors, feelings, and attitudes. Perhaps the most widely used instrument in the former of these regard was the Cook-Medley Hostility Scale (Barefoot et al. 1989). But the consensus opinion now is that four assessment instruments for type A behavior have acquired sufficient use, consistent success, and well-respected psychometric properties that they can be considered the mainstays of assessment in the type A story.

The structured interview (SI) for type A behavior was developed by Rosenman and his colleagues for use in the iconic Western Collaborative Group Study (WCGS) (Rosenman et al. 1966). The SI combined direct questions to respondents to elicit

self-reports of type A behaviors with deliberate behavioral challenges designed to provoke observable type A behaviors, which could then be noted and rated by trained observers. This unique combination of assessment components which aimed, among other things, to reduce the level of reporting bias in which purse self-report measures were supposedly subject, was considered by some (Chesney et al. 1980) to make the SI the instrument of choice in any serious epidemiological investigation of the TABP in relation to the risk of CHD. Strong validity and sound inter-rater reliability added to the confidence, which its developers held in the SI, and its predictive capacity in regard to CHD incidence in the WCGS was remarkable (Rosenman et al. 1976).

But the SI requires a significant time commitment for research participants and the involvement of highly interviewers and, in large sample, long-term follow-up studies; this may be seen as impractical. A number of self-report measures of the TABP have therefore been developed either to supplement the SI or, in many cases, to replace it entirely. Three will be noted here because of their wide use.

The Jenkins Activity Survey (JAS) was developed as a self-report measure of type A behavior to work alongside the SI in the WCGS (Jenkins et al. 1971). It is a quick and convenient instrument to use, predictive of CHD risk (Rosenman et al. 1976), and statistically related to ratings based on the SI. Not surprisingly, the JAS has become the benchmark for self-reported type A behavior over the past 40 years.

However, the other major, large cohort epidemiological support for a link between the TABP and CHD came from the Framingham Study (Haynes et al. 1980). Neither the SI nor the JAS, purpose-designed instruments, was used in this examination of the Framingham data – rather, the researchers constructed a proxy scale for type A behavior based on questions examining the psychosocial situations of participants in the study, questions which were believed a priori to reflect the TABP. And the scale was subsequently validated against the JAS (Suls and Marco 1990). Scores on the Framingham type A scale were able to predict future incidence of CHD, but not across both genders and all age groups. Nonetheless, the Framingham type A scale has been quite widely used in other – rather more modest – studies of the TABP and CHD.

And finally, addressing the need for a very brief scale of the TABP to be used in large-scale epidemiological studies of CHD, Bortner (1969) published a short rating scale to measure the construct in both clinical and nonclinical populations. The Bortner Scale validated well against other self-report measures of the TABP, but in view of its brevity and the somewhat constrained nature of its coverage, it did not achieve widespread use in large population studies of CHD incidence.

A major examination of the performance of the common type A scales in a large nonclinical population was published in 1985 by Byrne, Rosenman, Schiller, and Chesney. It was clear from this work that the major scales assessing the construct, including the SI, related strongly to one another, and from this, the thematic content of the various scales reflected a substantial overlap in the domains covered by the inquiry. But if there is to be a new attempt to develop yet another instrument assessing the

TABP sometime into the future, it is now clear that it should take strong account of the emotional side of the construct as well as the strictly behavioral.

The TABP in the 1980s

In 1987 Booth-Kewley and Friedman published three articles based on a review and a meta-analysis carried out on literature addressing the TABP (Friedman and Booth Kewley 1987a, b; Booth Kewley and Friedman 1987). Two of these articles are among the most cited articles in the area (Friedman and Booth Kewley 1987a; Booth Kewley and Friedman 1987). This is mainly because of a general impression at the time that the TABP was a flawed concept in explaining CHD development. The feeling that type A was an obsolete concept was based on results from a number of (largely) cross-sectional studies, carried out in the second half of the 1970s and first half of the 1980s. Several investigators have since claimed that the reason for the largely negative results relating the TABP to CHD was caused by flawed methodology in both design and measurement (Booth-Kewley and Friedman 1987) and also by confusing the behavioral concept with a personality type – recognized as the type A personality (Byrne 1996; Rosenman 1997, Lecture given at 14th world congress of pychosomatic medicine, 31st Aug–5th Sept 1997, personal communication). A change of journal editorial policies was also seen as an important factor (Booth-Kewley and Friedman 1987). Others have suggested that a concept which, to a large extent, conveniently explained CHD development at one stage of the CHD epidemic but reflecting characteristics of the society largely tied to this phase of time may not be transferable to new times and new lifestyles. There has also been a dramatic change of CHD incidence since the WCGS was undertaken, which could have changed the whole population of people in risk of having CHD (Espnes 1996; Booth-Kewley and Friedman 1987).

The most important conclusion concerning the TABP in the Friedman and Booth-Kewley evaluation of the literature was that the type A behavior pattern is sometimes referred to as type A personality (Booth-Kewley and Friedman 1987): "Type A behaviour is modestly but reliably related to CHD (and other occlusive diseases)," but "Rather, the true picture seems to be one of a person with one or more negative emotions: perhaps someone who is depressed, aggressively competitive, easily frustrated, anxious, angry or some combination" (Friedman and Booth-Kewley 1987a, p. 551).

The role of negative emotions and its connection to CHD have been tested in a number of studies, but the results are very contradictory (e.g., Espnes and Opdahl 1999; Todaro et al. 2003), and it is impossible presently to draw clear conclusions. One of the reasons for that has been the lack of a "solid" operational definition of which feelings or other psychological constructs should be included in "negative emotions."

In 1988 Karen Matthews wrote a commentary paper to the Friedman and Booth-Kewley studies, which she called an "Update on and Alternative to the Booth-Kewley

and Friedman (1987) Quantitative Review" (Matthews 1988). She underlines that [in a meta-analysis] "the reviewer must make a series of decisions about which studies should be included, and how to weight the available studies, which affect the resulting estimates." She also points out that even if cross-sectional and prospective data initially are analyzed separately in the Booth-Kewley and Friedman article (1987), they are both included in the estimates of the overall influence of type A behavior on CHD risk. She reminds the reader on the two independent epidemiological studies (Cohen and Reed 1985; Johnston et al. 1987) which have found significant relationships between TABP and CHD development in prospective studies but not in cross-sectional ones.

In a later paper in *Psychological Bulletin*, Friedman and Booth-Kewley (1988) addressed the critical comments made by Matthews (1988) and others. They underlined correctly enough in their response and as the most important argument in favor of their meta-analyses that "the construct of coronary prone behaviour and its incarnation as the Type A behaviour pattern have been defined in so many ways and assessed so unsystematically that some authors throw up their hands and conclude that the whole matter is not worthy of attention" (Friedman and Booth-Kewley 1988, p. 381).

What Friedman and Booth-Kewley were stressing here is obviously an important point. The line of research following up the Western Collaborative Group Study has been very diverse. However, there is simply no other way to comparatively analyze the predictive strength of the TABP for CHD for the present population than to follow the line of research that has used the SI (see earlier section on instruments) to obtain data.

Krantz et al.'s (1988) review also (inter alia) examined the current status of the TABP at that time. They began with a short overview of the landmark prospective studies which had given the TABP the status of the "coronary-prone behavior," including the WCGS, the Framingham study, the Belgian-French Collaborative Heart Study (see, e.g., Kornitzer et al. 1981), and the Recurrent Coronary Prevention Project (Friedman et al. 1982). Results from the last of these showed that the TABP could be altered by behavior intervention treatment, to then prevent recurrent incidences of CHD. Krantz et al. (1988) also offered four possible explanations for the paucity of findings relating the TAPB and CHD development in the previous years. Firstly, they suggested that global TABP is not a risk factor among CHD patients or with individuals with high levels of standard risk factors. Secondly, they suggest that the positive findings in the Recurrent Coronary Prevention Project but not in later similar studies might have been caused by the nonspecific stress-reducing effects of the intervention or effects of social support. They pointed to the fact that there had been a number of studies supporting the view that more global stress-reducing interventions promote better clinical outcomes. Thirdly, they underlined that most of the studies in the late 1970s and early and mid-1980s were designed as treatment trials to evaluate the efficacy of either drugs or behavior modification techniques to reduce CHD risk and participation in such projects may alter aspects of TABP or modify its pathogenic qualities. And finally, they noted that TABP may be so common among CHD patients that it could therefore be an insensitive predictor of subsequent clinical outcomes (Krantz et al. 1988).

Systematic database searches to the end of the 1980s reveal a number of articles on type A and CHD, but these appear to be papers simply summing up the past era of the TABP, sometimes employing instruments not validated against the benchmarks of the SI or JAS (Leon et al. 1988). These papers rarely deal with the major criticisms of the predictive validity of the TABP for CHD development. There appear, in fact, to be two parallel lines of publications at that time, those publishing on type A behavior pattern as if it had not conceptually moved from its origins in the 1960s and those heavily attacking type A for the lack of predictive value.

One example of the former approach is Harbin's (1989) paper. He reviewed reports linking type A behavior to physiological reactivity indicating both general arousal and cardiovascular activation, pointing out that the conclusions of the researchers investigating this possible link have been equivocal, with some asserting that type A persons are more reactive whereas others finding no evidence for such a conclusion. In Harbin's (1989) report, a meta-analysis was employed to provide a quantitative evaluation of the relationship between type A behavior and physiological reactivity. Results indicated that (1) type As respond to cognitive and psychomotor stimulus situations with greater heart rate and systolic blood pressure responses, (2) this relationship is not evident in females, (3) the relationship is more evident for some cognitive tasks than for others, and (4) the strength of the relationship depends upon the instrument used to assess type A behavior.

The TABP from the 1990s to the Change of the Millennium: What Happened to the Construct?

A simple count of articles emerging from database searches using the central keywords of TABP and CHD (spelled out in full) is one indication of the drop in interest for the TABP pattern after the critical and somewhat negative reviews to the end of the 1980s. One cannot, of course, be absolutely sure simply from this count that this is what has happened. It could be that researchers simply lost interest in investigations on the TABP and CHD, but nothing else points in that direction. The pattern is therefore quite clear – the interest of TABP seems to vanish through the 1990s (Table 1).

As was obvious from the above searches, some researchers had still strong belief in the TABP in the beginning of the 1990s (e.g., Craig and Weiss 1990; Zapotoczky and Wenzel 1990; Strube 1991; Monat and Lazarus 1991; Snyder and Forsyth 1991; Spielberger et al. 1991; Cooper and Payne 1991; Byrne and Caddy 1992; Goldeberger and Breznitz 1993; Siegman et al. 1994; Carey and McDevitt 1994; Friedman et al. 1996; Low 1991).

The overview of work from 1990 to the millennium change can fittingly start with a paper by one of the fathers of the concept, Ray Rosenman (1990). In his paper Rosenman gives a brief history of the type A behavior pattern (TABP) and discusses measurement issues including the construct validation of the TABP concept. Studies examining the relationship between TABP and coronary heart disease are discussed,

Table 1 Showing the development of publications containing the central keywords; type A behavior pattern and coronary heart disease from 1990 to 2000

Year	1990	91	92	93	94	95	96	97	98	99	Total
D-base											
PubMed	25	19	8	10	8	4	8	5	4	3	94
MEDLINE	5	3	2	1	2	-	1	1	1	1	17
PsychINFO	10	20	7	7	7	4	5	5	6	3	74
Total	40	42	17	18	17	8	14	11	11	7	217
Book chapters	3	12	2	2	3	2	4	2	3	1	35

and factors that may be responsible for inconsistencies in the literature are emphasized. Interventions for TABP are mentioned; with an acknowledgment that researcher's varying conceptualizations of TABP make it difficult to develop effective interventions. Physiological and cardiovascular reactivity, and the roles of hostility and competitiveness in TABP, are also described. Rosenman here especially emphasizes the role of hostility as a predictor and as an important part of the type A construct. This paper is one of the first argument against the conclusions drawn in findings reported in the reviews and meta-analyses in the late 1980s. He makes it clear that the inclusion of papers based on methodological flaws is at the root cause of much of the negative views surrounding the TABP. Rosenman gives in this article the most recent and comprehensive definition of the TAB: The TABP is, he states:

> . . .an action-emotion complex involving behavioural predispositions such as ambitiousness, aggressiveness, competitiveness, and impatience; specific behaviors such as muscle tenseness, alertness, rapid and emphatic vocal stylistics, and accelerated pace of activities; and emotional responses such as irritation, hostility, and increased potential of anger. (p. 2)

And it is clear here that in this new definition (Rosenman 1990), while the focus remains on behaviors, there is now a place for emotions as well.

But as opposed to studies of TABP from the 1980s, a new focus has emerged – there has been a developing interest in finding which of the components included in the TABP might be uniquely cardiotoxic and may not be of the same level of importance for the development of CHD (e.g., Williams et al. 1980).

In 1991 a new meta-analysis was published investigating Booth-Kewley and Friedman's (1987) and Matthews' (1988) meta-analyses (Miller et al. 1991) and the trend toward null findings in research attempting to link the TABP and CHD. These authors also point to the fact that even over this period, there had been studies where earlier findings of predictive validity had been replicated. Based on earlier publications (Matthews 1988; Pearson 1994; Pickering 1985), Miller et al. (1991)

offer a possible – and interesting – explanation for the null findings, which they name disease-based spectrum bias (DBS). DBS is present in studies where subjects are directed into or excluded from a study sample according to their disease status. An example is the case when healthy individuals are excluded from and diseased individuals are directed into referred samples (see Miller et al. 1988). The findings of Kittel (1986) in her Belgian Heart Disease Prevention Project might be a good example of DBS. Her study involved a successful intervention designed to prevent CHD by reducing traditional risk factors. Kittel reported a strong relationship between CHD and TABP in the control group, but no such relationship in the treatment group. After having carried out a careful reanalysis of the literature, Miller et al. (1991) emphasize that the finding that DBS occurs in studies of high-risk populations really is an indication that the magnitude of the relation between TABP and CHD is larger than has been suggested in recent research and points especially to the findings of Booth-Kewley and Friedman (1987).

The suggestion that the *global* measure of TABP might not be the most profitable strategy to use in the prediction of CHD incidence was also underlined strongly by Edwards and Baglioni (1991) and Raeikkonen (1992). Raeikkonen (1992) goes on to state that the many differing operational definitions of type A have resulted both in conceptual confusion and in confusion with regard to the nature of the type A risk, and she emphasizes that TABP should now be treated as a multidimensional construct, since some aspects play a more important role than others in mediating the association between this behavior pattern and CHD. Edwards and Baglioni (1991) compared the global and component measures of TABP and concluded that component TABP analyses show a great number of advantages over global TABP measures. They also suggest that effort should be made to construct good component measurements and note that in their study, the behavioral entities that showed the clearest relationship with the development of CHD were those components reflecting speed and time pressure.

In 1993, 4 years after Harbin's (1989) meta-analysis of the research on the relationship between type A and physiological reactivity, a new meta-analysis of the data was published (Lyness 1993). Based on information from a total of 99 studies which were included for analysis, Lyness concludes that type A persons showed greater stress reactivity than did the type Bs, even if the effect is small. She also argues that there is reason to believe that the difference in reactivity between the As and the Bs may actually be larger than found in this meta-analysis, making reference to the fact that recent studies (Chesney et al. 1988; Ganster et al. 1991; Williams and Barefoot 1988) have gone into finer detail concerning pathogenic components of the type A behavior patterns, such as hostility, anger suppression, or speech characteristics, and their relationship to cardiovascular reactivity (Lyness 1993).

A great number of the relevant studies published at the beginning of the 1990s were obviously in line with suggestions made in both Booth-Kewley and Friedman's (1987) and Matthews' (1988) meta-analyses (e.g., Edwards and Baglioni 1991; Grennglass and Julkunen 1991; Raeikkonen 1992). These studies include both TABP (or type A personality) and other related personality or emotionality variables and their impact on CHD development. But in a greater number of studies on the

psychosocial correlates of CHD, the TABP was often no longer included in investigations of the psychosocial explanations for CHD. What arose from this line of investigations was the view that the main psychosocial factors impacting onto CHD development were those already suggested in Booth-Kewley and Friedmans's (1987) meta-analysis, that is, anger and aggression, hostility, irritability, suspicion, frustration, and guilt (see, e.g., Kopper 1993; Weekes and Waterhouse 1991; Eriksen 1994; Hill et al. 1991). But here as well, definitions and conceptualizations of the TABP were often not especially precise.

Publications at that time quite often addressed both psychosocial risk factors for CHD development and the personality characteristics in persons who had suffered CHD, often mixed together. These studies did not take sufficient care that risk factors for a first clinical event of CHD and a recurrent attack very well might be two quite, if not, totally different things (e.g., Espnes 1996).

In 1995 a new paper on the reactivity of TABP persons appeared (Myrtek 1995). This article presents a meta-analysis of the relationship between TABP or hostility and personality factors, based on English and German articles published between 1983 and 1992. The author argues that the population effect sizes for other cardiovascular and peripheral parameters are very small, some supporting and others contradicting the hypothesis of hyperreactivity in type A persons. The author found no evidence for a significant effect on the catecholamine response associated with individual characteristics of the TABP (Myrtek 1995).

Based on the information from this research, Byrne (1996) felt that the time was right to carefully go through the newest research on TABP and to analyze what this meant for the understanding and use of the TABP construct as coronary-prone behavior. His attempt to solve the dispute on TABP was to fit the new information into a model of how the TABP could explain both benign and pathological outcomes with CHD. There had been a number of studies over some years attempting to reveal the toxic components of TABP, commencing at the beginning of the 1980s (see, e.g., Williams et al. 1980; Shekelle et al. 1983; Barefoot et al. 1983). Byrne himself had been a part of these attempts through his own research (see Byrne and Rosenman 1990). In this light, he suggested a model of the psychopathological paths which the TAPB follows to "produce" CHD risk (p. 234). In his view, the competitiveness aspect of TABP must be viewed as a "global motivational predisposition to behavior," while the rest of the TABP characteristics constitute the A behavior pattern (recognized as goal oriented, achievement oriented, control oriented, time urgent, job involved, and acquisitive). He argued that it is the ways in which the individual characterized by the TABP solves the behavioral demands, whether that pattern of behavior leads to expression or frustration of type A attributes, and decides whether the likelihood of CHD risk is elevated or not. If the psychosocial situation allows expression of the TABP, what follows will be emotional equilibrium and satisfaction, and the CHD risk will not rise above the age standard risk. However, if the psychosocial context causes frustration of type A behaviors in individuals characterized by the TABP, what follows will be emotional distress and dissatisfaction and a potentially elevated level of coronary risk.

Byrne's (1996) article was meant to be a way of reconceptualizing the TABP, based on the evidence of previous research so that future research on the TABP in relation to CHD risk might be guided by a new and original theoretical model. Unfortunately, this attempt at reconceptualizing the type A construct did not lead to new studies elucidating the link between the TABP and CHD, perhaps due to a now rapidly declining interest in the whole notion of type A behavior.

In publications after 1996, the TABP was found to be measured with the original SI method in only one study (Markovitz et al. 1996), and even here, the SI was used merely as a psychologically stressful task (together with one other cognitive task) to elicit physiological effects of a mental stressor. These studies in fact reveal encouragingly positive results in regard to the TABP and risk of CHD.

As part of the Normative Aging Study in Boston, a longitudinal study which commenced in 1961 (Kawachi et al. 1998), the authors, in spite of negative findings, conclude of the TABP that one rather than abandon the TABP concept need to search for the sources of disagreement between studies and find whether the problem lies in the concept itself or whether it lies in the methods used to measure it, and further, they concur with what Matthews (1988) suggests in her review that occurrence of some failures to replicate does not justify abandoning the concept (Kawachi et al. 1998).

The type A behavior pattern has also been suggested to be an independent risk factor for left ventricular hypertrophy in male patients with essential hypertension (Munakata et al. 1999). Using yet another assessment technique, namely, the adolescent/adult type A scale (AATABS) (Forgays et al. 1993) which has been validated against the Framingham scale with a high level of correspondence, Richards et al. (2000) found significant correlations between hurry/impatience and total serum cholesterol and competitiveness and exercise (not surprisingly) and finally a negative correlation between achievement orientation and low-density lipoprotein.

Research on the TABP in the Twenty-First Century

There is no doubt, as already suggested, that the publication rate of journal articles researching the TABP has fallen dramatically over the last three decades. In this final part of the chapter, this trend will be illustrated graphically, and published research reports investigating the TABP as a contributor to CHD development will be discussed. Published papers that simply mention the TABP, even though appearing in literature searches, will not be included.

In 2000 Elianne Riska published a paper titled "The rise and fall of Type A man" in *Social Science and Medicine*. She claims that the fall of type A man started when researchers moved to viewing the type A concept more as a personality type than a straightforward description of overt patterns of behaviors. Of course, this became evident as far back as the 1970s and 1980s, in Riska's assessment of the area. The conceptual importance of this paper lies with the inevitable questions it poses on the evolution and the decline of a once strong and widely accepted construct.

Table 2 Showing the development of publications containing the central keywords; type A behavior pattern and coronary heart disease from 2000 to 2013

Year	20 00	01	02	03	04	05	06	07	08	09	10	11	12	13	Total
D-base															
PubMed	8	4	3	8	7	4	9	8	6	3	-	1	2	-	
MEDLINE	2	-	-	1	1	-	2	1	1	-	-	-	-	-	
PsychINFO	5	-	2	1	2	-	4	1	1	1	-	1	-	-	
Total	15	4	5	10	11	4	14	11	8	4	-	2	2	-	
Book chapters	-	-	1	-	-	-	-	2	-	-	-	-	-	-	

One of the articles found in MedLine in 2006 was a book review on Risk as Masculinity and Mens Health, 2004. Two PhD dissertations 2004 and 2005 was also reported in MedLine

What happened? Had the TABP become out of date? Had scientific trials shown it to be seriously flawed, either conceptually or in definition? Or had those contributing to the scientific evidence underlying the acquisition of CVD risk research simply forgotten about it (Table 2)?

Riska's (2000) paper sums up the whole area of TABP research and tries to come to terms with what happened over the course of time to a concept leading to a description of a pattern of behavior, most often seen in white middle-class men, where the possession of this behavior pattern endowed a conspicuous health risk. One clear conclusion emerged from her conceptual analysis; the problem appeared to arise when the TABP ceased to be a simple and pragmatic way to identify future cardiac patients in the medical setting and evolved into a more complex psychological or personality "type." While originally only the surface of the type man was mapped by means of behavioral typing, now the exploration of the interior of the type A man had begun. Where the physicians saw behaviors, the psychologists were looking for inner reasons and tried to redesign the TABP in line with their conceptual predispositions. In a review of Riska's book, Goldstein (2006) concluded that Riska had shown that TABP and related concepts "medicalized" man's suffering in ways that denied the important role of social position.

The paper is interesting for many reasons; it gives an account of an alternative way to evaluate what had happened with the construct of the TABP, but it is also consistent with the critical comments often leveled at the two originators of the TABP, Rosenman and Friedman. These critics seldom surfaced as long as the TABP was a popular psychological construct. But Friedman and Rosenman were themselves quite often critical to the approach that psychologists took to the whole concept, and Rosenman more than once expressed the view that "I know nothing about personality and personality traits, I only know that this behaviour pattern as we have described shows with great certainty who is going to suffer a cardiac attack" (Rosenman 1997, Lecture given at 14th world congress of pychosomatic medicine, 31st Aug–5th Sept 1997, personal communication). Friedman was of the same opinion and in a paper written in 1984 criticizing psychologists and the way they treated the TABP (Friedman and Ulmer 1984). Another veteran of the type A

conceptual debate, Virginia Price, was equally critical. She wrote: "In fact, the failure to develop a conceptual model of Type A grounded in contemporary psychology seems to be responsible for the rather slow accumulation of generalizable and replicable findings in Type A research" (Price 1982, p. xiii).

Some of this understanding is also present in a later article (Myrtek 2001), in which the author fails to use the descriptor "TAPB" when referring to the concept in the title but rather refers to it as type A personality. It is quite clear from a conceptual perspective that it is the type A personality he wants to explore and not the TABP – because it employs only the keywords TAP (type A personality) and coronary heart disease, to reveal 559 published studies. The article reports a meta-analysis of prospective studies on CHD, type A [personality], and hostility covering the period 1966–1998. By doing so, he appears to fall into the same trap as others have; he mixes different concepts in undertaking the analyses without perhaps realizing that semantic or superficial relationships between the concepts used (the TABP, type A personality, and simply type A), with their varying meanings and definitions, do not allow the research outcomes to be directly comparable to one another.

The Fukoua Heart Study Group (2001) and Yoshimasu et al. (2002) report a retrospective study of type A behavior patterns and job-related psychological factors to the risk of myocardial infarction in 290 persons who have experienced a nonfatal clinical event. Here yet another scale was in use, the Tokai Activity Survey (Maeda 1991), and while they report no association between type A and coronary atherosclerosis, the use of a nonstandard scale to measure the TABP does not allow for direct comparison with studies of a similar intent.

In an attempt to establish a national consensus of psychosocial risk factors for CHD, the *Medical Journal of Australia* a decade ago published a national position statement on "stress" and coronary heart disease (Bunker et al. 2003). In this statement it was noted that while there was a good deal of positive evidence from early studies linking the TABP with CVD risk, many later studies concluded that there was no evidence for an effect of the TABP on risk of CVD (Bunker et al. 2003).

Gallacher et al. (2003) reported on an investigation into whether the TABP acts as a trigger for clinical events of CHD. The study included 2394 men and the TABP was assessed by three different self-report instruments, the Jenkins Activity Survey, the Bortner scale, and the Framingham scale. Interestingly, the most important finding from the study was that while there was no difference in type A scores between those who suffered a clinical event and those who do not, the TABP was strongly associated with the timing of the event.

Discussed the relation between behaviors believed to be related to the development of CHD and behaviors making up the TABP complex. They concluded that both hostility and time urgency, both well-known behavioral characteristics of the TABP, had been closely related to CHD development in published studies.

Oashi (2003) reviewed techniques reported in the published literature to be able to alter the TABP as a risk factor for CHD. On the basis that the modification of the TABP has resulted, in a number of reported investigations, to lower risk of CHD, he concluded that the TABP remained an important risk for CHD development.

Based on a further review of the contemporary literature, Amelang and Schmidt-Rathjens (2003) make it clear that research on TABP and similar variables in relation to CHD risk has decreased over time, while biomedical variables and their links to CHD remain widely researched. In 2004 a new research article from the Framingham Offspring Study concluded that anger and hostility would appear to be more relevant and important to the study of CHD mortality and risk of arrhythmias than TABP as a global construct has shown to be. Accordingly, Karen Matthews (2005) suggests that the time was then right to construct a new and comprehensive model for understanding the psychosocial contributors to CHD risk that broadly integrates socioeconomic status, environmental stress, and person-level factors from a life-span perspective.

From around 2006 onward, there have been very few studies specifically focusing on TABP and its relation to CHD. Rebollo and Boomsma (2006) scrutinized the hereditary impact on TABP as a risk factor for CHD development, leading to the conclusion that research in the area has now changed, from looking at CHD risk endowed by the TABP as a multidimensional construct to risk related more to emotional components like anger. However, a single empirical study from Japan that year on the impact from type A behavior on brachial-ankle pulse (as a marker for arteriosclerosis) showed that the TABP was a risk factor for arteriosclerosis and also may increase the risk of cardiovascular disease related to arteriosclerosis (Liu et al. 2006).

Of more anecdotal value are two interesting studies on TABP having outcome foci other than CHD. In the first one, the researchers used the TABP pattern to look into risk of road traffic accidents (Nabi et al. 2005) concluding that persons with the TABP had an increased risk of being involved in road traffic accidents. The other one related scores on the Jenkins Activity Survey (JAS-C) as a measure of the TABP to mood and found that the construct distinguished depressed unipolar people from depressed bipolar II patients (Wang et al. 2011).

During 2007 two further and important studies were published on TABP in relation to CHD. One was the Cardiovascular Risk in Young Finns Study (Keltikangas-Järvinen et al. 2007) where the relation of TABP to adult carotid artery intima-media thickness (IMT) was investigated. The researchers concluded that there was a significant effect of the eagerness-energy component in TABP, and that this component is a robust predictor of IMT.

The other article focused on whether diet was a potent way of mediating the association between TABP and CHD. However, the researchers were led to conclude that the association between type A behavior and CHD is unlikely to be mediated by the use of diet. Two book chapters on TABP were also published in 2007, but both were more or less historical overviews of the type A behavior research tradition and contributed little that was new to the debate.

Only a single journal article was found for 2008 (Ikeda et al. 2008). That article reports research on a prospective study of TABP in a very large population ($N = 86{,}361$) and with a CHD incidence of 669 cases at follow-up. The findings were quite clear-cut, and conclusions were that TABP does not predict CHD onset in a Japanese population; however, the authors suggest that the cardiotoxic effect from TABP is both gender specific and culturally contingent.

In 2009, again only a single relevant article for this discussion was found. It is on the psychological vulnerability of persons from a university sample who display the type A behavior pattern. The results indicate that type A individuals may experience psychosocial vulnerability, particularly stress, which may put them at risk of the experience of negative health outcomes.

For 2010 no research activity from international databases were reported, and for the following 2 years, there was just one article on TABP and its relation to CHD (Liu et al. 2012) but also a further article on the TABP and its relationship to type D personality (Zhao et al. 2011) which also have attracted attention as a CHD-prone characteristic in the research in the area. These together with a book chapter by Robert Allan in *Heart and Mind*: *The practices of Cardiac Psychology* in 2011 are the last publications on TABP and conclude this overview of TABP-related publications in the present era.

Conclusions

It is quite obvious from the evidence presented above that many of the studies of type A behavior published in the last 20 years suffer from (1) poor and imprecise operationalization of the theoretical concepts; (2) the use of number of different but poorly validated scales and instruments which have been widely used to assess TAPB or related concepts too often confused with the TABP; (3) investigations focusing on groups and samples in which the links between the TAPB and CHD have not been found for almost 40 years, namely, persons with existing CHD, or those at high risk of a recurrent attack; (4) poor, inaccurate, or vague definitions of the TAPB or its related constructs (e.g., type A personality), so mitigating against the possibility of comparing studies across the field or of reexamining them; and (5) a focus of the research in recent years on Eastern cultures that research which, incidentally, suffers from many of the methodological and conceptual problems outlined above. On these grounds, while there is clearly a need to critically consider the concept of the TABP and the evidence linking it with CHD, caution is needed lest we abandon the construct too quickly and throw out the baby with the bathwater.

Large cohort prospective studies of the TABP and CVD have not been abandoned; the TABP is clearly an area of continuing interest in Japan and other Eastern populations.

On balance, the emerging evidence indicates to us that completely discarding the TABP would at this point be premature. A better integration of demographic and cultural factors into predictive equations and the commitment to undertake the "definitive" epidemiological study with sufficient statistical power, where the TABP was the major focus of interest (a new WCGS, perhaps), would effectively address the controversy once and for all. And so a final "burial" of the construct is not yet indicated – the promise is still there.

A Dedication

It is with both affection and humility that we dedicate this chapter to Dr Ray H Rosenman, the co-originator of the Type A construct, who passed away on 20 May 2013. Ray was a good friend and a generous mentor to many of us then working in the field of Psychocardiology. His profound and original clinical insight in recognizing in his patients what subsequently became known as Type A Behaviour, and his outstanding scientific skill in turning this astute clinical observation into an operational definition capable of objective measurement, gave rise to one of the undisputed research landmarks in the area. He will be remembered by so many with respect, admiration and appreciation.

References

Amelang, M., & Schmidt-Rathjens, C. (2003). Persönlichkeit, krebs und koronare herzerkrankungen: Fiktionen und fakten in der ätiologieforschung [Personality cancer and coronary heart disease: Fictions and facts in the etiological research]. *Psychologische Rundschau, 54*(1), 12–23.

Barefoot, J. C., Dahlstrom, W. G., & Williams, R. B. (1983). Hostility, CHD incidence and total mortality. *Psychosomatic Medicine, 45*, 59–64.

Barefoot, J. C., Dodge, K. A., Peterson, B. L., Dahlstrom, W. G., & Williams, R. B. (1989). The Cook-Medley hostility scale: Item content and ability to predict survival. *Psychosomatic Medicine, 51*(1), 46–57.

Booth-Kewley, S., & Friedman, H. S. (1987). Psychological predictors of heart disease: A quantitative review. *Psychological Bulletin, 101*(3), 343–362.

Bortner, R. W. (1969). A short rating scale as a potential measure of pattern A behavior. *Journal of Chronic Diseases, 22*, 87–91.

Bunker, S. J., Colquhoun, D. M., MD, E., Hickie, I. B., Hunt, D., Jelinek, V. M., et al. (2003). "Stress" and coronary heart disease: Psychosocial risk factors. *Medical Journal of Australia, 178*(6), 272–276.

Byrne, D. G. (1996). Type A behavior, anxiety, and neuroticism: Reconceptualizing the pathophysiological paths and boundaries of coronary-prone behavior. *Stress Medicine, 12*, 227–238.

Byrne, D. G., & Caddy, G. R. (1992). *International perspectives in behavioral medicine* (Vol. 1). Norwood: Ablex Publishing.

Byrne, D. G., & Rosenman, R. H. (1990). *Anxiety and the heart*. New York: Hemisphere.

Carey, W. B., & McDevitt, S. C. (1994). *Prevention and early intervention: Individual differences as risk factors for the mental health of children: A festschrift for Stella Chess and Alexander Thomas*. New York: Brunner/Mazel.

Chesney, M. A., Eagleston, J. R., & Rosenman, R. H. (1980). The Type A structured interview: A behavioural assessment in the rough. *Journal of Behaviour Assessment, 2*(4), 255–272.

Chesney, M. A., Hecker, M. H. L., & Black, G. W. (1988). Coronary-prone components of Type A behavior in the WCGS: A new methodology. In B. K. Houston & C. R. Snyder (Eds.), *Type A behavior pattern: Research, theory, and intervention* (Wiley series on health psychology/behavioral medicine, pp. 168–188). New York: Wiley-Interscience.

Cohen, J. B., & Reed, D. (1985). The Type A behavior pattern and coronary heart disease among Japanese men in Hawaii. *Journal of Behavioral Medicine, 8*, 343–352.

Cooper, C. L., & Payne, R. (1991). *Personality and stress: Individual differences in the stress process* (Wiley series on studies in occupational stress). Chichester: Wiley.

Craig, K. D., & Weiss, S. M. (1990). *Health enhancement, disease prevention, and early intervention: Biobehavioral perspectives*. Conference proceedings based on the 18th Banff International Conference on Behavioral Sciences, held in Banff, Alberta, Canada in 1986.

Edwards, J. R., & Baglioni, A. J. (1991). Relationship between Type A behavior pattern and mental and physical symptoms: A comparison of global and component measures: Correction. *Journal of Applied Psychology, 76*(5), 643.

Eriksen, W. (1994). The role of social support in the pathogenesis of coronary heart disease: A literature review. *Family Practice, 11*(2), 201–209.

Espnes, G. A. (1996). The Type 2 construct and personality traits: Aggression, hostility, anxiety and depression. *Personality & Individual Differences, 20*(5), 641–648.

Espnes, G. A., & Opdahl, A. (1999). Associations among behavior, personality, and traditional risk factors for coronary heart disease: A study at a primary health care center in mid-Norway. *Psychological Reports, 85*(2), 505–517.

Forgays, D. K., Forgays, D. G., Bonaiuto, P., & Wrezsniewski, K. (1993). Measurement of the Type A behaviour pattern from adolescence through midlif: Further development of the Adolescent/Adult Type A Behavior Scale (AATABS). *Journal of Behavioral Medicine, 16*, 64–77.

Friedman, H. S., & Booth-Kewley, S. (1987a). The "disease-prone personality" a meta-analytic view of the construct. *American Psychologist, 42*(6), 539–555.

Friedman, H. S., & Booth-Kewley, S. (1987b). Personality, Type A behavior, and coronary heart disease: The role of emotional expression. *Journal of Personality and Social Psychology, 53*(4), 83–792.

Friedman, H. S., & Booth-Kewley, S. (1988). Validity of the Type A construct: A reprise. *Psychological Bulletin, 104*(3), 381–384.

Friedman, M., & Rosenman, R. H. (1974). *Type A behavior and your heart*. New York: Knopf.

Friedman, M., & Ulmer, D. (1984). *Treating Type A behavior and your heart*. New York: Knopf.

Friedman, M., Thoresen, C. E., Gill, J. J., Ulmer, U., Thompson, L., Powell, L., Price, V., Elek, S. R., Rabin, D. D., Breall, W. S., Piaget, G., Dixon, T., Bourg, E., Levy, R. A., & Tasto, D. L. (1982). Feasibility of altering type A behavior pattern after myocardial infarction. Recurrent Coronary Prevention Project Study: Methods, baseline results and preliminary findings. *Circulation, 66*, 83–92.

Friedman, M., Fleischmann, N., & Price, V. (1996). Diagnosis of Type A behavior pattern. In R. Allan & S. Scheit (Eds.), *Heart and mind: The practice of cardiac psychology* (pp. 179–196). Washington, DC: American Psychological Association.

Gallacher, J. E., Sweetnam, P. M., Yarnell, J. W., Elwood, P. C., & Stansfeld, S. A. (2003). Is type A behavior really a trigger for coronary heart disease events? *Psychosomatic Medicine, 65*(3), 339–346.

Ganster, D. C., Schaubroeck, J., Sime, W. E., & Mayes, B. T. (1991). The nomological validity of the Type A personality among employed adults. *Journal of Applied Psychology, 76*(1), 143–168.

Gildea, E. (1949). Special features of personality which are common to certain psychosomatic disorders. *Psychosomatic Medicine, 11*, 273–277.

Goldberger, L., & Breznitz, S. (1993). *Handbook of stress: Theoretical and clinical aspects* (2nd ed.). New York: The Free Press.

Goldstein, M. S. (2006). Masculinity and Men's Health: Coronary Heart Disease in Medical and Public Discourse, *International Journal of Men's Health, 5*(1), 107–108.

Greenglass, E. R., & Julkunen, J. (1991). Cook-Medley hostility, anger, and the Type A behavior pattern in Finland. *Psychological Reports, 68*(32), 1059–1066.

Harbin, T. J. (1989). The relationship between the type A behavior pattern and physiological responsivity: A quantitative review. *Psychophysiology, 26*(1), 110–119.

Haynes, S. G., Feinleib, M., & Kannel, W. B. (1980). The relationship of psychosocial factors to coronary heart disease in the Framingham study. III. Eight-year incidence of coronary heart disease. *American Journal of Epidemiology, 3*, 37–58.

Hill, D. R., Kelleher, K., & Shumaker, S. A. (1991). Psychosocial interventions in adult patients with coronary heart disease and cancer: A literature review. *General Hospital Psychiatry, 14*(6), 28–42.

Ikeda, A., Hiroyasu, I., Kawashi, I., Inoue, M., Tsugane, S., & for the JPHC Study Group. (2008). Type A behaviour and risk of coronary heart disease: The JPHC study. *International Journal of Epidemiology, 37*(6), 1395–1405.

Jenkins, C. D., Zyzanski, S. J., & Rosenman, R. H. (1971). Progress toward validation of a computer scored test for the Type A coronary prone behavior pattern. *Psychosomatic Medicine, 33*, 193–202.

Johnston, D. W., Cook, D. G., & Shaper, A. G. (1987). Type A behaviour and ischemic heart disease in middle aged British men. *British Medical Journal, 295*, 86–89.

Kawachi, I., Sparrow, D., Kubzansky, L. D., Spiro, A., 3rd, Vokonas, P. S., & Weiss, S. T. (1998). Prospective study of a self-report type A scale and risk of coronary heart disease: Test of the MMPI-2 type A scale. *Circulation, 98*, 405–412.

Keltikangas-Järvinen, L., Hintsa, T., Kivimäki, M., Puttonen, S., Juonala, M., Viikari, J. S. A., & Raitakari, O. T. (2007). Type A eagerness-energy across developmental periods predicts adulthood carotid intima-media thickness: The Cardiovascular Risk in Young Finns Study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 27*, 1638–1644.

Kemple, C. (1945). Rorschach method and psychosomatic diagnosis: Personality traits of patients with rheumatic disease, hypertension, cardiovascular disease, coronary occlusion and fracture. *Psychosomatic Medicine, 7*, 85–89.

Kittel, F. (1986). Type A behavior and other psychological factors in relation to coronary heart disease. In T. H. Smidt, D. M. Dembroski, & G. Blumchen (Eds.), *Biological and psychological factors in cardiovascular disease* (pp. 63–84). West Berlin: Springer.

Kopper, B. A. (1993). Role of gender, sex role identity, and Type A behavior in anger expression and mental health functioning. *Journal of Counseling Psychology, 40*(2), 232–237.

Kornitzer, M., Kittel, F., De Backer, G., & Dramaix, M. (1981). The Belgian Heart Disease Prevention Project: Type "A" behavior pattern and the prevalence of coronary heart disease. *Psychosomatic Medicine, 43*(2), 133–145.

Krantz, D. S., Contrada, R. J., Hill, D. R., & Friedler, E. (1988). Environmental stress and biobehavioral antecedents of coronary heart disease. *Journal of Consulting & Clinical Psychology, 56*(3), 333–341.

Leon, G. R., Finn, S. E., Murray, D., & Bailey, J. M. (1988). Inability to predict cardiovascular disease from hostility scores or MMPI items related to Type A behavior. *Journal of Consulting & Clinical Psychology, 56*(4), 597–600.

Liu, H., Saijo, Y., Zhang, X., Shiraishi, Y., Luo, Y., Maruyama, M., et al. (2006). Impact of Type A behaviour on brachial-ankle pulse wawe velocity in Japanese. *Tohku Journal of Experimental Medicine, 209*(1), 15–21.

Liu, T., Deng, G.-h., Zhang, L.-y., & Jing, M. (2012). Effect of the Type A behaviour pattern on the heart autonomic nerve activity in healthy males. *Chinese Journal of Clinical Psychology, 20*(3), 301–304.

Low, K. G. (1991). Psychosocial variables, Type A behavior pattern, and coronary heart disease in women. *Dissertation Abstracts International, 52*(1-A), 85.

Lyness, S. A. (1993). Predictors of differences between Type A and B individuals in heart rate and blood pressure reactivity. *Psychological Bulletin, 114*(2), 266–295.

Maeda, S. (1991). Application of a brief questionnaire for the behaviour pattern survey. *Taipu A, 2*, 33–40.

Markovitz, J. H., Matthews, K. A., Kiss, J., & Smitherman, T. (1996). Effects of hostility on paletelet reactivity to psychological stress in coronary heart disease patients and in healthy controls. *Psychosomatic Medicine, 58*(2), 143–149.

Matthews, K. A. (1988). Coronary heart disease and Type A behaviors: Update on and alternative to the Booth-Kewley and Friedman (1987) quantitative review. *Psychological Bulletin, 104*(3), 373–380.

Matthews, K. A. (2005). Psychological perspectives on the development of coronary heart disease. *American Psychologist, 60*(8), 783–796.

Menninger, K. A., & Menninger, W. C. (1936). Psychoanalytic observationes in cardiac disorders. *American Heart Journal, 11*, 10–26.

Miller, T. Q., Turner, C. W., Tindale, R. S., & Posavac, E. J. (1988). Disease-based spectrum bias in referred samples and the relationship between Type A behaviour and artheroschlerosis. *Journal of Clinical Epidemiology, 41*, 1139–1149.

Miller, T. Q., Turner, C. W., Tindale, R. S., Posavac, E. J., & Dugoni, B. L. (1991). Reasons for the trend toward null findings in research on Type A behavior. *Psychological Bulletin, 110*(3), 469–485.

Monat, A., & Lazarus, R. S. (1991). *Stress and coping: An anthology*. New York: Columbia University Press.

Munakata, M., Hiraizumi, T., Nunokawa, T., Ito, N., Taguchi, F., Yamauchi, Y., & Yoshinaga, K. (1999). Type A behavior is associated with an increased risk of left ventricular hypertrophy in male patients with essential hypertension. *Journal of Hypertension, 17*(1), 115–120.

Myrtek, M. (1995). Type A behavior pattern, personality factors, disease, and physiological reactivity: A meta-analytic update. *Personality & Individual Differences, 18*(4), 491–502.

Myrtek, M. (2001). Meta-analyses of prospective studies on coronary heart disease, type A personality, and hostility. *International Journal of Cardiology, 79*, 245–251.

Nabi, H., Consoli, S. M., Chastang, J.-F., Chiron, M., Lafont, S., & Lagarde, E. (2005). Type A behavior pattern, risky driving behaviors, and serious road traffic accidents: A prospective study of the GAZEL cohort. Epidemiologic reviews. *American Journal Epidemiology, 161*(9), 864–870.

Oshi, O. (2003). A review of the psychological interventions for the modification of Type A behavior pattern. *Japanese Journal of Counseling Science, 36*(2), 175–186.

Osler, W. (1892). *Lectures on angina pectoris and allied states*. New York: D. Appelton.

Osler, W. (1910). Lectures on angina pectoris. *Lancet, 1*, 839–844.

Pearson, T. A. (1994). Coronary arteriography in the study of the epidemiology of coronary heart disease. *Epidemiological Reviews, 6*, 140–166.

Pickering, T. G. (1985). Should studies of patients undergoing angiography best used to evaluate the role of behavioral risk factors for coronary heart disease. *Journal of Behavioral Medicine, 8*(3), 203–213.

Price, V. A. (1982). *Type A behavior pattern: A model for research and practice*. New York: Academic.

Raeikkoenen, K. (1992). Modern views on the concept of Type A behavior. *Psychiatria Fennica, 23*, 89–94.

Rebollo, I., & Boomsma, D. I. (2006). Genetic analysis of anger: Genetic dominance or competitive sibling interaction. *Behavior Genetics, 36*(2), 216–228.

Review Panel. (1981). Coronary-prone behaviour and coronary heart disease: A critical review. *Circulation, 63*, 1199–1215.

Richards, J. C., For, A., & Alvarenga, M. (2000). Serum lipids and their relationships with hostility and angry affect and behaviors in men. *Health Psychology, 19*(4), 393–398.

Riska, E. (2000). The rise and fall of Type A man. *Social Science and Medicine, 51*, 1665–1674.

Rosenman, R. H. (1990). Type A behavior pattern: A personal overview. *Journal of Social Behavior & Personality, 5*(1), 1–24.

Rosenman, R. H., Friedman, M., Straus, R., Wurm, M., Kositchek, R., Hahn, W., & Werthessen, N. (1964). A predictive study of coronary heart disease. The Western Collaborative Group Study. *Journal of the American Medical Association, 189*, 15–26.

Rosenman, R. H., Straus, R., Wurm, M., Jenkins, C. D., & Messinger, H. B. (1966). Coronary heart disease in the Western Collaborative Group Study: A follow-up experience of two years. *Journal of the American Medical Association, 195*(2), 86–92.

Rosenman, R. H., Brand, R. J., Jenkins, C. D., Friedman, M., Straus, R., & Wurm, M. (1975). Coronary heart disease in the western collaborative heart study: Final follow up experience of 8½ year. *Journal of the American Medical Association, 233*, 420–425.

Rosenman, R. H., Brand, R. J., Sholtz, R. I., & Friedman, M. (1976). Multivariate prediction of coronary heart disease during the 8.5 year follow-up in the Western Collaborative Group Study. *American Journal of Cardiology, 37*(6), 903–910.

Shekelle, R. B., Gale, M., Ostfeld, A. M., & Paul, O. (1983). Hostility, risk of coronary heart disease, and mortality. *Psychosomatic Medicine, 45*, 109–114.

Siegman, A. W., & Smith, T. W. (1994). *Anger, hostility, and the heart*. Hillsdale: Lawrence Erlbaum Associates.

Snyder, C. R., & Forsyth, D. R. (1991). *Handbook of social and clinical psychology: The health perspective* (Pergamon general psychology series). Elmsford: Pergamon.

Spielberger, C. D., Sarason, I. G., et al. (1991). *Stress and anxiety* (The series in clinical and community psychology, Vol. 13). New York: Hemisphere.

Strube, M. J. (1991). *Type A behavior*. Thousand Oaks: Sage.

Suls, J., & Marco, C. A. (1990). Relationship between the JAS and FTAS-TABP and non-CHD illness: A prospective study controlling for negative affectivity. *Health Psychology, 9*(4), 479–492.

Todaro, J. F., Shen, B.-J., Niaura, R., Spiro, A., III, & Ward, K. (2003). Effect of negative emotions on frequency of coronary heart disease (the Normative Aging Study). *The American Journal of Cardiology, 92*(15), 901–906.

Wang, Y., Terao, T., Hoaki, N., Goto, S., Tsuchiyama, K., Iwata, N., et al. (2011). Type A behavior pattern and hyperthymic temperament: Possible association with bipolar IV disorder. *Journal of Affective Disorders, 133*(1–2), 22–28.

Weekes, B. S., & Waterhouse, I. K. (1991). Hostile attitudes and the coronary prone personality. *Australian Psychologist, 26*(1), 33–36.

Williams, R. B., Jr., & Barefoot, J. C. (1988). Coronary-prone behavior: The emerging role of the hostility complex. In B. K. Houston & C. R. Snyder (Eds.), *Type A behavior pattern: Research, theory, and intervention* (Wiley series on health psychology/behavioral medicine, pp. 189–211). New York: Wiley-Interscience.

Williams, R. B., Jr., Janey, T. L., Kee, K. L., Kong, Y., Blumenthal, J. A., & Whalen, R. E. (1980). Type A behavior, hostility, and coronary atheroschlerosis. *Psychosomatic Medicine, 42*, 539–549.

Yoshimasu, K., & Fukoua Heart Study Group. (2001). Relation of type A behavior pattern and job-related psychosocial factors to nonfatal myocardial infarction: A case-control study of Japanese male workers and women. *Psychosomatic Medicine, 63*(5), 797–804.

Yoshimasu, K., Washio, M., Tokunaga, S., Tanaka, K., Liu, Y., Kodama, H., et al. (2002). Relation between type A behavior pattern and the extent of coronary atherosclerosis in Japanese women. *International Journal of Behavioral Medicine, 9*(2), 77–93.

Zapotoczky, H.-G., & Wenzel, T. (1990). *The scientific dialogue: From basic research to clinical intervention* (Annual series of European research in behavior therapy, Vol. 5). Conference Proceedings from Congress of the European Association of Behaviour Therapy, 19th, Vienna.

Zhao, X.-r., Bai, J.-y., Li, N., & Xu, X.-f. (2011). Two year follow-up on the psychosocial factors influencing the prognosis of the patients with coronary heart disease. *Chinese Journal of Clinical Psychology, 19*(9), 106–109.

Anger, Hostility, and Cardiovascular Disease in the Context of Interpersonal Relationships

Ephrem Fernandez and Timothy W. Smith

Contents

Abstract

Anger and hostility are described with special attention to their cognitive-motivational properties. Varying operational definitions related to anger self-report and behavioral observation are presented. The idea that anger can be maladaptive is now widely accepted as in DSM and alternative classifications of dysfunctional anger. The idea that maladaptive anger raises risks for hypertension and coronary heart disease is reviewed with reference to empirical findings on mediators such as atherosclerosis, cardiovascular reactivity, immune system

E. Fernandez (✉)
Department of Psychology, University of Texas, San Antonio, TX, USA
e-mail: ephrem.fernandez@utsa.edu

T.W. Smith
Department of Psychology, University of Utah, Salt Lake City, UT, USA
e-mail: tim.smith@psych.utah.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_31

changes, and unhealthy lifestyles. Given that anger is a relational emotion, it is not surprising that it befalls many interpersonal relations including close/intimate relationships. Dimensions of affiliation and control in relationships are presented as a framework for understanding how anger and hostility can develop and persist in these contexts. The further connection between such anger and cardiovascular function is illustrated. Fortunately, maladaptive anger is treatable, as explained with meta-analytic evidence on cognitive behavioral therapy (CBT). Also available are recent enhancements like CBAT that involve sequencing multiple cognitive, behavioral, and affective strategies appropriate to the process of anger from onset, through progression, to offset. Finally, traditional interpersonal therapies and newer therapeutic formulations such as acceptance and commitment therapy may address major themes in interpersonal conflict underlying the onset and maintenance of cardiovascular disease. Yet, many of these potential applications still await research and implementation in the field of psychocardiology.

Keywords

Anger • Hostility • Cardiovascular disease • Reactivity • Hypertension • Interpersonal relationships • Affiliation • Dominance-submission • Cognitive behavioral affective therapy • CBAT

Introduction

Of the psychosocial factors implicated in cardiovascular disease (CVD), anger and hostility have remained in the foreground for several decades (Chida and Steptoe 2009; Smith et al. 2004). In this chapter, evidence and theories are presented on the connection between CVD and anger/hostility. The focus will be on interpersonal contexts of anger and CVD, given the substantial accumulation of literature on this topic. As a preliminary, the concept of anger and related constructs are defined.

Phenomenology of Anger and Related Constructs

The many definitions of anger differ in points of emphasis. At a basic level, anger can be defined as, "an unpleasant emotion ranging in intensity from irritation or annoyance to fury or rage" (Smith 1994, p. 25). Some definitions emphasize that anger is a moral emotion in the sense that it implies a perceived discrepancy with a standard of conduct (e.g., Hutcherson and Gross 2011). Others see it as an approach emotion that occurs when progress toward desired goals is impeded (e.g., Carver and Harmon-Jones 2009), though indirect and even detached expression of anger should not go unrecognized especially in the present population of interest. Finally, a number of scholars point out that anger is a relational emotion that occurs in a socially constructed context (Laughlin and Warner 2005); this is highly consistent with the interpersonal perspective of anger in cardiovascular disease (Smith and Cundiff 2011).

There is little disagreement that anger is essentially unpleasant. Though it can certainly be functional in alerting one to a transgression or communicating displeasure to the offender, anger is hardly welcome to its experiencer or its recipient. The expression of anger can have beneficial consequences as when an opponent concedes or submits, but this does not mean that one likes to be angry for the sake of itself. The risks posed by anger include interpersonal conflict, impaired judgment, and a host of physical symptoms of which particularly pertinent for present purposes is the toll anger takes on cardiovascular health (Smith et al. 2004; Smith and Traupman 2011). As noted by Howells (2004), "the argument that angry emotions, when poorly regulated, understood and expressed, make a major contribution to human distress is a compelling one" (p. 195). The arousal of anger is often associated with universally recognized patterns of facial activation and expression and as described below a set of potentially unhealthy psychophysiological responses especially involving the cardiovascular system.

In keeping with the cognitive-motivational structure of emotions (Lazarus 2000), anger comprises a cognitive element of appraised wrongdoing and an action tendency to counter or redress that wrongdoing (Smedslund 1993; Wranik and Scherer 2010). Cognitive schemas closely associated with anger are often labeled *hostility*, referring to a "negative attitude toward others consisting of enmity, denigration, and ill will" (Smith 1994, p. 26). These cognitive styles include cynicism (i.e., a belief that other people are motivated largely by selfish concerns), mistrust (i.e., expectations that others are likely sources of mistreatment), and hostile attribution (i.e., the tendency to construe the actions of others as aggressive or hurtful in intent). Thus, cognitive-motivationally, hostility has been defined as "a devaluation of the worth and motives of others, an expectation that others are likely sources of wrongdoing, a relational view of being in opposition toward others, and a desire to inflict harm or see others harmed" (Smith 1994, p. 26).

Aggression, though often used as a proxy for measuring anger does not necessarily contain anger, as observed by Averill (1983) in his landmark paper. To be aggressive, according to the social psychological perspective, is to perform behavior that is intended to harm, hurt, or damage – physically or psychologically. These "attacking, destructive, or hurtful actions" (Smith 1994, p. 26.) range in degree or severity, from sarcasm or subtle criticism to direct and pointed insults, to intimidating postures and facial expressions (e.g., glaring, scowling), and to physically threatening behavior. A subtype of physical aggression is violence in which case the intended harm/hurt/damage does materialize.

In addition to its structure, anger, like all affective qualia, can be characterized in terms of form. Specifically, does it take the form of an emotion, mood, or temperament? (Fernandez 2008). As a discrete emotion, it has a marked onset and offset and this episode is labeled state anger. In the form of mood, it is relatively continuous and lower in intensity. As a recurrent occurrence, it is often regarded as temperament or trait anger. This is often used synonymously with the term hostility, which connotes a proneness to anger (Ramirez and Andreu 2006); as noted previously, hostility is often attributed to an attitudinal bias or underlying

schema of strong disapproval toward others (Brodsky 2011). In short, anger takes three main forms depending on such parameters as frequency, duration, and intensity. To say that someone is in an angry state is quite different from saying that she/he is in an irritable/irascible mood, which in turn differs from characterizing someone as having a hostile temperament (Fernandez 2013).

Operational Definitions and Anger Assessment

The operationalization of anger, hostility, and related characteristics in research and practice has been handled using a range of psychological tests and structured interviews. The vast majority of these are self-report questionnaires. Beginning with offshoots of the MMPI (e.g., Cook-Medley Hostility Scale or Ho Scale; Cook and Medley 1954), attention was directed at hostility or trait anger. The early Buss-Durkee Hostility Inventory (BDHI; Buss and Durkee 1957) later revamped into the Buss-Perry Aggression Questionnaire (Buss and Perry 1992) introduced a valuable distinction between direct and indirect expression of anger. Other tests veered toward hypothetical scenarios of anger provocation (e.g., Novaco Anger Scale and Provocation Inventory (Novaco 1994, 2003)). Another wave of questionnaires highlighted distinctions between trait versus state anger and styles of anger expression (i.e., anger-in vs. anger-out). The most common of these is the State-Trait Anger Expression Inventory (STAXI; Spielberger 1988, 1991, 1999) which is referred to in several of the studies reported later. In fact, much of the literature on anger and CVD is based on MMPI derivatives such as the Ho Scale and from the more recent STAXI. Despite acceptable psychometrics, these instruments are not without shortcomings in how the vast and complex topography of anger is represented. A new generation of anger assessment instruments attempts to overcome some of these shortcomings by introducing a variety of additional parameters and expression styles of anger (see review by Fernandez et al. 2015).

Beyond the most commonly used self-report approaches, behavioral ratings of anger and hostility have been developed for use with structured interviews (Smith 1994), and informant ratings for these traits are also available (Smith et al. 2007). Although self-reports of anger, hostility, and aggressiveness predict the development and course of CVD and are consistently correlated with behavioral and informant ratings, the latter assessments are often more closely related to cardiovascular disease (Miller et al. 1996; Newman et al. 2011; Smith et al. 2007). This may reflect the fact that because anger and related traits are socially undesirable, individuals are often unwilling or unable to provide accurate self-reports, whereas their tendency to experience and display anger may be readily apparent to others. In clinical contexts, interview-based behavioral ratings and informant reports may be valuable additions to the typical self-report approaches.

Diagnosis of Dysfunctional Anger

In DSM-5 (American Psychiatric Association 2013), a mental disorder is "a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning" (p. 20). No longer is there a reference to significantly increased risk of "pain, disability, death, or important loss of freedom" as in DSM-IV (American Psychiatric Association 2000, p. xxxi). Thus, anger that portends such dire consequences as violence and incarceration would not ipso facto amount to a mental disorder. Yet, aggressive or violent anger raises the possibility of marked disturbance in actions, thoughts, or emotional control that render it dysfunctional. Despite that, anger, unlike depression and anxiety, does not appear as a separate diagnostic category in DSM. Rather it appears as isolated disorders or else it is embedded as a symptom within other disorders. Two of these in which anger is a defining feature are Intermittent Explosive Disorder (IED) and Disruptive Mood Dysregulation Disorder (DMDD). The former is described as recurrently uncontrolled anger culminating in disproportionate physical or verbal aggression. The latter includes not only angry outbursts but also chronic irritability and hypomania. While it is beyond the scope of the present paper to discuss these disorders, it is worth keeping in mind that anger in CVD populations may be dysfunctional in ways that resemble IED or DMDD.

Anger, Hostility, and Cardiovascular Disease

The study of anger and related traits as influences on the development and course of coronary heart disease (CHD) and other forms of cardiovascular disease (CVD) such as essential hypertension and stroke has a long history in medicine (Smith et al. 2004). In more recent decades, this topic was an outgrowth of research on the Type A coronary-prone behavior pattern (Miller et al. 1996; Byrne 2000), in which research sought to identify the "toxic core" of the multifaceted Type A pattern. Quantitative reviews of prospective studies indicate that high levels of anger, hostility, and aggressiveness increase the risk of the initial development of CHD, as well as increase the risk of recurrent cardiac events and earlier mortality among patients with existing disease (Miller et al. 1996; Chida and Steptoe 2009).

Given the decades-long natural history of CHD (see chapter 1, this volume), these associations raise an important question as to which phases of the disease are potentially influenced by anger and hostility. The current evidence suggests a role in multiple disease stages. For example, among persons without any clinical signs of clinical CVD, anger and hostility are associated with early, asymptomatic indicators of atherosclerosis, including endothelial dysfunction and arterial stiffness (Gottdiener et al. 2003; Williams et al. 2006), atherosclerosis in the carotid arteries (Everson-Rose et al. 2006), and coronary artery calcification (Smith et al. 2007).

Episodes of anger can also precipitate or "trigger" acute cardiac events, such as myocardial infarction (Mostofsky et al. 2013, 2014). Among patients with advanced coronary atherosclerosis, experimentally evoked anger (e.g., recall and discussion of anger-arousing events) can evoke myocardial ischemia (Strike and Steptoe 2005). Thus, anger and hostility most likely predict the development of CHD morbidity and mortality because they promote the initial development and progression of the underlying atherosclerosis but also because these traits can contribute to the precipitation of ischemia and acute coronary crises among persons with advanced disease.

These associations likely reflect multiple biobehavioral mechanisms. For example, anger and hostility are associated with unhealthy lifestyles, including tobacco use, alcohol abuse, physical inactivity, and poor diet (Bunde and Suls 2006). In some studies, these poor health behaviors mediate the association between anger / hostility and CHD outcomes (e.g., Boyle et al. 2008). However, in many other instances, anger and hostility predict CHD morbidity and mortality even when health behaviors are statistically controlled, suggesting a role for mechanisms beyond poor health habits.

The physiological effects of psychological stressors (e.g., Esler et al. 2008; Wright and Stewart 2012) also may play an important role. Frequent and pronounced increases in heart rate, blood pressure, and neuroendocrine events (e.g., catecholamines, cortisol) in response to stressful circumstances and the delayed recovery of these physiological responses can contribute to atherosclerosis and the triggering of acute CHD events (Chida and Steptoe 2009; Steptoe and Kivimaki 2013). Chronically angry and hostile persons, compared to more even-tempered and agreeable individuals, show heightened physiological responses to a variety of stressors but especially those involving interpersonal conflict or mistreatment (Smith et al. 2004). Anger and hostility also interfere with the otherwise beneficial effects of social support in dampening these physiological stress responses (Holt-Lunstad et al. 2008; Smith et al. 2004). That is, unlike more trusting and agreeable persons, chronically angry and hostile individuals do not display attenuated physiological responses to acute stressors when they receive social support. Trait anger and hostility are also associated with chronic systemic inflammation (Smith et al. in press; Suarez 2012), and this sustained immune system response is closely tied to the development and progression of atherosclerosis (Steptoe and Kivimaki 2013). Thus, increased frequency, degree, and duration of physiological stress responses may contribute to the association of anger and hostility with CVD in general and with CHD in particular.

Physiological stress responses typically recover during sleep, falling below daytime levels. Thus, adequate restorative sleep is associated with lower risk of CVD, whereas poor or inadequate sleep is associated with greater risk (e.g., King et al. 2008). Chronic anger and hostility are associated with poor sleep (Brissette and Cohen 2002), which may be an additional mechanism contributing to the association with CVD.

Anger in Interpersonal Relationships

High trait anger or hostility is associated with a wide variety of difficulties in interpersonal relationships, and these social processes may also contribute to their unhealthy effects (Smith et al. 2004; Smith and Cundiff 2011). For example, anger and hostility are associated with low levels of social support (Smith et al. 2004) and high levels of conflict and disruption in close relationships, such as marriage (Baron et al. 2007; Renshaw et al. 2010). Low social support and higher strain in intimate relationships are both associated with greater risk of CHD morbidity and mortality (Barth et al. 2010; Robles et al. 2014; Smith et al. 2011). Thus, anger and hostility may contribute to CHD in part because they are closely tied to other psychosocial risk factors, specifically those related to the quality of social relationships.

The interpersonal perspective in personality and clinical psychology (Horowitz and Strack 2011; Pincus and Ansell 2013) is useful in describing this association among multiple psychosocial risk factors for CHD and ultimately in providing an integrative account that could inform risk reduction efforts (Smith and Cundiff 2011; Smith et al. 2004). In this perspective, personality and emotional traits are seen as inseparably tied to recurring patterns of social interaction. Specifically, aspects of the social environment that are substantial and stable enough to affect the decades-long development and course of CHD (e.g., social support, isolation, conflict) are in large part manifestations of the individual's personality. Such recurring interpersonal events not only reflect the individual's personality and emotional adjustment but shape and maintain personality characteristics and emotional adjustment, as well, in an ongoing reciprocal process.

As seen in Fig. 1, interpersonal actions and stimuli can be described as varying blends of two basic dimensions of social behavior. *Affiliation* varies from warm, close, and supportive behavior to cold, hostile, and quarrelsome behavior. *Control* varies from dominant and directive actions to deferent, accommodating, or submissive responses. Anger and hostility are obviously associated with the tendency to express low levels of affiliation (i.e., low warmth and closeness, high isolation, and antagonism). Importantly, chronically angry and hostile persons not only display this pattern of low affiliation *toward* others, they also experience a similar pattern of behavior *from* others. Many different aspects of anger and hostility are consistently associated with this pattern of low affiliation, but they vary widely in terms of control. Some forms of anger and hostility, such as verbal aggressiveness and the tendency to express rather than suppress angry affect (i.e., anger-out), are characterized by a hostile-dominant interpersonal style. Other forms (e.g., resentment, cynicism, anger-in) are associated with a hostile-submissive interpersonal style (Smith et al. 2010). This will be taken up further in the section on anger suppression.

In the interpersonal perspective, the behavior of one individual tends to invite or evoke a restricted class of responses from interaction partners. Specifically,

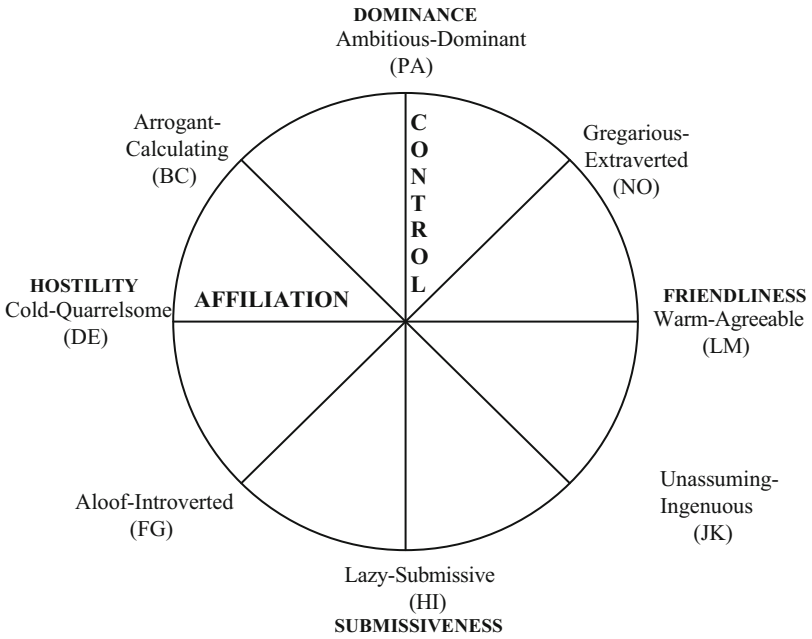


Fig. 1 The interpersonal circumplex. Social behavior is described as various blends of the two basic dimensions of *affiliation* and *control*. Anger, hostility, and aggressiveness are all associated strongly with low affiliation, but different aspects of this domain range from hostile dominance to hostile submissiveness

expressions of warmth invite warmth in return, whereas expressions of hostility tend to invite or evoke quarrelsomeness, coldness, and other hostile actions in return. This general view, labeled the principle of complementarity in interpersonal theory (Pincus and Ansel 2013) may explain the fact that chronic anger and hostility are consistently associated with low levels of social support and high levels of interpersonal conflict. Warm expression of dominance tend to evoke friendly cooperation or deference in return, but hostile dominance evokes either resentful compliance from others or more pointed contexts for dominance and control. Thus, in social interactions, angry and hostile persons tend to reap what they sow, and over time these reactions from their social environment provide ample evidence for the angry and hostile person that their antagonistic stance toward others is well justified, in a recurring pattern of self-fulfilling prophecy. In this way, anger and hostility do not simply reflect characteristics of the individual but are fully embedded in a larger, ongoing interpersonal environment of low support and high conflict which itself confers risk for CVD.

This dysfunctional interpersonal pattern is depicted in Fig. 2. Aspects of the angry and hostile individual's internal experience (e.g., cynical beliefs about the motives of others, expectations of mistreatment, hostile attributions, and

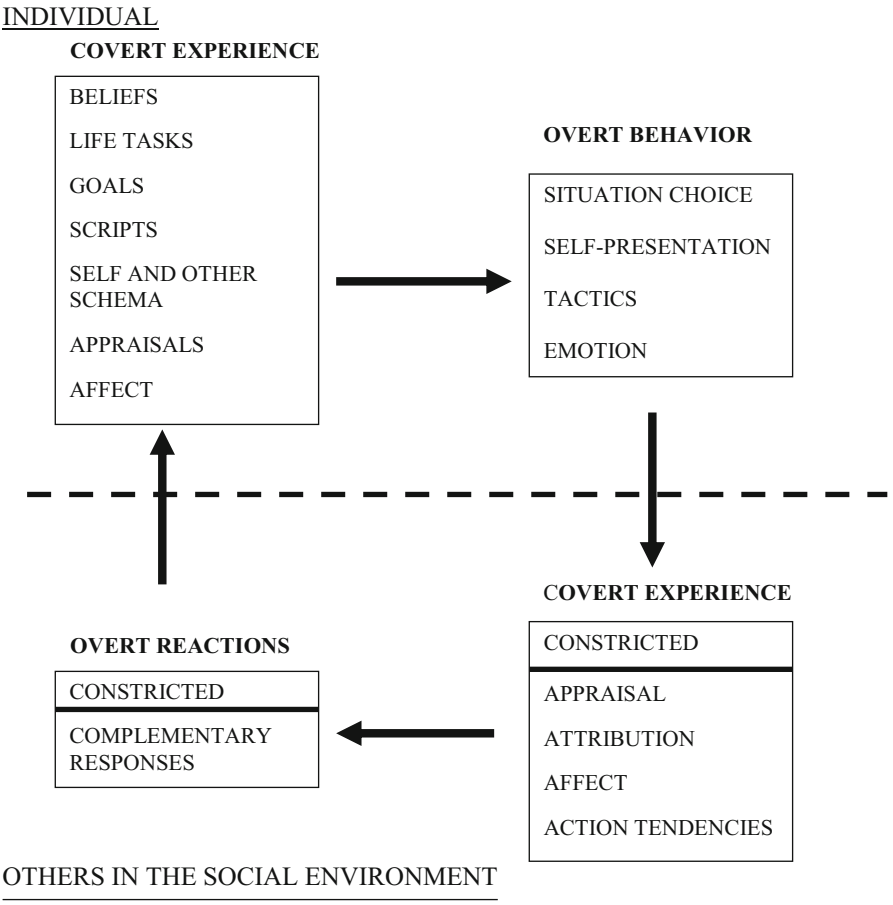


Fig. 2 The transactional cycle. Individuals' covert experiences (e.g., goals, affect, beliefs) guide their overt behavior, in ways that tend to constrict the range of possible covert and overt reactions by their interaction partners

explanation for other's actions) lead him/her to behave outwardly with low warmth and high hostility. These behavioral expressions limit the subjective impact of the angry actor's behavior on their interaction partners, increasing the likelihood that angry, hostile, and aggressive behavior will be reciprocated, further maintaining and perhaps exacerbating the angry actor's emotional, cognitive, and behavioral tendencies.

This perspective suggests an expanded view of the role of physiological reactivity in the association of anger and hostility with CVD. As illustrated in Fig. 3, compared to the blood pressure response of the friendly person depicted in the lower panels, the hostile-dominant individual depicted in the upper panels responds with larger and more prolonged increases in blood pressure in response to the same

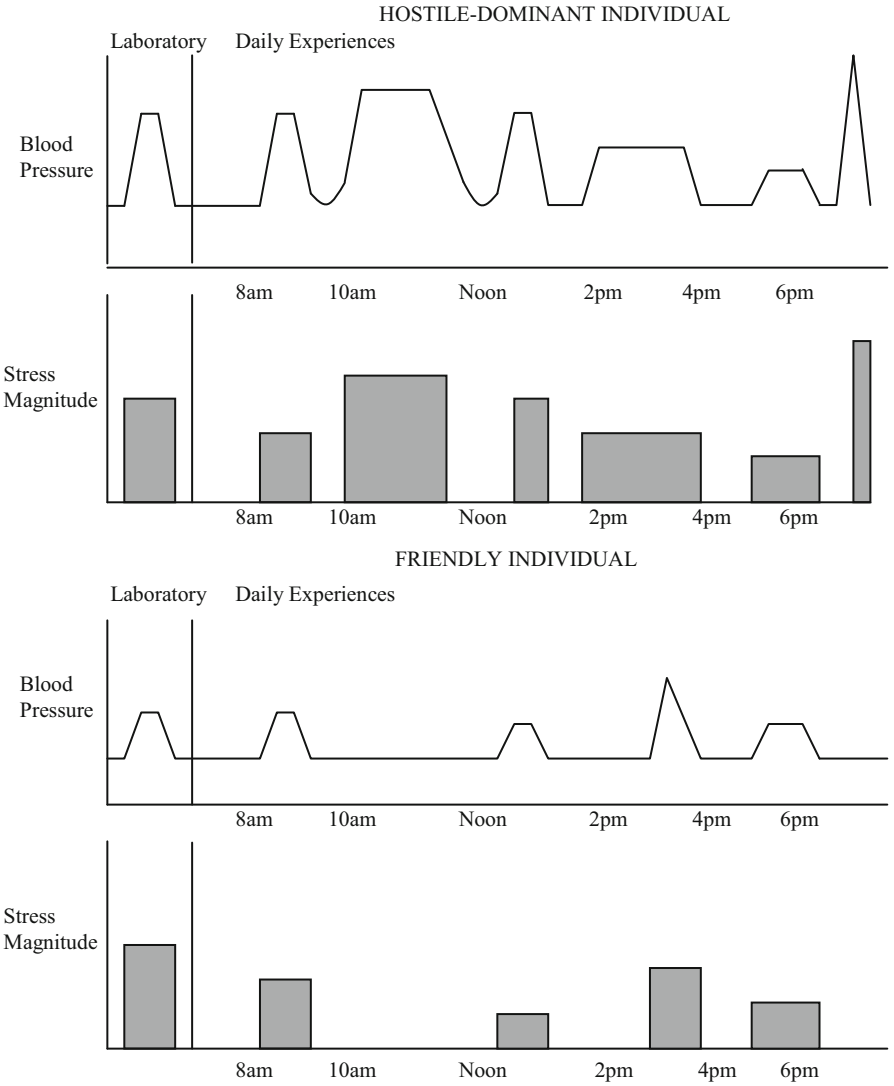


Fig. 3 Conceptual depiction of effects of individual differences in stress reactivity and exposure on overall levels of blood pressure observed during controlled laboratory conditions and during daily life for a hostile-dominant person (*upper portion*) and a friendly individual (*lower portion*). When experiencing the same stressor, the hostile-dominant individual displays greater blood pressure increase than the friendly person. In everyday life, the hostile-dominant person also encounters more frequent, severe, and prolonged stressors as a result of the impact on others of their own interpersonal behavior

laboratory stressor, such as a discussion of a previous anger-arousing event. Outside the laboratory, the hostile-dominant persons also responds to a common stressor (e.g., traffic congestion) with larger increases in blood pressure than shown by a friendly individual facing this same stressor. However, the overall much greater

degree of blood pressure reactivity in the daily life of the hostile-dominant individual is due to not only greater reactivity to equivalent stressors but also to their exposure to more frequent, severe, and prolonged interpersonal stressors, relative to the friendly individual. That greater stress exposure, in turn, reflects the tendency of the hostile-dominant individual to create more frequent and severe interpersonal difficulties, through the impact of their actions and emotional expression on others. This pattern is also exacerbated by the hostile-dominant individual's tendency to mentally rehearse past interpersonal difficulties and grievances (i.e., rumination), their tendency to undermine potential sources of social support, and their tendency to fail to benefit physiologically from social support when they get it.

Anger Suppression and CVD

The proverbial explosion or outburst is not the only way in which anger poses a threat to cardiovascular health. Rather, anger can be suppressed or else manifested in relatively attenuated and indirect ways (Fernandez 2008) consistent with the hostile-submissive personality style (Smith et al. 2010). Interpersonal relations within work and social contexts may place a premium on inhibition of angry behavior. However, this often comes at a cost of well-being, especially a cost to cardiovascular health (Mauss and Gross 2004).

Research points to a fairly reliable relationship between anger suppression and blood pressure. For example, Hosseini et al. (2011) compared hypertensive patients with a group of healthy normals matched on age, gender, and educational level. Anger-in but not anger-out (as measured by the STAXI) was significantly higher in the case group than the control group. Sharma (2003) found that in comparison to normotensive individuals, hypertensive patients reported more stress from life events, more suppression of anger, and more trait anger and trait anxiety. Conversely, hypertensives showed lower outward expression and control of angry feelings as measured on the STAXI.

Going beyond self-reports of trait anger, Quartana and Burns (2010) used a laboratory context to assess cardiovascular reactivity to experimentally induced anger. It was reported that when participants underwent an experimental manipulation to suppress anger, there was a delayed increase in systolic blood pressure.

Special attention has been directed at the cardiovascular effects of anger suppression in women, in the light of gender differences in expression but not experience of anger (Fernandez and Malley-Morrison 2013). Based on a Canadian sample of female managers, Greenglass (1996) suggested that cynical distrust and internalized anger might be precursors of hypertension. Thomas (1997) reported that when women suppressed anger in the home environment, it was accompanied by increases in systolic blood pressure and diastolic blood pressure. Using electron beam computed tomographic scans to determine coronary artery calcification, Low et al. (2011) observed that in postmenopausal women, anger-in was part of a psychosocial risk index predicting a significant increase in coronary artery calcification and a trend toward atherosclerosis over a 3-year period. In a review of the

literature on psychosocial risks of CVD, Low et al. (2010) concluded that for women, there is ample evidence that anger suppression and the stress of family and interpersonal relationships are among the main psychosocial factors associated with increased CHD.

For a critical review of the research on the cardiovascular effects of emotion suppression, see Mauss and Gross (2004). As the authors point out, there is a complexity in emotion suppression that may require further elaboration of the findings in this area.

Treatment Options for Anger in CVD

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is the dominant approach to treating anger. At a minimum, it is a two-pronged strategy of getting the angry person to reappraise and de-arouse, and this is particularly applicable in interpersonal conflict where misattributions and agitation abound. Meta-analysis of about 50 studies of CBT for anger produced a grand weighted mean effect size of +0.70, meaning that the average subject receiving CBT was better off than 76 % of no-treatment control subjects, on dependent measures of anger (Beck and Fernandez 1998). This was replicated in a subsequent meta-analysis by Di Giuseppe and Tafrate (2003). This approach has also been found to produce clinically meaningful reductions in anger, hostility, and aggressiveness for individuals diagnosed with Intermittent Explosive Disorder (McCloskey et al. 2008). Based on these findings, it is arguable that CBT can be applied to treat anger in patients with CVD.

Cognitive Behavioral Affective Therapy (CBAT)

In addition to reappraisal and de-arousal, other cognitive and behavioral techniques can be included to enhance CBT. Furthermore, a whole class of affective techniques can be incorporated so that feelings are directly accessed and modified, as is appropriate especially when anger is suppressed. These techniques are consistent with some of the experiential and emotion-focused therapies (Greenberg and Goldman 2008; Paivio and Pascual-Leone 2010). The product is a new enhanced and integrative therapy termed cognitive behavioral affective therapy (CBAT; Fernandez 2010, 2013).

Fundamental to CBAT for anger is the premise that anger is a process. Specifically, anger unfolds over three main phases: onset, progression, and offset, respectively. Therefore, treatment is also triphasic, the first phase being prevention which is followed by intervention which is followed by postvention. The first phase entails preparation for possible anger-provoking events, the second involves intervention

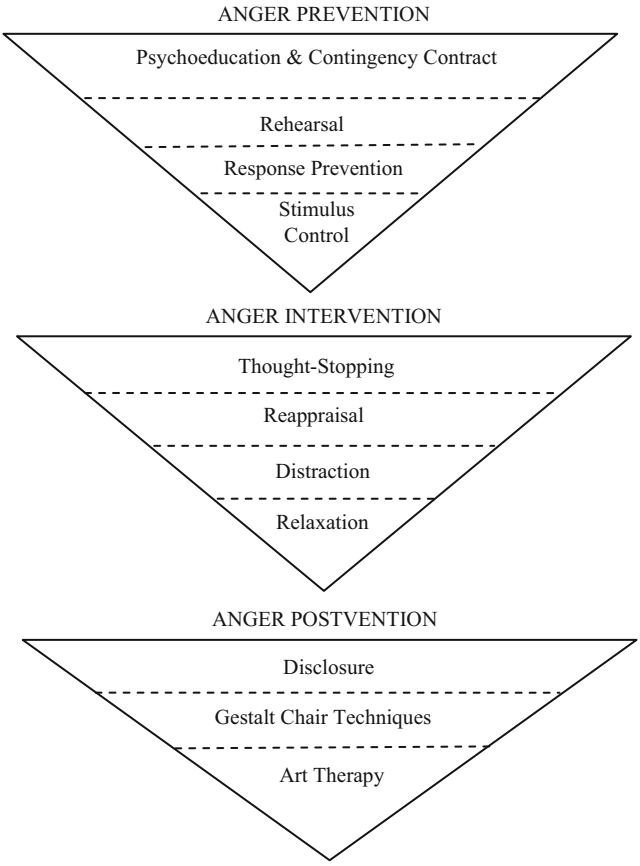


Fig. 4 Anger filtered through phases of cognitive behavioral affective therapy

on outbursts or escalation of anger, and this is followed by a third phase, postvention, to remove residual traces of anger as may be found in anger suppressors.

Figure 4 (adapted from Fernandez and Kerns in press) illustrates this progressive filtering of anger. As shown, different techniques are not made available in a menu-driven manner but are sequenced to fit into specific phases. Within each phase too, techniques are presented in a contingent fashion so that the end result is a programmatic delivery of skills for the self-regulation of anger. A detailed exposition of CBAT self-regulation for anger can be found in Fernandez (2010) and Fernandez and Kerns (in press).

Preliminary research has found an effect size ranging from +0.80 to +0.99 on various dependent measures of anger targeted by CBAT (Fernandez and Scott 2009). While this is encouraging, new research is needed to determine the outcome efficacy of CBAT in CVD patients in whom anger is a comorbid problem.

Interpersonal Therapy and Other Perspectives

One reminder at this point is that like CBT for anger, CBAT is delivered very much in the format of a skills training program. Rather than engaging in psychotherapeutic dialogue, participants actually learn skills for implementation in everyday naturalistic settings when anger is likely to occur. In other words, anger is treated primarily as an intrapsychic problem. However, this chapter stresses that the anger of CVD patients often arises within a relational context that is often beset with perceived wrongdoings and conflict. The importance of addressing such interpersonal conflict is acknowledged in psychodynamic therapy. The tried and tested tools of marital and family therapy are particularly relevant in this context. Also productive may be strategies that have evolved within the conflict resolution literature. In more recent times, acceptance and commitment therapy (ACT) has rekindled interest in forgiveness, mindfulness, and other perspectives (e.g., Day et al. 2008) that have roots in many theological and philosophical traditions.

Usefulness in the Management of Coronary Disease

Some rehabilitation programs for CVD have had elements of counseling and therapy. A meta-analytic review found that stress management and related psychosocial interventions for CHD patients reduce recurrent cardiac events and mortality (Linden et al. 2007). Group-based therapy to reduce Type A behavior has been found to reduce recurrent coronary events among CHD patients (Friedman et al. 1986), and this approach also reduces anger and hostility (Mendes de Leon et al. 1991). Although relaxation training and reduced stress is a cornerstone of many of the CBT approaches to the treatment of anger described above, few studies have examined the effects of anger treatment in CHD patients. In one exception, a course of eight 90-min group CBT sessions reduced self-reports and behavioral ratings of anger and hostility and also reduced resting blood pressure (Gidron et al. 1999). The intervention also reduced rehospitalizations and related medical costs (Davidson et al. 2007). This specific approach utilized cognitive restructuring techniques to reduce hostile cognition, relaxation to address angry arousal, and related CBT approaches to modify aggressive behavior. This preliminary evidence suggests that cognitive, behavioral, and affective approaches to modifying anger and hostility in CHD patients may have clinical benefits, and this is encouraging news for further research in this field.

Conclusions

Anger and the closely related traits of hostility and aggressiveness are associated with an increased risk of CVD generally and CHD in particular. These associations have been demonstrated along the full course of the disease process, from the early indications of asymptomatic atherosclerosis to the later emergence and course of

clinical manifestations of disease. This association may involve the mediating effects of poor health practices and physiological stress responses. Stress resulting from problematic interpersonal relationships may be a central mechanism in this regard, as chronically angry and hostile persons generally experience limitations in social support and heightened exposure to interpersonal conflict. In some situations, this is compounded by the overcontrol or suppression of angry behavior. There is robust empirical support for the value of CBT in the regulation of anger and preliminary support for the value of this approach to the management of CVD patients. The efficacy of such treatments may be strengthened by also taking into consideration the recurring interpersonal difficulties and themes of conflict that underlie anger and hostility.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.) Washington, D.C.: American Psychiatric Publishing.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5)*. Washington, DC: American Psychiatric Publishing.

Averill, J. R. (1983). Studies on anger and aggression: Implications for theories of emotion. *American Psychologist, 38*, 1145–1160.

Baron, K., Smith, T. W., Butner, J., Nealey-Moore, J., Hawkins, M., & Uchino, B. (2007). Hostility, anger, and marital adjustment: Concurrent and prospective associations with psychosocial vulnerability. *Journal of Behavioral Medicine, 30*, 1–10.

Barth, J., Schneider, S., & von Kanel, R. (2010). Lack of social support in the etiology and the prognosis of coronary heart disease: A systematic review and meta-analysis. *Psychosomatic Medicine, 72*, 229–238.

Beck, R., & Fernandez, E. (1998). Cognitive-behavioral therapy in the treatment of anger: A meta-analysis. *Cognitive Therapy and Research, 22*, 63–74.

Boyle, S. H., Mortensen, L., Gronbaek, M., & Barefoot, J. C. (2008). Hostility, drinking patterns and mortality. *Addiction, 103*, 54–59.

Brissette, I., & Cohen, S. (2002). The contribution of individual differences in hostility to the association between daily interpersonal conflict, affect, and sleep. *Personality and Social Psychology Bulletin, 28*, 1265–1274.

Brodsky, S. L. (2011). Hostility and scorn. In S. L. Brodsky (Ed.), *Therapy with coerced and reluctant clients* (pp. 141–155). Washington, DC: American Psychological Association.

Bunde, J., & Suls, J. (2006). A quantitative analysis of the relationship between the Cook-Medley Hostility Scale and traditional coronary artery disease risk factors. *Health Psychology, 25*, 493–500.

Buss, A. H., & Durkee, A. (1957). An inventory for assessing different kinds of hostility. *Journal of Consulting Psychology, 21*, 343–349.

Buss, A. H., & Perry, M. (1992). The aggression questionnaire. *Journal of Personality and Social Psychology, 63*, 452–459.

Byrne, D. G. (2000). The frustration of success: Type A behavior, occupational stress and cardiovascular disease. In *Stress and health: Research and clinical applications* (pp. 411–436). Amsterdam: Harwood Academic Publishers.

Carver, C. S., & Harmon-Jones, E. (2009). Anger is an approach-related affect: Evidence and implications. *Psychological Bulletin, 135*, 183–204.

Chida, Y., & Steptoe, A. (2009). The association of anger and hostility with future coronary heart disease: A meta-analytic review of prospective evidence. *Journal of the American College of Cardiology, 53*, 774–778.

Cook, W. W., & Medley, D. M. (1954). Proposed hostility and pharisaic virtue scales for the MMPI. *Journal of Applied Psychology, 38*, 414–418.

Davidson, K. W., Gidron, Y., Mostofsky, E., & Trudeau, K. J. (2007). Hospitalization cost offset of a hostility intervention for coronary heart patients. *Journal of Consulting and Clinical Psychology, 75*, 657–662.

Day, A., Howells, K., Mohr, P., Schall, E., & Gerace, A. (2008). The development of CBT programmes for anger: The role of interventions to promote perspective-taking skills. *Behavioural and Cognitive Psychotherapy, 36*(3), 299–312.

DiGiuseppe, R., & Tafrate, R. C. (2003). Anger treatment for adults: A meta- analytic review. *Clinical Psychology: Science and Practice, 10*, 70–84.

Esler, M., Schwarz, R., & Alvarenga, M. (2008). Mental stress is a cause of cardiovascular diseases: From scepticism to certainty. *Stress and Health: Journal of the International Society for the Investigation of Stress, 24*, 175–180.

Everson-Rose, S. A., Lewis, T. T., Karavalos, K., Matthews, K. A., Sutton-Tyrrell , K & Powell, L. H. (2006). Cynical hostility and carotid atherosclerosis in African American and white women: the Study of Women's Health Across the Nation (SWAN) Heart Study. *American Heart Journal, 152*, 982, e7–13.

Fernandez, E. (2008). The angry personality: A representation on six dimensions of anger expression. In G. J. Boyle, D. Matthews, & D. Saklofske (Eds.), *International handbook of personality theory and testing: Vol. 2: Personality measurement and assessment* (pp. 402–419). London: Sage Publications.

Fernandez, E. (2010). Toward an integrative psychotherapy for maladaptive anger. In M. Potegal, G. Stemmler, & C. Spielberger (Eds.), *The international handbook of anger: Constituent and concomitant biological, psychological, and social processes* (pp. 499–514). New York: Springer.

Fernandez, E. (2013). Anger dysfunction and its treatment. In E. Fernandez (Ed.), *Treatments for anger in specific populations: Theory, application, and outcome* (pp. 1–14). New York: Oxford University Press.

Fernandez, E., & Kerns, R. D. (in press). New prospects for the alleviation of anger in the context of chronic pain. In Z. Bajwa, C. Warfield, & J. Wootton (Eds.), *Principles and practice of pain medicine* (3rd ed.). New York: McGraw-Hill.

Fernandez, E., & Malley-Morrison, K. (2013). Gender-inclusive and gender informed treatment of anger. In E. Fernandez (Ed.), *Treatments for anger in specific populations: Theory, application, and outcome* (pp. 213–235). New York: Oxford University Press.

Fernandez, E., & Scott, S. (2009). Anger treatment in chemically-dependent inpatients: Evaluation of phase effects and gender. *Behavioural and Cognitive Psychotherapy, 37*, 431–447.

Fernandez, E., Day, A., & Boyle, G. J. (2015). Measures of anger and hostility in adults. In G. J. Boyle, D. Saklofske, & G. Matthews (Eds.), *Measures of personality and social psychological constructs* (pp. 74–100). London: Academic Press.

Friedman, M., Thoreson, C. E., Gill, J. J., Ulmer, D., Powell, L. H., Price, V., et al. (1986). Alteration of Type A behavior and its effects on cardiac recurrences in post-myocardial infarction patients: Summary of results from the Recurrent Coronary Prevention Project. *American Heart Journal, 112*, 653–665.

Gidron, Y., Davidson, K., & Bata, I. (1999). The short-term effects of a hostility-reduction intervention on male coronary heart disease patients. *Health Psychology, 18*, 416–420.

Gottdiener, J. S., Kop, W. J., Hausner, E., McCeney, M. K., Herrington, D., & Krantz, D. S. (2003). Effects of mental stress on flow-mediated brachial artery dilation and influence of behavioral factors and hypercholesterolemia in subjects without cardiovascular disease. *American Journal of Cardiology, 92*, 687–691.

Greenberg, L. S., & Goldman, R. N. (2008). *Emotion-focused couples therapy: The dynamics of emotion, love, and power* (pp. 351–364). Washington, DC: American Psychological Association.

Greenglass, E. R. (1996). Anger suppression, cynical distrust, and hostility: Implications for coronary heart disease. In *Stress and emotion: Anxiety, anger, and curiosity* (Vol. 16, pp. 205–225). Philadelphia: Taylor & Francis.

Horowitz, L. M., & Strack, S. (2011). Handbook of interpersonal psychology: Theory, research, assessment, and therapeutic interventions (2011). John Wiley & Sons Inc, Hoboken, NJ.

Holt-Lunstad, J., Smith, T. W., & Uchino, B. N. (2008). Can hostility interfere with the health benefits of giving and receiving social support? The impact of cynical hostility on cardiovascular reactivity during social support interactions among friends. *Annals of Behavioral Medicine, 35*, 319–330.

Hosseini, S. H., Mokhberi, V., Mohammadpour, R. A., Mehrabianfard, M., & Lashak, N. B. (2011). Anger expression and suppression among patients with essential hypertension. *International Journal of Psychiatry in Clinical Practice, 15*, 214–218.

Howells, K. (2004). Anger and its links to violent offending. *Psychiatry, Psychology and Law, 11*, 189–196.

Hutcherson, C. A., & Gross, J. J. (2011). The moral emotions: A social–functionalist account of anger, disgust, and contempt. *Journal of Personality and Social Psychology, 100*(4), 719–737.

King, C. R., Knutson, K. L., Rathouz, P. J., Sidney, S., Liu, K., & Lauderdale, D. S. (2008). Short sleep duration and incident coronary artery calcification. *Journal of the American Medical Association, 300*, 2859–2866.

Laughlin, M. J., & Warner, K. (2005). A relational approach to anger: A case study. *Journal of Systemic Therapies, 24*, 75–89.

Lazarus, R. S. (2000). Cognitive-motivational-relational theory of emotion. In Y. L. Hanin (Ed.), *Emotions in sport* (pp. 39–63). Champaign: Human Kinetics.

Linden, W., Phillips, M. J., & Leclerc, J. (2007). Psychological treatment of cardiac patients: A meta-analysis. *European Heart Journal, 28*(24), 2964–2966.

Low, C. A., Thurston, R. C., & Matthews, K. A. (2010). Psychosocial factors in the development of heart disease in women: Current research and future directions. *Psychosomatic Medicine, 72*, 842–854.

Low, C. A., Matthews, K. A., Kuller, L. H., & Edmundowicz, D. (2011). Psychosocial predictors of coronary artery calcification progression in postmenopausal women. *Psychosomatic Medicine, 73*, 789–794.

Mauss, I. B., & Gross, J. J. (2004). Emotion suppression and cardiovascular disease: Is hiding feelings bad for your heart? In *Emotional expression and health: Advances in theory, assessment and clinical applications* (pp. 61–81). New York: Brunner-Routledge.

McCloskey, M. S., Noblett, K. L., Deffenbacher, J. L., Gollan, J. K., & Coccaro, E. F. (2008). Cognitive-behavioral therapy for intermittent explosive disorder: A pilot randomized clinical trial. *Journal of Consulting and Clinical Psychology, 76*, 876–886.

Mendes De Leon, C. F., Powell, L. H., & Kaplan, B. H. (1991). Change in coronary-prone behaviors in the Recurrent Coronary Prevention Project. *Psychosomatic Medicine, 53*, 407–419.

Miller, T. Q., Smith, T. W., Turner, C. W., Guijarro, M. L., & Hallett, A. J. (1996). A meta-analytic review of research on hostility and physical health. *Psychological Bulletin, 119*, 322–348.

Mostofsky, E., Maclure, M., Tofler, G. H., Muller, J. E., & Mittleman, M. A. (2013). Relation of outbursts of anger and acute myocardial infarction. *American Journal of Cardiology, 112*, 343–348.

Mostofsky, E., Penner, E., & Mittleman, M. A. (2014). Outbursts of anger as a trigger of acute cardiovascular events: A systematic review and meta-analysis. *European Heart Journal, 35*, 1404–1410.

Newman, J. D., Davidson, K. W., Shaffer, J. A., Schwartz, J. E., Chaplin, W., Kirkland, S., & Shimbo, D. (2011). Observed hostility and the risk of incident ischemic heart disease: A prospective population study from the 1995 Canadian Nova Scotia Health Survey. *Journal of the American College of Cardiology, 58*, 1222–1228.

Novaco, R. W. (1994). Anger as a risk factor for violence among the mentally disordered. In J. Monahan & H. J. Steadman (Eds.), *Violence and mental disorder* (pp. 21–59). Chicago: University of Chicago Press.

Novaco, R. W. (2003). *The novaco anger scale and provocation inventory: Manual*. Los Angeles: Western Psychological Services.

Paivio, S. C., & Pascual-Leone, A. (2010). *Emotion-focused therapy for complex trauma: An integrative approach*. Washington, DC: American Psychological Association.

Pincus, A. L., & Ansell, E. B. (2013). Interpersonal theory of personality. In T. Millon & M. J. Lerner (Eds.), *Handbook of psychology (vol. 5): Personality and social psychology* (2nd ed., pp. 141–159). New York: Wiley.

Quartana, P. J., & Burns, J. W. (2010). Emotion suppression affects cardiovascular responses to initial and subsequent laboratory stressors. *British Journal of Health Psychology, 15*, 511–528.

Ramírez, J. M., & Andreu, J. M. (2006). Aggression, and some related psychological constructs (anger, hostility, and impulsivity): Some comments from a research project. *Neuroscience and Biobehavioral Reviews, 30*, 276–291.

Renshaw, K. D., Blais, R. K., & Smith, T. W. (2010). Components of negative affectivity and marital satisfaction: The importance of actor and partner anger. *Journal of Research in Personality, 44*, 328–334.

Robles, T. F., Slatcher, R. B., Trombello, J. M., & McGinn, M. M. (2014). Marital quality and health: A meta-analytic review. *Psychological Bulletin, 140*, 140–187. doi:10.1037/a0031859.

Sharma, S. (2003). Life events stress, emotional vital signs and hypertension. *Psychological Studies, 48*, 53–65.

Smedslund, J. (1993). How shall the concept of anger be defined? *Theory and Psychology, 3*, 5–33.

Smith, T. W. (1994). Concepts and methods in the study of anger, hostility, and health. In A. W. Siegman & T. W. Smith (Eds.), *Anger, hostility, and the heart* (pp. 23–42). Hillsdale: Lawrence Erlbaum.

Smith, T. W., & Cundiff, J. M. (2011). *An interpersonal perspective on risk for coronary heart disease* (pp. 471–489). Hoboken: Wiley.

Smith, T. W., & Gallo, L. C. (1999). Hostility and cardiovascular reactivity during marital interaction. *Psychosomatic Medicine, 61*, 436–445.

Smith, T. W., & Traupman, E. K. (2011). Anger, hostility, and aggressiveness in coronary heart disease: Clinical applications of an interpersonal perspective. In R. Allan & J. Fisher (Eds.), *Heart and mind: The practice of cardiac psychology* (pp. 197–217). Washington, DC: American Psychological Association. doi: http://dx.doi.org/10.1037/13086-008.

Smith, T. W., Glazer, K., Ruiz, J. M., & Gallo, L. C. (2004). Hostility, anger, aggressiveness, and coronary heart disease: An interpersonal perspective on personality, emotion, and health. *Journal of Personality, 72*, 1217–1270.

Smith, T. W., Uchino, B. N., Berg, C. A., Florsheim, P., Pearce, G., Hawkins, M., . . . Yoon, H. C. (2007). Hostile personality traits and coronary artery calcification in middle-Aged and older married couples: Different effects for self-reports versus spouse-ratings. *Psychosomatic Medicine*, *69*, 441–448.

Smith, T. W., Traupman, E., Uchino, B. N., & Berg, C. (2010). Interpersonal circumplex descriptions of psychosocial risk factors for physical illness: Application to hostility, neuroticism, and marital adjustment. *Journal of Personality, 78*, 1011–1036.

Smith, T. W., Uchino, B. N., Florsheim, P., Berg, C. A., Butner, J., Hawkins, M., . . . Yoon, H.-C. (2011). Affiliation and control during marital disagreement, history of divorce, and asymptomatic coronary artery calcification in older couples. *Psychosomatic Medicine*, *73*, 350–357.

Smith, T. W., Baron, C. E., & Grove, J. L. (2014). Personality, emotional adjustment, and cardiovascular risk: Marriage as a mechanism. *Journal of Personality, 82*, 502–514.

Smith, T. W., Uchino, B. N., Bosch, J. A., & Kent, R. G. (in press). Trait hostility is associated with systemic inflammation in married couples: An actor-partner analysis. *Biological Psychology*.

Spielberger, C. D. (1988). *Manual for the state–trait anger expression inventory*. Odessa: Psychological Assessment Resources.

Spielberger, C. D. (1991). *State-trait anger expression inventory: Revised research edition: Professional manual*. Odessa: Psychological Assessment Resources.

Spielberger, C. D. (1999). *STAXI-2: State–trait anger expression inventory professional manual*. Odessa: Psychological Assessment Resources.

Steptoe, A., & Kivimaki, M. (2013). Stress and cardiovascular disease: An update on current knowledge. *Annual Review of Public Health, 34*, 337–354.

Strike, P., & Steptoe, A. (2005). Behavioral and emotional triggers of acute coronary syndromes: A systematic review and critique. *Psychosomatic Medicine, 67*, 179–186.

Suarez, E. C. (2012). The association between measures of inflammation and psychological factors associated with an increased risk of atherosclerotic cardiovascular disease: Hostility, anger, and depressed mood and symptoms. In S. C. Segerstrom (Ed.), *The Oxford handbook of psychoneuroimmunology* (pp. 170–194). New York: Oxford University Press.

Thomas, S. P. (1997). Women's anger: Relationship of suppression to blood pressure. *Nursing Research, 46*, 324–330.

Williams, J. E., Din-Dzietham, R., & Szklo, M. (2006). Trait anger and arterial stiffness: Results from the atherosclerosis risk in communities study. *Preventive Cardiology, 9*, 14–20.

Wranik, T., & Scherer, K. R. (2010). Why do I get angry? A componential appraisal approach. In M. Potegal, G. Stemmler, & C. Speilberger (Eds.), *International handbook of anger* (pp. 243–266). New York: Springer.

Wright, R. A., & Stewart, C. C. (2012). Multifaceted effects of fatigue on effort and associated cardiovascular responses. In *How motivation affects cardiovascular response: Mechanisms and applications* (pp. 199–218). Washington, DC: American Psychological Association.

Gender Differences in Psychological Risk Factors for Development of Heart Disease

Geir Arild Espnes, Camilla Nguyen, and Don Byrne

Contents

This chapter presents a revised version of a paper originally published in *Stress and Health* (2008), 24, 188–195, (Wiley Interscience) by two of the present authors (Espnes and Byrne). The revision has been made with the permission of the publisher.

G.A. Espnes (✉)
Center for Health Promotion Research, Department of Social Work and Health Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Australian National University, Canberra, ACT, Australia
e-mail: geirae@svt.ntnu.no; geir.arild.espnes@svt.ntnu.no

C. Nguyen
Center for Health Promotion Research, Department of Social Work and Health Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway
e-mail: camilla.nguyen@svt.ntnu.no

D. Byrne
ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia

ANU Medical School, Research School of Psychology, Australian National University, Acton, Canberra, ACT, Australia
e-mail: Don.Byrne@anu.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_32

Abstract

While coronary heart disease (CHD) for decades was understood as mainly a male disease group, it has through the last years become increasingly evident that it is now an important disease causing premature death also in the female populations throughout the Westernized world. Present paper scrutinizes via literature searches and discussions of relevant data the sex and gender differences in psychological risk factors for CHD with an emphasis on female risk. It is concluded that the risk factor picture in females is, due to limited research, still far from clear, even if there are indications of sex differences in both the risk factors picture and the trajectories of the disease development.

Keywords

Female • Women • Gender • Coronary heart disease (CHD) • Myocardial infarction (MI) • Ischemic heart disease (IHD)

Introduction

Myocardial infarction (MI), angina and coronary artery atherosclerosis, collectively known as coronary heart disease (CHD) or cardiovascular disease (CVD), has for many decades, based on epidemiological data, mainly been considered and constructed as a male disease (Lockyer and Bury 2002); Riska 2002). This has to a great extent obscured the picture regarding sex differences in disease development (e.g., Hirsch and Meagher 1984) and the risk factor profile in women has simply been assumed to parallel that of men (Asia Pacific Cohort Studies Collaboration 2005). The obvious exception is the belief that higher estrogen levels in women, relative to men, give a protective effect against CHD development; this has been shown not to be the case (Barrett-Connor 1997). It has also been expected that hormone replacement therapy (HRT) with estrogens could have positive effects, but research in recent years have concluded that women should not use estrogen replacement with an expectation of cardiovascular benefit (Herrington et al. 2000), and it has been pointed out that HRT in some cases in fact can increase the risk of cardiovascular events (Grady 2003; Mosca et al. 2004).

In the 1990s, however, it became increasingly evident that there had been a change in the proportion of CHD incidents between males and females in Western societies. This is partly due to the observation that rates of CHD among men have shown a decrease in these societies (Demirovic et al. 1993) and partly because the

opposite has happened in women, where in some societies, the female incidence in fact has shown a remarkable upsurge in both severe and less severe coronary events (e.g., Sclavo 2001; Burell and Granlund 2002).

Today it has become quite clear that there are important gender differences in both physiological and biochemical risk factors for CHD and in symptoms of CHD manifestation (Chiamvimonvat and Sternberg 1998; Miller 2002; Kyker and Limacher 2002; Franklin 2002). It is now a consistent view that a better understanding of the sex differences in risk factors will potentially lead to a slowing of the CHD epidemic in women (Polk and Naqvi 2005; Witt and Roger 2003).

This chapter is an update of a journal article presented in *Stress and Health* in 2008 (Espnes and Byrne 2008). The literature searches have been following the same patterns both times.

The objective of the present paper is to (1) examine the epidemiological evidence from Western countries to establish consistency; (2) examine the primary psychological coronary risks, impacting on women relative to men generally, and risks from stress in particular (and to go at least part way to understanding the narrowing margin in cardiovascular risk between women and men); (3) examine the most important implications of these data for possible interventions to lower cardiovascular risk in women and men; and (4) analyze and critique what seems to be the existing assumption that identical approaches to women and men with regard to managing cardiovascular risk represent best practice in both prevention and treatment.

Literature Search Procedures

The literature searches for this review have been done at two different occasions but following the exact same pattern (see Fig. 1). They were carried out on the Internet using relevant library databases (PsycInfo, Medline, and PubMed). The first searches were done by entering the primary search term related to psychological

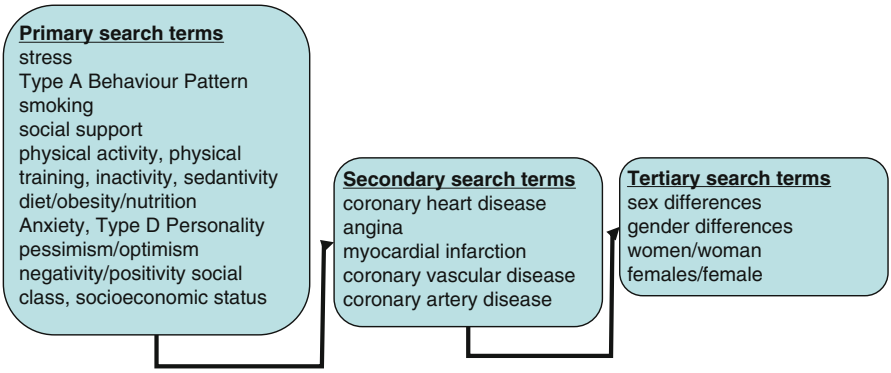


Fig. 1 Model for the literature search hierarchy

risk factors. To narrow the searches, the second search term was entered, and, finally, to be sure that we had narrowed down to absolute possible hits, the tertiary terms were entered (see Fig. 1).

For the period before 2008, we ended up with 95 papers, 68 of which have been included in the review because they add valuable information to the focus of the paper; for the period post 2008, the numbers were, respectively, 48 and 20. The searches were carried out in 2003/2004, 2007, and again in 2015.

The Epidemiological Background

While a total of around 510,000 men in the USA died from CVD during 1980, less than 440,000 did in 2000. The trend among women, however, is almost opposite; while about 470,000 died from CVD in 1970, about 505,000 died from CVD in 2000 (American Heart Association 2003, p. 4). Looking at CHD alone, representing about 50 % of all CVD mortality, around 1,000,000 people every year experience an initial or recurrent coronary event in the USA alone, and around 450,000 die from CHD (both sexes included).

Somewhat curiously, however, our reanalysis of the data used by the American Heart Association to form the statistics for the period of 1987–1997 (WHO data set) indicated that the trend for women relative to men was considerably better than what the AHA publication (American Heart Association 2003, p. 4) suggested. There are also studies from specific locations in Northern America which actually show a drop in CHD mortality for both men and women in some ares (Rosamond et al. 1998) and a drop, at least, in female incidence of CHD in other areas (Hu et al. 2000). Lang et al. (1999) concluded that conflicting data may stem from disparate reporting conventions and different definitions of or criteria for CHD prevalence and incidence. It is, however, now clear that the total incidence of CHD for women after menopause now equals that of men (Chiamvimonvat and Sternberg 1998) and that death rates increase exponentially with age, beginning at the age of 20 or 30, with no change in slope of CHD rates between the ages of 45 and 55 years. CHD is therefore an adult phenomenon in women and not just a postmenopausal one (Barrett-Connor and Stuenkel 1999). The seriousness of the problem of CHD in women is clearly addressed in the World Health Organization Newsletter, *Heart Beat* (Nishtar 2003) where it is referred to as "the escalating burden of cardiovascular diseases among women."

CVD is still the leading cause of mortality in both women and men worldwide; it was responsible for 17.5 million deaths in 2012 (WHO 2014b) and is now considered one of the most important health threats in the United Nations (UN) and the World Health Organization's (WHO) fight against noncommunicable diseases (NCDs) (WHO 2014a; UN 2012). Data from the (WHO 2014c) showed that, in 2012, the CVD mortality rates in the USA were 169.5 and 107.8 per 100,000 for males and females consecutively. According to their recent report, the annual CVD mortality is estimated to increase further toward 2030 (WHO 2014b).

Psychological and Psychosocial Factors

When searching the literature for sex or gender differences of psychological risk factors for developing CHD, we found that we can, in a broad overview, name three main groups of psychological factors that have been researched for their connection to CHD development. The groups can be named (I) emotional, (II) behavioral, and (III) environmental. Together these three groups contain eight different subgroups of risk factors. These are, first, the emotional (1) stress, (2) type A behavior pattern, (3) different troublesome emotions (including the dichotomy of pessimism and optimism), and (4) social support will, even if this factor can be defined to be both behavioral and environmental, be included here. This group of factors will be of special interest to this paper. The second group, behavioral factors, contains (5) smoking, (6) physical inactivity/sedantivity, and (7) obesity/diet. These factors are not the primary subjects to this paper and research from these areas will not be included. There is also a purely environmental set of factors which we have called (8) social class or socioeconomic status. This last group will be offered some more attention since social class or occupational class has been shown to have impact on stress development (e.g., Wamala et al. 2001) and will therefore be treated in connection to stress. Of course, some of these factors are individually related, precursors for, or facilitating or mediating each other, but they also appear as independently investigated.

Stress

The term or concept stress is often defined as the physical and psychological result of internal or external pressures. Stress is the one biopsychological factor that has been linked to the largest number of diseases and, particularly, been connected to development of CHD. Links between hypertension and stress have for many years constituted the archetypal example of how physiological (or clinical) and psychological phenomena may be causally related. Stressors, whether mental or environmental, are readily identified and reproduced, and one of the most active areas in psychosomatic research has been the investigation of cardiovascular reactivity to mental stress. Stress has been found to be a precursor for the development of other risk factors, particularly hypertension and lipid levels. In the recent past, it has been questioned as to whether stress is caused by the same kind of strain, whether stress and strain are the same, and finally whether stress has the same consequences for both sexes (Weidner et al. 1997, 2001; Taylor et al. 2000).

The Stockholm Female Coronary Risk Study demonstrated that women who had suffered an episode of CHD showed lower heart rate responses to mental stress than did their male counterparts (Weidner et al. 2001). Summing up another Swedish study, the authors claim that stress is the main risk factor for development of CHD in women and that women have more problems with stress stemming from home and from within the family than do men (Balog et al. 2003). These results are supported by results from the Family Heart Study (USA) showing that females

seem to feel less job strain from working outside the house than do either homemakers or men (Weidner et al. 1997; Ferris et al. 2005) and also from studies on burnout (Kinnunen et al. 2006).

As previously mentioned, the cause of stress can stem from a variety of strain situations. To come from a disadvantaged social class or socioeconomic status and to belong to a low occupational class are such situations that have been found to be associated with CHD development. It has earlier been suggested that this stressor (social class disadvantage) may have the same effect on CHD development in males and females (Brezninka and Kittel 1995; Wamala et al. 2001), but there are present indications of differences (e.g., Mobley et al. 2004). Lawlor et al. (2005), examining socioeconomic position through the life span and its association to CHD development in women, suggesting that neither cigarette smoking nor other adult risk factors can fully explain the elevated CHD risk in females coming from adverse socioeconomic positions. It is important, as underlined in one of the studies (Wamala et al. 2001), that it is the cumulative effect of socioeconomic disadvantage that is of interest. This is backed up by several independent studies (Gliksman et al. 1995; Galobardes et al. 2006). However, there are also results that indicate that the adult socioeconomic status is a more important predictor of morbidity from coronary disease than measures of social status earlier in life (Marmont et al. 2002), and in the NHANES III study, an overrepresentation of CHD development was found among lone mothers (Young et al. 2005) compared to partnered mothers.

To conclude, it seems that psychological stress might be caused by different strain situations in the two sexes and give quite different CHD pathological outcomes as well.

The main findings of CHD development linked to psychological factors remain mainly the same from 2008 to 2015 without new relevant findings. A review from 2011 (articles = 67) further confirms that stress associated with relationships or family responsibilities is linked with increased CHD risk among women, while work-related stress is less consistently associated with CHD among women compared to men (Low et al. 2010). In another systematic review of 26 studies, the focus was on psychological job stress, which was found to be a significant cause to CHD development in men but not in women (Backé et al. 2012). An empirical study explored the potential association in job characteristics, biopsychosocial, lifestyle, and coronary heart disease (CHD). Even though men were significantly worse on all objective measures of CHD risk, there were no significant differences between men and women in the relationships between variables (Ferris et al. 2012). Among middle-aged patients with acute myocardial infarction, higher levels of perceived stress were detected in women compared to men. This was mainly explained by differences in comorbidities, physical and mental health status, intrafamily conflict, caregiving demands, and financial hardship (Xu et al. 2015). This is supporting studies we have shown earlier, which suggest that women and men experience strain from different situations (Ferris et al. 2005; Balog et al. 2003; Weidner et al. 1997).

Type A Behavior Pattern

This particular behavior pattern was first discovered, defined, and reported as the coronary-prone behavior pattern in the 1950s by Meyer Friedman and Ray Rosenman (1959) and has been more precisely defined later (Rosenman 1990; Byrne 1996). Since it has so many emotional characteristics, there has always been a tradition to treat this behavior pattern among other psychosocial risk factors. Even if the type A behavior pattern's (TABP) ability to predict CHD has been heavily questioned, several of the characteristics that constitute the pattern, a strong need to compete, hostility, and frustration, have through the last decade still been reported to be strongly related to CHD development (Byrne 1996; Espnes and Smedslund 2001). Differences in expression of the TABP between males and females have been revealed. Females tend to display much less of the behaviors most strongly connected to CHD development, and findings support the notion of differences in the gender-related subcomponent routes for achieving type A status. This may have implications for the higher incidence of CHD in males compared to females scoring high on TABP (see, e.g., Wright et al. 1994; Matthews et al. 1998; Espnes and Opdahl 1999).

Negative and Troublesome Feelings

Hostility, Anger, Aggression, and Irritability

Given that hostility has been suggested, and indeed shown, to have impact on CHD development in male populations (e.g., Fowkes et al. 1992), it appears that surprisingly few studies have investigated possible sex differences in hostility, irritability, aggression, and anger connected to CHD development. In a meta-analysis of relevant studies, it was concluded that no differences could be found between the two sexes on how hostility influences CHD (Miller et al. 1996). Development of coronary stenosis has however been shown to relate to hostility (Low et al. 1998), and there has been a reported difference in hostility as a reaction to psychological challenge as measured on cardiac reactivity (Guyll and Contrada 1998; Sloan et al. 2001) and on irritability scores in relation to CHD in men and women (Siegman et al. 2000). There is also some evidence that level of hostility (assessed by the structured interview) reliably predicts resting blood pressure (BP) in both males and females but not in the same way for each; hostility relates to higher resting BP in men but lower resting BP in women (Davidson et al. 1996). Hostility has also been found to be an independent risk factor for recurrent CHD in postmenopausal women (Chaput et al. 2002).

Investigations of stress in marital situations have shown that high trait-anger wives, who are also high on stress, display larger increases in blood pressure and heart rate than those wives who are not high on trait anger (Glazer et al. 2002).

Studies on potential sex differences in hostility, irritability, aggression, and anger linked to CHD development post 2008 still remain limited. A study from the UK showed that in White men, hostility was associated with glucose metabolism and dyslipidemia, while hostility was associated with autonomic dysfunction in South Asian men (Williams et al. 2011). Interestingly, hostility was not associated with any biological CHD risk factors in females from the respective groups, suggesting that hostility might have a greater impact in males than in females.

Distinctive types of anger expression have been suggested to be associated with CHD. In a study where anger was divided in three types of anger expression: constructive anger (discussing anger to resolve the situation), destructive anger justification (blaming others for one's anger), and destructive anger rumination (brooding over an anger-inducing incident), higher levels of clinically assessed constructive anger have been associated with lower risk of incident CHD in men but not in women, while higher levels of destructive anger justification were significantly linked with increased 10-year incident CHD in both genders (Davidson and Mostofsky 2010).

Depression

There have been reports of a relationship between depression and CHD for almost seven decades (Malzberg 1937). This relationship has been shown in numerous studies, especially in the 1970s through the 1990s (e.g., Booth-Kewley and Friedman 1987), but there are few reports on depression and CHD in female populations or on sex differences. However, in a study among elderly in New Haven, USA, the researchers reported that even if the influence of depression should not be an independent risk factor for CHD development, depression increased the CHD risk among relatively healthy older women (Mendes de Leon et al. 1998). We now suspect that depression has impact on the disease development in a number of ways and, possibly, also in different ways in the two sexes. For example, there have been findings of greater impact from depression on development of hypertension in women than in men (Raikkonen et al. 2001). Based on a large-scale study in Greece involving 848 men and women hospitalized for their first CHD incidence, and 1,078 controls, the researchers concluded that they found evidence for a greater association between depression and CHD risk in women than in men (Chrysohoou et al. 2003). There are also findings that suggest that sex differences, both in the *ways* that depression is a risk factor and has impact on CHD (Polk and Naqvi 2005) and that the *amount* of effect depression has on CHD development, are gender dependent (Espnes and Opdahl 1999; Espnes 2002).

The existence of characteristic differences between men and women with depression has been supported by a number of studies after 2008 as well. Doering et al. (2011) sought to distinguish men and women with depressive symptoms and CHD. Women were found more likely to be single, unemployed, poorly educated,

and anxious and to perceive lower control over health than men. These findings were similar to previous findings, where socioeconomic and psychosocial factors were demonstrated to have a higher impact on women with CAD compared to men (Möller-Leimkühler 2008). The female patients also showed higher levels of depression than the male patients. A meta-analysis, exploring gender differences in the prevalence of major depression in CAD patients, further confirms that the prevalence of major depression was significantly greater in women than men (Shanmugasegaram et al. 2012).

Anxiety

Anxiety, often defined as generalized, persuasive fear, is often seen together with depression both when analyzing prognosis after having had a CHD event and also when analyzing risk factors for CHD. Brezinka and Kittel suggested as long ago as 1995, after a large review of the area (with results primarily from the Framingham Study on housewives), that anxiety is one of the "chronic troubling emotions" that is a risk factor for CHD development in females. There are however no studies, to our knowledge, showing sex differences in anxiety which might explain how anxiety differentially affects CHD development in women. But given that anxiety (Stern et al. 1977; Schleifer et al. 1989; Forrester et al. 1992; Lesperance and Frasure-Smith 2000) is more common in women than men, and especially elder women, an overrepresentation of anxiety could easily have a more severe impact among women than among men (Rudisch and Nemeroff 2003).

The number of studies after 2008 that has explored the independent association between anxiety and CHD is scarce. Findings from the Croatian Adult Health Cohort Study (CroHort) showed a significant association between women with psychological distress and the prevalence of hypertension, myocardial infarction, angina pectoris, and self-reported heart failure. In men, a significant association was only shown for psychological distress and self-reported heart failure (Rukavina et al. 2012), indicating that psychological distress has a more negative association in women compared to men. There have been reports that the somatic symptoms of anxiety are more strongly associated with an increased risk of CHD in women than in men (Nabi et al. 2010).

Type D Personality and Negative Emotions

More recently the type D personality construct, or a tendency toward experiencing negative emotion and inhibition of expression in social interactions, has received some attention as a possible risk factor for long-term cardiac events (Denollet and Van Heck 2001). There is however few studies published on type D, specifically, and on the negative emotions as a total concept in the understanding of CHD development.

Type D personalities have in previous studies shown to comprise dysfunctional personality patterns not covered by depression and anxiety scales (Beutel et al. 2012), and interestingly the prevalence of type D has been shown to be higher among women than men (Bergvik et al. 2010).

Pessimism and Optimism

Although pessimism has been identified as a risk factor for poor psychological and physical health (Peterson et al. 1988), no studies have to our knowledge explored whether a sense of optimism may protect health and certainly nothing which might indicate a sex difference. (For definitions, see Peterson et al. 1988; Jenkins 1996). It is, though, on the basis of experimental research, now suggested that optimism/pessimism have quite different effects of the different treatments in males and females after experiencing a CHD (Burell and Granlund 2002), but there is no research as far as we have been able to find that give argument for a gender difference in pessimism/optimism orientation impact on the development of CHD.

After 2008, only a limited number of studies have looked at optimism. One study examined sense of coherence (SOC) as a predictor of Quality of Life (QoL), 1 year after myocardial infarction (MI) in men and women. The male participants demonstrated stronger SOC and a better QoL in all dimensions (physical, emotional, social, and global score) compared to the female participants (Wrześniewski and Włodarczyk 2012).

Social Support

We certainly know that women with low social participation have an increased risk of CHD development (Sundquist et al. 2004), as was earlier shown for men, but we have found no evidence so far for a difference between the two sexes when it comes to an effect from social support on CHD risk. To the contrary Rueda (2006) claims that the impact on CHD risk from poor social support is the same for both sexes.

Loneliness is often considered as a lack of social support and is more often seen in connection with health deterioration in the last years. A prospective study, examining associations between loneliness and risk of incident CHD, showed that in women, high levels of loneliness were associated with increased risk of incident CHD. Interestingly, no such significant association was found among men (Thurston and Kubzansky 2009), suggesting that loneliness has a more negative effect in women. These findings are supported to those by Piwonsky et al. (2012) who found an association between low social support and CHD risk and depressive symptoms in both genders, especially evident in women. Collectively these studies highlight the special attention that needs to be paid on women who are experiencing low levels of social support.

We will now turn to a short discussion and a conclusion of the research findings of sex differences on psychological risk factors for CHD and which implications the new knowledge may give.

Implications of the New Knowledge of Sex (and Gender) Differences for the Understanding of Development of CHD

As we have seen, even if the total epidemiological evidence does not fully support the view of the American Heart Association (AHA) (2003) regarding a postulated upsurge of CHD among females, it more than indicates that the rates of cardiovascular disease among women are now far closer to those of men than they were three or more decades ago, and in some societies they may be higher than for males.

The lack of adequate knowledge, as revealed in previous part of this paper, calls for action, both in promotional and preventive strategies, in treatment and in rehabilitation. There is now sufficient research to conclude that the knowledge and interventions, aimed at preventing the male population from suffering from CHD or to assist with the treatment those who have suffered, are only partly relevant to deal with prevention and treatment in female populations. In the American Heart Association's Guidelines for Cardiovascular Disease Prevention for Women – Expert Panel/Writing Group (Mosca et al. 2004), the expert panel produced a list of clinical recommendations based on the best evidence available. The best there is to say about this list is that it really underlines the lack of knowledge and that fact has to be taken very seriously.

This review, however, has established that there is some knowledge to use as a basis for future research and practice. The specific knowledge profile that can be singled out based on the present review is that:

- Psychological stress seems to be as an important factor in the development of CHD in females as in males, but the stress involved in the development of CHD in females may have its origin from other strain situations. The trajectories through which stress may manifest a pathological effect seem to be very different between males and females, and knowledge of that phenomenon is very limited. This may in future research also impact on the understanding of whether social support or lack of social support can influence CHD development differently in the sexes.
- When it comes to understanding gender differences on the impact of emotional psychopathological precursors (a wide variety of troublesome feelings) on CHD development, the information is very sparse at the moment, and it is very clear from the results presented in this paper that there is not enough data to draw any consistent conclusions about sex differences either in disease development or disease course. Depression is the only topic among the emotional pathologies where there are clear indications of gender differences. Here females have been found to be at particular risk, though it is necessary to be cautious about the relationships found and conclusions drawn about depression as a risk factor for CHD in women since most of it is based on results from retrospective and cross-sectional studies, and few prospective studies actually exist to guide definitive conclusions.

Conclusion

What all this points to is the need for a substantial growth in research on the interactions between psychosocial and biomedical factors in the development of CHD in women, and it is important as shown in this chapter that both protective factors and risk factors, as well as symptomatology, diagnostic criteria, procedures of treatment, and rehabilitation, are covered in that research. CHD is clearly an emerging problem for women (WHO 2014; UN 2012), and, in the absence of a thorough knowledge of gender differences in all aspects of CHD development, the creation of sound, evidence-based strategies for both prevention and treatment will be significantly impaired.

References

American Heart Association. (2003). *Heart disease and stroke statistics – 2003 update*. Dallas: National Center.

Asia Pacific Cohort Studies Collaboration. (2005). Does sex matter in the associations between classic risk factors and fatal coronary heart disease in populations from the Asia Pacific Region? *Journal of Women's Health, 14*, 820–928.

Backé, E. M., Seidler, A., Latza, U., Rossnagel, K., & Schumann, B. (2012). The role of psychosocial stress at work for the development of cardiovascular diseases: A systematic review. *International Archives of Occupational and Environmental Health, 85*(1), 67–79.

Balog, P., Janszky, I., Leineweber, C., Blom, M., Wamala, S. P., & Orth-Gomer, K. (2003). Depressive symptoms in relation to marital and work stress in women with and without coronary heart disease. The Stockholm Female Coronary Risk Study. *Journal of Psychosomatic Research, 54*, 113–119.

Barrett-Connor, E. (1997). Sex differences in coronary heart disease. Why are women so superior? The 1995 Ancel Keys Lecture. Circulation, 95(1): 252–64.

Barrett-Connor, E., & Stuenkel, C. (1999). Hormones and heart disease in women: Heart and estrogen/progestin replacement study in perspective. *The Journal of Clinical Endocrinology & Metabolism, 84*(6), 1848–1853.

Bergvik, S., Sørli, T., Wynn, R., & Sexton, H. (2010). Psychometric properties of the type D scale (DS14) in Norwegian cardiac patients. *Scandinavian Journal of Psychology, 51*(4), 334–340.

Beutel, M. E., Wilthink, J., Till, Y., Wild, P. S., Münzel, T., Ojeda, F. M., . . . Michal, M. (2012). Type D personality as a cardiovascular risk marker in the general population: Results from the Gutenberg health study. *Psychother Psychosom*, *81*(2), 108–117.

Booth-Kewley, S., & Friedman, H. S. (1987). Psychological predictors of hearth disease: A quantitative review. *Psychological Bulletin, 101*, 343–362.

Brezinka, V., & Kittel, F. (1995). Psychological factors of coronary heart disease in women: A review. *Social Science and Medicine, 42*(11), 1351–1365.

Burell, G., & Granlund, B. (2002). Women's hearts need special treatment. *International Journal of Behavioral Medicine, 9*(3), 228–242.

Byrne, D. G. (1996). Type A behaviour, anxiety and neuroticism: Reconceptualizing the pathophysiological paths and boundaries or coronary-prone behaviour. *Stress Medicine, 12*, 227–238.

Chaput, L. A., Adams, S. H., Simon, J. A., Blumenthal, R. S., Vittinghoff, E., Lin, F., Loh, E., & Matthews, K. (2002). Hostility predicts recurrent events among postmenopausal women with coronary heart disease. *American Journal of Epidemiology, 156*, 1092–1099.

Chiamvimonvat, V., & Sternberg, L. (1998). Coronary artery disease in women. *Canadian Family Physician, 44*, 2709–2717.

Chrysohoou, C., Demosthenes, B. P., Pitsavos, C., Kokkinos, P., Marinakis, N., Stefanadis, C., & Toutouzsas, P. K. (2003). Gender differences on the risk evaluation of acute coronary syndromes: The CARDIO2000 study. *Preventive Cardiology, 6*(2), 71–77.

Davidson, K. W., & Mostofsky, E. (2010). Anger expression and risk of coronary heart disease: Evidence from the Nova Scotia Health Survey. *American Heart Journal, 159*(2), 199–206.

Davidson, K., Hall, P., & McGregor, M. (1996). Gender differences in the relation between interview-derived hostility scores and resting blood pressure. *Journal of Behavioural Medicine, 19*(2), 185–201.

Demirovic, J., Blackburn, H., McGovern, P., Sprafka, J. M., & Doliszny, K. (1993). Sex differences in coronary heart disease mortality trends: The Minnesota heart survey, 1970–1988. *Epidemiology, 4*, 1.

Denollet, J., & Van Heck, G. L. (2001). Psychological risk factors in heart disease what typed personality is (not) about. *Journal of Psychosomatic Research, 51*, 465–468.

Doering, L. V., McKinley, S., Riegel, B., Moser, D. K., Meischke, H., Pelter, M. M., & Dracup, K. (2011). Gender-specific characteristics of individuals with depressive symptoms and coronary heart disease. *Heart and Lung, 40*(3), e4–e14.

Espnes, G. A. (2002). The type A behavior pattern and coronary heart disease: A critical and personal look at the type A behavior pattern at the turn of the century. *International Congress Series, 1241*, 99–104.

Espnes, G. A., & Byrne, D. (2008). Gender differences in psychological risk factors for development of heart disease. *Stress and Health, 24*, 188–195.

Espnes, G. A., & Opdahl, A. (1999). Associations among behavior, personality, and traditional risk factors for coronary heart disease: A study at a primary health care center in mid-Norway. *Psychological Reports, 85*(2), 505–517.

Espnes, G. A., & Smedslund, G. (2001). *Health psychology*. Oslo: Gyldendal.

Ferris, P. A., Sinclair, C., & Kline, T. J. (2005). It takes two to tango: Personal and organizational resilience as predictors of strain and cardiovascular disease risk in a work sample. *Journal of Occupational Health, 10*, 225–238.

Ferris, P. A., Kline, T. J., & Bourdage, J. S. (2012). He said, she said: Work, biopsychosocial, and lifestyle contributions to coronary heart disease risk. *Health Psychology, 31*(4), 503–511.

Forrester, A. W., Lipsey, J. R., Teitelbaum, M. L., DePaulo, J. R., & Andrezejewsky, P. L. (1992). Depression following myocardial infarction. *International Journal of Psychiatry Medicine, 22*, 33–46.

Fowkes, F. G., Leng, G. C., Donnan, P. T., Deary, I. J., Riemersma, R. A., & Housley, E. (1992). Serum cholesterol, triglycerides, and aggression in the general population. *Lancet, 24*(340), 995–998.

Franklin, S. S. (2002). Definition and epidemiology of hypertensive cardiovascular disease in women: The size of the problem. *Journal of Hypertension, 20*(2), 3–5.

Friedman, M., & Rosenman, R. (1959). Association of specific overt behaviour pattern with blood and cardiovascular findings. *Journal of the American Medical Association, 169*, 1286–1296.

Galobardes, B., Smith, G. D., & Lynch, J. W. (2006). Systematc review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. *Annals of Epidemiology, 16*, 91–104.

Glazer, K., Smith, T.W., Nealy, J., & Hawkins, M. (2002). Hostility and marital adjustment. Paper presented at the annual meeting of the Society of Behavioral Medicine.

Gliksman, M. D., Kawach, I., Hunter, D., Colditz, G. A., Manson, J. E., Stampfer, M. J., Speizer, F. E., Willett, W. C., & Hennekens, C. H. (1995). Childhood socioeconomic status and risk of cardiovascular disease in middle aged US women: A prospective study. *Journal of Epideiological Community Health, 49*(1), 10–15.

Grady, D. (2003). Myocardial infarction during menses: Lessons from trials and errors. *The American Journal of Medicine, 1*(114), 611–612.

Guyll, M., & Contrada, R. J. (1998). Trait hostility and ambulatory cardiovascular activity: Responses to a social interaction. *Health Psychology, 17*, 30–39.

Herrington, D. M., Reboussin, D. M., Briosniha, N. B., Sharp, P. C., Shumaker, S. A., Snyder, T. E., Furberg, C. D., Kowalchuk, G. J., Stuckey, T. D., Rogers, W. J., Givens, D. G., & Waters, D. (2000). Effects of estrogen replacement on the progression of coronary-atherosclerosis. *The New England Journal of Medicine, 343*(8), 522–529.

Hirsch, G. A., & Meagher, D. M. (1984). Women and coronary heart disease: A review of the literature. *Health Care Women International, 5*(5–6), 299–306.

Hu, F. B., Stampfer, M. J., Manson, J. A. E., Grodstein, F., Colditz, G. A., Speizer, F. E., & Willett, W. C. (2000). Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. *The New England Journal of Medicine, 343*(8), 530–537.

Jenkins, C. D. (1996). While there's hope, there's life: An editorial comment. *Psychosomatic Medicine, 58*, 122–124.

Kinnunen, U., Feldt, T., Geurts, S., & Pulkkinen, L. (2006). Types of work-family interface: Well-being correlates of negative and positive spillover between work and family. *Scandinavian Journal of Psychology, 47*, 149–162.

Kyker, K. A., & Limacher, M. C. (2002). Gender differences in the presentation and symptoms of coronary artery disease. *Current of Womens Health Reports, 2*(2), 115–119.

Lang, T., Ducimetère, P., Arveiler, D., Amouyel, P., Ferrières, J., Ruidavets, J.-B., Montaye, M., Haas, B., & Bingham, A. (1999). Trends and geographical disparities in coronary heart disease in France: Are results concordant when different definitions of events are used? *International Journal of Epidemiology, 28*, 1050–1058.

Lawlor, D. A., Ebrahim, S., & Smith, G. D. (2005). Adverse socioeconomic position across the lifecourse increases coronary heart disease risk cumulatively: Findings from the British women's heat and health study. *Journal of Epidemiological Community Health, 59*, 785–793.

Lesperance, F., & Frasure-Smith, N. (2000). Depression in patients with cardiac disease: A practical review. *Journal of Psychosomatic Research, 48*, 379–391.

Lockyer, L., & Bury, M. (2002). The construction of a modern epidemic: The implications for women of the gendering of coronary heart disease. *Journal of Advanced Nursing, 39*(5), 432–440.

Low, K. G., Fleisher, C., Colman, R., Dionne, A., Casey, G., & Legendre, S. (1998). Psychosocial variables, age, and angiographically-determined coronary artery disease in women. *Annals of Behavioural Medicine, 20*(3), 221–226.

Low, C. A., Thurston, R. C., & Matthews, K. A. (2010). Psychosocial factors in the development of heart disease in women: Current research and future directions. *Psychosomatic Medicine, 72*(9), 842–854.

Malzberg, B. (1937). Mortality among patients with involutional melancholia. *American Journal of Psychiatry, 93*, 1231–1238.

Marmont, M., Shipley, M., Brunner, E., & Hemingway, H. (2002). Relative contribution at early life and adult socioeconomic factors to adult morbidity in the Whitehall II study. *Journal of Epidemiology and Community Health, 55*, 301–307.

Matthews, K. A., Owens, J. F., Kuller, L. H., Sutton-Tyrrell, K., & Jansen-McWilliams, L. (1998). Are hostility and anxiety associated with carotid atherosclerosis in healthy postmenopausal women? *Psychosomatic Medicine, 5*, 633–638.

Mendes de Leon, C. F., Krumholz, H. M., Seeman, T. S., Vaccarino, V., Williams, C. S., Kasl, S. V., & Berkman, L. F. (1998). Depression and risk of coronary heart disease in elderly men and women: New Haven EPESE, 1982–1991. Established populations for the epidemiologic studies of the elderly. *Archives of Internal Medicine, 23*(158), 2341–2348.

Miller, C. L. (2002). Integrative literature reviews and meta-analyses. A review of symptoms of coronary artery disease in women. *Journal of Advanced Nursing, 39*(1), 17.

Miller, T. Q., Smith, T. W., Turner, C. W., Guijarro, M. L., & Hallet, A. J. (1996). Meta-analytic review of research on hostility and physical health. *Psychological Bulletin, 119*(2), 322–348.

Mobley, L. R., Finkelstein, E. A., Khavjou, O. A., & Will, J. C. (2004). Spatial analysis of body mass index and smoking behavior among WISEWOMAN participants. *Journal of Women's Health, 13*(5), 519–528.

Möller-Leimkühler, A. M. (2008). Women with coronary artery disease and depression: A neglected risk group. *World Journal of Biological Psychiatry, 9*(2), 92–10.

Mosca, L., Appel, L. J., Benjamin, E. J., Berra, K., Chandra-Strobos, N., Fabunmi, R. P., Grady, D., Haan, C. K. M. D., Hayes, S. N., Judelson, D. R., Keenan, N. L., McBride, P., Oparil, S., Ouyang, P., Oz, M. C., Mendelsohn, M., Pasternak, R. C., Pinn, V. W., Robertson, R. M., Schenck-Gustafsson, K., Sila, C. A., Smith, S. C., Sopko, G., Taylor, A. L., Walsh, B. W., Wenger, N. K., & Williams, C. L. (2004). Evidence-based guidelines for cardiovascular disease prevention in women. (Expert Panel/Writing Group). *Circulation, 109*, 672–693.

Nabi, H., Hall, M., Koskenvuo, M., Singh-Manoux, A., Oksanen, T., Suominen., ...Vahtera, J. (2010). Psychological and somatic symptoms of anxiety and risk of coronary heart disease: The health and social support prospective cohort study. *Biological Psychiatry*, *67*(4): 378–385.

Nishtar, S. (2003, September). Women and heart disease. Heart Beat. *The World Heart Federation Newsletter*

Peterson, C., Seligman, M. E. P., & Vaillant, G. E. (1988). Pessimistic explanatory style is a risk factor for physical illness: A thirty-five year longitudinal study. *Journal of Personal and Social Psychology, 55*, 23–27.

Piwoński, J., Piwońska, A., & Sygnowska, E. (2012). Is level of social support associated with health behaviours modifying cardiovascular risk? Results of the WOBASZ study. *Kardiologia Polska, 70*(8), 803–809.

Polk, D. M., & Naqvi, T. Z. (2005). Cardiovascular disease in women: Sex differences in presentation, risk factors, and evaluation. *Current Cardiology Reports, 7*, 166–172.

Raikkonen, K., Matthews, K. A., & Kuller, L. H. (2001). Trajectory of psychological risk and incident hypertension in middle aged women. *Hypertension, 38*, 798–802.

Riska, E. (2002). From type A man to the hardy man: Masculinity and health. *Sociology of Health and Illness, 24*(3), 347–358.

Rosamond, W. D., Chambless, L. E., Folsom, A. R., Cooperm, L. S., Conwill, D. E., Clegg, L., Wang, C. H., & Heiss, G. (1998). Trends in the mortality of myocardial infarction and in mortality due to coronary heart disease, 1987–1994. *The New England Journal of Medicine, 339*(13), 861–867.

Rosenman, R. (1990). Type A behaviour pattern. A personal overview. In M. J. Straube (Ed.), *Type A behavior* (pp. 1–24). Newbury Park: Sage.

Rudisch, B., & Nemeroff, C. B. (2003). Epidemiology of comorbid coronary artery disease and depression. *Biological Psychiatry, 54*, 227–240.

Rueda, B. (2006). Gender and social support in the context of cardiovascular disease. *Women & Health, 43*, 59–73.

Rukavina, T. V., Brborović, O., Fazlić, H., Sović, S., & Civljak, M. (2012). Association of the psychological distress and cardiovascular risk behaviors, conditions and diseases: The CroHort study. *Collegium Antropologicum, 36*(1), 157–164.

Schleifer, S. J., Macari-Hinson, M. M., Coyle, D. A., Slater, W. R., Kahn, M., Gorlin, R., et al. (1989). The nature and course of depression following myocardial infarction. *Archives of Internal Medicine, 149*, 1785–1789.

Sclavo, M. (2001). Cardiovascular risk factors and prevention in women: Similarities and differences. *Italian Heart Journal, 2*(2), 125–141. based on abstract.

Shanmugasegaram, S., Russell, K. L., Kovacs, A. H., Stewart, D. E., & Grace, S. L. (2012). Gender and sex differences in prevalence of major depression in coronary artery disease patients: A meta-analysis. *Maturitas, 73*(4), 305–311.

Siegman, A. W., Townsend, S. T., Civelek, A. C., & Blumenthal, R. S. (2000). Antagonistic behavior, dominance, hostility, and coronary heart disease. *Psychosomatic Medicine, 62*(2), 248–257.

Sloan, R. P., Bagiella, E., Shapiro, P. A., Kuhl, J. P., Chernikhova, D., Berg, J., & Myers, M. M. (2001). Hostility, gender and cardiac autonomic control. *Psychosomatic Medicine, 63*, 434–440.

Stern, M. J., Pascale, L., & Ackerman, A. (1977). Life adjustment postmyocardial infarction. Detecting predictive variables. *Archives of Internal Medicine, 137*, 1680–1685.

Sundquist, K., Lindström, L., Malsmström, M., Johansson, S.-E., & Sundquist, J. (2004). Social participation and coronary heart disease: A follow up study of 6900 women and men in Sweden. *Social Science & Medicine, 58*, 615–622.

Taylor, S. E., Klein, L. C., Lewis, B. P., Grunewald, T. L., Regan, A. R., & Updegraff, J. A. (2000). Biobehavioral responses to stress in females: Tend-and-befriend, not fight-or flight. *Psychological Review, 107*, 411–429.

Thurston, R. C., & Kubzansky, L. D. (2009). Women, loneliness, and incident coronary heart disease. *Psychosomatic Medicine, 71*(8), 836–842.

UN General Assembly. (2012). *Resolution adopted by the general assembly. Political declaration of the high-level meeting of the general assembly on the prevention and control of non-communicable diseases*. Retrieved 28 Apr 2015 from: http://www.who.int/nmh/events/un_ncd_summit2011/political_declaration_en.pdf.

Wamala, S. P., Lynch, J., & Kaplan, G. A. (2001). Women's exposure to early and later life socioeconomic disadvantage and coronary heart disease risk: The Stockholm Female Coronary Risk Study. *International Journal of Epidemiology, 30*, 275–284.

Weidner, G., Boughal, T., Connor, S. L., Pieper, C., & Mendell, N. R. (1997). Relationship of job strain to standard coronary risk factors and psychological characteristics in women and men of the Family Heart Study. *Health Psychology, 16*, 239–247.

Weidner, G., Kohlmann, C. W., Horsten, M., Wamala, S. P., Schenck-Gustafsson, K., Hogbom, M., & Orth-Gomer, K. (2001). Cardiovascular reactivity to mental stress in the. *Stockholm Female Coronary Risk Psychosomatic Medicine, 63*(6), 917–2.

Williams, E. D., Steptoe, A., Chambers, J. C., & Kooner, J. S. (2011). Ethnic and gender differences in the relationship between hostility and metabolic and autonomic risk factors for coronary heart disease. *Psychosomatic Medicine, 73*(1), 53–58.

Witt, B. J., & Roger, V. L. (2003). Sex differences in heart incidence and prevalence: Implications for intervention. *Expert Opinion Pharmacotherapy, 4*(5), 675–683.

World Health Organization. (2014a). *Global action plan for the prevention and control of NCDs 2013–2020*. Geneva: World Health Organization.

World Health Organization. (2014b). *Global status report on noncommunicable diseases 2014*. Geneva: World Health Organization.

World Health Organization. (2014c). *Global health observatory data repository*. Retrieved 23 Apr 2015 from: http://apps.who.int/gho/data/node.main.A865CARDIOVASCULAR?lang=en.

Wright, L., Abbanato, K. R., Lancaster, C., & Bourke, L. (1994). Gender-related subcomponent differences in high type A subjects. *Journal of Clinical Psychology, 50*, 677–680.

Wrześniewski, K., & Włodarczyk, D. (2012). Sense of coherence as a personality predictor of the quality of life in men and women after myocardial infarction. *Kardiologia Polska, 70*(2), 157–163.

Xu, X., Bao, H., Strait, K., Spertus, J.A., Lichtman, J. H., D'Onofrio, G., ... Krumholz, H. M. (2015). Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. *Circulation*, *131*(7):614–623.

Young, L. E., Cunningham, S. L., & Buist, D. S. M. (2005). Lone mothers are at higher risk for cardiovascular disease compared with partnered mothers. Data from the National Health and Nutrition Examination Survey III (NHANES III). *Health Care For Women International, 26*, 604–621.

Stress and Social Support in Cardiovascular Disease

Kristina Orth-Gomér

Contents

Abstract

The concept and the impact of inadequate social networks and poor social support on health have been intuitively known since long. But it was not until the 1970s that the significance of social relations was demonstrated, for the first time in the Alameda county study in California.

Within a few years, several population-based prospective studies came to the same conclusion: Poor social networks and support increased total and cardiovascular mortality. This was true even in the North Karelia, Eastern Finland, but only in men. In North Karelian women, and also in other groups of women, the function of the social relationships appeared to be more important than the

K. Orth-Gomér (✉)
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
e-mail: kristina.orth-gomer@ki.se

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_29

structure. North Karelia is a part of rural Finland, situated directly at the border between Russia and Finland.

In Stockholm, women patients with coronary disease and social isolation modified the role of depression so that only when they exist together, the factors worsen prognosis and accelerate progression of coronary artery disease, as measured by quantitative coronary angiography (QCA). Similarly using QCA methodology, we could show that exhaustion, more clearly than depression, worsened prognosis in women. The stress burden originating from the family was more important than the stress burden of the job, although almost all of the Stockholm women were employed outside home. Therefore, we designed a cognitive behavioral intervention to reduce women's stress. In a randomized controlled trial, this proved to both prolong women's lives and attenuate their negative emotions.

Altogether around 800 women patients have been followed for up to 20 years. They have been examined with a variety of psychosocial measures. Of psychosocial measures, vital exhaustion was best fitting to the pattern of coronary artery atherosclerosis progression and also seemed to yield the best fit to the multivariate model of disease progression. Their precise psychobiological mechanisms remain unclear. However, multivariate evaluations suggest that standard coronary risk factors partly "explain" and metabolic, hemodynamic, immunologic, and autonomic imbalances contribute to the final and complete remaining psychobiological pathogenic pathways.

Keywords
Cardiovascular disease • Stress • Social network • Social support • Depression

Introduction

This chapter will review the epidemiological evidence of social support in cardiovascular disease (CVD) with a focus on methods to measure and quantify this support. In addition, clinical and pathogenic issues around coronary heart disease will be examined, and preventive psychosocial interventions aimed at strengthening social support in CVD will be outlined.

The Concept of Social Support

"A lonely man is a strong man" is an old saying in Scandinavia: "A strong man makes his own decisions without being in any way influenced by external cues. He is independent, and therefore his decisions are clear and sound." This may be true in the cold and dark regions of Northern Sweden. This may be true for the inhabitants of Kiruna in Northern Sweden and for people living in Rovaniemi in Northern Finland or Tromso in North Norway. These places are all situated around the North Peak of Scandinavia above the 65th northern latitude and above the Northern Polar Circle.

However, not even in these regions, where populations are scarce, where the sun and the daylight vanish from November to February, where the children are happy when the first snow comes so that they can ski to school and see the road in the reflection of the white snow, not even where the distances are so long that you will easily travel a hundred kilometers to visit a friend or look after an old relative, not even in these regions are lonely men strong men. Life is hard; winters are dark, long, and cold; and people do not talk more to each other than is absolutely necessary. But still, people know that social ties are vital, that one cannot survive without them, and that they need to be cherished and cultivated. Social supports are as vital to the people in the depopulated North, as they are to the much more densely inhabited regions around Copenhagen, Denmark, or Malmö, Sweden (Janlert et al. 1992).

Social supports can be divided, on one hand, into the purely quantitative assessment of social networks and the qualitative and functional assessment of support on the other hand. Both aspects of social support constitute the basic human need for social contact and for closeness (Ruberman et al. 1984).

The concept of social supports is almost as old as the Old World. Aristotle argued around 350 years BCE that "friendship was a basic human need, along with food, shelter and clothing. A totally loveless life – a life without friends of any sort – is a life deprived of much needed good." Much later, in 1599, Paracelsus, a physician, alchemist, and natural scientist, prescribed "love as the best possible cure for several diseases" (Rose 1992).

The first modern scientific evidence of a link between social support and health was provided by Emil Dürkheim (1858–1917) in his extensive sociological studies on the origins of suicide and self-destructive behavior. He found that marriage and religion were the best protectors against such deviant self-destructive behavior. Kropotkin, a Russian ethologist and psychobiologist, gave support to this notion by stating in 1908 that "mutual help and support is a factor of great significance for the maintenance of life and health in animals and in humans" (Stamler 1980).

The Biological Effect of Social Networks and Social Supports on Heart Disease

The effect of social support on the heart has been intuitively known for centuries. However, modern cardiology demands empirical evidence. In both the research and clinical settings, the effects of social support on the heart have required verification. The following population- and patient-based longitudinal studies describe this.

Population-Based Studies of Social Networks and CVD

Jim House et al. (1988) in a summarizing review compared health effects of social networks in cigarette smokers. They looked at longitudinal, representative population-based cohorts in the USA from Alameda County (Berkmann and Syme 1979),

Tecumseh (Michigan; House et al. 1982), Evans County (South Georgia; Blazer 1982), East Boston, Iowa, and New Haven (House et al. 1988). They also described the findings from European studies, including North Karelia in Finland (Kaplan et al. 1988), Gothenburg in Sweden (Orth-Gomer et al. 1993), and the SC ULF study (Orth-Gomer et al. 1987), based on a representative sample of all Swedish men and women, aged 15–75. All study groups were followed for several years, looking at the same medical end points. All these longitudinal studies generally agreed on the same broad conclusion, namely, that while the magnitude of the health risks was about the same, social networks consistently promoted health, that is, more frequent social contacts were prospectively associated with better physical and mental health. The conclusions were clear and unambiguous (Orth-Gomer 1987). However, it was difficult to understand what the counts of friends, neighbors, work mates, etc. really meant. It was hard to know which impacted psychological function or which were the personality characteristics of individuals who were sensitive to the variations in social ties. As a result, the literature was further explored and a set of psychometric investigations were carried out, aimed at finding or developing active and more easily interpreted examination methods for the role of social support. The Interview Schedule for Social Interaction (ISSI; Henderson et al. 1980) was found. This survey instrument was designed as an interview instrument to assess the availability and perceived adequacy for any individual of a number of facets of social relationships. The instrument is sufficiently valid and reliable and also sensitive to predictable variations between sociodemographic groups, so its use can be justified in clinical and epidemiological studies, both in psychiatry and general medicine.

Psychometric Studies of Social Supports

The ISSI had the functional approach that we were looking for, but it was very cumbersome to use. In a pilot study, we developed a paper and pencil test, paying particular attention to psychometric properties, including split-half reliability, face validity, and internal consistency (Orth-Gomer and Unden 1987; Undén 1991).

The resulting scale had 13 items, 6 describing "attachment" and 7 describing "social integration." The instrument has now been implemented in several population-based cohorts, such as in young men in North Sweden, Gampöjka; in 50-year-old men in Göteborg (Janlert et al. 1992); and in women with clinically manifest CVD in Stockholm (Orth-Gomér et al. 1998, 2000; Horsten et al. 2000).

Functional Measures of Social Supports

The Northern part of Scandinavia has been identified as an extremely isolated region (Zapf 2009). Our experience from the Northern part of Scandinavia confirms the special emotional profile, which could be ascribed to the harsh living conditions in that region. As a part of the MONICA project, we described the social support

profiles in different age and gender groups in the most Northern part of Sweden. We used the self-report measures that were agreed upon in the multicenter MONICA studies, thus disentangling size and density of social networks from the quality and function of social support. In most cohorts, we found the former scale, *social integration*, to be predictive of health outcomes in the expected direction.

That is, the more numerous and more frequent social contacts were associated with better health outcomes. One group in the North stood out on another dimension, namely, that of attachment, meaning the quality and function of close emotional ties, relationships which are found within the family or with very close friends. The items were concerned with whether there is someone to "hold you for comfort," and whether there is "someone to share happiness with, someone that would be happy just because you are...."

The young men in Northern Sweden were nicknamed "*Gampöjka*." They were the only ones left when everybody else in the village had moved to the cities in the South (such as Stockholm). These young men actually confirmed that they had few or no relationships providing them with a sense of "attachment." In addition they were mostly unemployed and without family, many of them living with a widowed mother. There was literally none to hold them for comfort as all the young women from the north had gone south (Janlert et al. 1992).

Fifty-Year-Old Men in Göteborg

In a more representative Swedish population-based cohort study, a thousand men born in 1913 in Göteborg were approached. This was actually the first epidemiological study carried out in Sweden, and the results were both reassuring and alarming. In these men, their social contact networks were examined along with a set of carefully validated measures of standard risk factors. At baseline examination, they were all 50 years old. In a long-term follow-up study, social networks and social interaction predicted mortality independent of other standard risk factors. The results showed that more social contacts were associated with lower mortality. These findings were the first population-based social network-related results outside the USA, and their significance was discussed in terms of the need for more accurate, functional measures – and the need for psychosocial interventions.

In a collaborative study, we had the opportunity to approach the next generation of 50-year-old Göteborg men, those born in 1933. We carefully prepared interviewers to cautiously present our functional scale to the Göteborg men. We thought that some of the questions might be perceived as offensive. This had already happened before. Some men, taking the test, had become really angry, "this is none of your business," and torn the papers apart. But we needed not to worry about that. Every single item was filled out. Non-response was minimal. At 6-year and at 15-year follow-up, our hypotheses were confirmed.

Both the quantitative and the qualitative measures of social supports were independent predictors of CVD (Orth-Gomér et al. 1993).

Stockholm Women: Their Social Supports and Cardiovascular Disease

Coronary heart disease is traditionally thought of to be a man's disease. Women have been previously thought to be free from heart disease; they were even thought to be immune. Although about as many women as men are found to die from cardiovascular causes, women have not been present in the intensive coronary care units, where the acutely ill patient is monitored during the first 48 h, or so, after onset of symptoms. Thus, this might be a reason for this erroneous perception.

It was argued that women patients were not properly cared for and that they did not get full access to the technical equipment and treatment methods, which men had been blessed with during the past decades of advances in cardiology. Men in their 60s are usually found in the CCU, but aged-matched women are usually not, possibly due to the relative protection against CVD, at least during the first years of their menopause. Thus, while most women menstruate until around age 51, their endogenous estrogen provides protection against atherosclerosis and coronary disease for many years after the cessation of menses.

Women's coronary risk factors, which are counteracted by estrogen, continue to increase in frequency and effect after menopause, so that about the age of 70, women's experience of heart disease matches that of men at same age. At that age women are no longer a rare occurrence in the CCUs. As women seem to develop their heart disease about 10 years later in life than men, they ought to have access to preventative and state-of-the-art interventions as much as men do, unless older age is somehow an obstacle.

Women, of course, differ from men, also in other aspects of health and disease. We know that the average life expectancy is higher in women than in men and that the gender gap is to a large extent due to differences in coronary disease incidence. In most countries, this gender gap is about 5 years (such as in Western Europe and in the USA), but there are Eastern European countries, like Russia, in which the gender gap is approaching 15 years. Little is known about the precise causes. However, it is generally agreed that women's burden of disease is higher than men's, in particular if calculated as disability-adjusted life years (DALYs) and comprising all causes for disability, such as depression, anxieties, and sleep disturbances.

The age gap between sexes may also influence the psychosocial environment, as in the case of access to social supports. Elderly women are more often living alone; they are more often widowed, divorced, or separated. In a New England population survey of mental health-related factors, women differed from men in identifying their most important support person. About 60 % of men, – but only 25 % of women – named their spouse. Note that men and women came from the same population. This finding may be quite relevant for women's hearts. We found, in Stockholm women coronary patients, below age 65, that depression and social isolation worsened the prognosis of women's heart disease (Horsten et al. 2000) similarly

as had previously been found in men (Orth-Gomer et al. 1998). However, when examining the causes of distress, important gender differences were identified.

Women who had poor marital relationships, we called it marital stress, had three times the risk of getting a recurrent coronary attack, as compared to women patients without marital stress with the best prognosis found in women who had a good job and a happy marriage (Orth-Gomér et al. 2000). In a subgroup analysis, this latter group was found to be even more "health prone." In coronary angiographic examination with subsequent quantitative evaluation (QCA), which was repeated after a 3-year follow-up period, coronary artery disease did not progress as expected. In contrast, in this particular group of women patients, their CAD actually regressed as if they had been on systematic statin therapy. However, none of them was taking any statins at all. These were not used until much later in Swedish patients.

New Psychosocial Intervention Trial

Based on these findings, a clinical trial of cognitive psychosocial intervention was designed (Blom 1997; Orth-Gomér 2012). Stockholm women patients were highly motivated to cardiac rehabilitation, provided it did not happen in the customary male setting. We had barely ended the collection of data for the observational Stockholm Female Coronary Risk study, when we were asked by patients to offer them rehabilitation. They came to us and said: "You should do something for us! Look how the men patients get to exercise – while their pretty physical therapists are surveying them on their bikes! However, we do not want to share their program, we do not want to sweat with them! We would like our own program, and we would like to talk rather than exercise!"

The SWITCHD study (Stockholm Women's Intervention Trial for Coronary Heart Disease) included 237 consecutively admitted women patients with coronary heart disease. It was the very first randomized controlled trial to follow the CONSORT criteria and to show evidence of a significant benefit of psychosocial intervention on hard clinical outcomes. The 1-year behavioral therapy program focused on how to reduce stress, mostly from poor interpersonal relations; at follow-up there was a threefold reduction in long-term mortality (mean follow-up 7 years). Mean age in both groups was 61 years at baseline, around half of the women had a transmural myocardial infarction, most of them had no or little symptoms of cardiac failure (NYH = 1 or 2) and angina pain (Canadian classification) was rare. Almost all patients were on daily pharmacotherapy (i.e., statins, beta blockers, diuretics, and ASA). The most pronounced effect was found in the group of women who received both CBT and statins; their mortality rate was <1 % in 7 years. Women without both statins and the rehab program had 20 % mortality and the other two groups were intermediate (Orth-Gomér et al. 2009).

Psycho-cardiology

The turn of the new century, between 2000 and 2004, became a marker for a new line of scientific concepts (Wang et al. 2005). Our original work on the "ESC clinical guidelines for CVD prevention in clinical practice" focused on psychosocial risk factors. These clinical guidelines were published for the first time in December 2003, together with consecutive publications in other journals (De Backer et al. 2003), and provided a new perspective of understanding from the patient's perspective after an acute coronary event. Behavioral and psychosomatic medicine then became recognized specialities, which were taken seriously and acknowledged by the research community.

A year later, another important event occurred, the publication of the INTERHEART study. Largely the same psychosocial risk factors were cited as in the guidelines (see below). In addition, for the first time, coronary risk that could be attributed to psychosocial factors was estimated to be around 30 %. As the INTERHEART study included some 16,000 CVD patients and an equal number of controls, representing over 50 countries, the results were robust and significant. In addition, other risk factors detrimental to cardiac health were identified. These included: Low SES, emotional stress from work and family, lack of social support, and social isolation, along with the accompanying negative emotions (depression, exhaustion, hopelessness, anger, and hostility), were definite, scientifically based coronary risk factors (Yusuf et al. 2004).

Traditionally, an important part of cardiac rehabilitation is physical exercise. More recently "rehabilitation has been found to be as much about reducing anxiety and depression as it is about lifestyle change." Of the ten core components of an ideal rehabilitation program, psychosocial management ought to be considered the most important.

The other nine core components can be addressed with lifestyle change. However, although patients are carefully instructed, with great detail about what they should do in order to prevent heart disease, little is said about how it is done. Therefore, failure of cardiac rehabilitation could be attributed to this aspect of lack of psycho-education. It is well known that the modern, life-saving acute heart disease care constitutes a heavy burden on the healthcare system. The acute phase is characterized by high impact and resourceful intensive care. An acute patient with severe central chest pain, especially if it is a male patient, will be treated using the best and newest technology and personnel skills. Often, even before the patient has reached the hospital, his acute EKG will be transmitted from the ambulance and interpreted by the cardiologist or related specialist who is on call in the clinic. Yet an important question remains: Why are patients not following this excellent expert advice? The pattern is clear: Cardiologists of today have realized that patients have both body and mind and that both need to be cared for. But they may not be able to fully meet the needs of the important "mental half" of the body-mind complex. Help ought to be obtained from psycho-cardiology.

A Clinical Case of Sudden Cardiac Death

My personal experience with cardiologic acute care made a significant impact.

On an August afternoon, I went swimming in the cold Baltic Sea, with a neighbor, a healthy man in his 60s. Afterwards he felt uneasy and suddenly got such intense chest pain that he couldn't walk. We were out in the archipelago so I was worried about how transporting him to a clinic would go. While I was still talking to the ambulance driver, I heard the sound of a helicopter over our heads, which came to pick him up. The pilot landed in the garden right next to us, a coronary care nurse came out of the helicopter, and she briefly viewed the EKG and then inserted a needle and gave him a needle shot. The pain subsided and he was immediately taken to the closest cardiology clinic, which was about 100 km away.

The Stockholm archipelago consists of 25,000 smaller and bigger islands, and we were lucky not to be on the most remote island. I got into my car and drove as quickly as I could. This was clearly a life-threatening situation and I wanted to be nearby if anything was needed. When I got to the hospital, the catheterization was already done. On his bed was a photo of the right coronary artery *before* – and one *after* the intervention. He had received a few stents at the place of his right coronary "narrowings" and his life was saved.

If he had not been so efficiently cared for, if he had not been so quickly and professionally managed, he might have died from sudden cardiac death. This condition hits more men than women, especially men who are under age 65. Typically these patients have such sudden symptoms that they do not even make it to the emergency room, rather they tend to die on the way to the hospital.

By definition symptoms of chest pain hit the patient as might lightning from a clear sky, although may have had some nausea or tightness during the preceding hours. The underlying coronary artery disease is usually not impressive. On the contrary, the extent of coronary disease is often lower than expected. The demonstrated mechanism of sudden cardiac death is most likely cardiac arrhythmia. Commonly, it appears to start with ectopic activity, generated in the ventricles of the heart. The ectopic beats become more and more frequent and more and more malignant in character and finally they change into ventricular tachycardia and at last ventricular fibrillation. At that stage, of course, the heart muscle does not contract to pump the blood into the circulatory system. Within a few minutes, the patient is dead.

I looked at my watch. My neighbor had received the first treatment within 12 min and the stents within an hour after his first cardiac symptoms! Not long ago we had been out swimming in the Baltic Sea! I was stunned that the acute hospital care could be so efficient. Later I learned that this has become a fairly standard procedure, particularly as early symptoms and instant treatment are so crucial for successful therapy in acute coronary disease.

If there is a suspicion of coronary artery "narrowing" or occlusion, the well-equipped and trained personnel of the ambulance will communicate during the

transportation, giving their opinion, which is almost always right, directly to the clinic. This is how the angiographic laboratory can be prepared while the patient is arriving to the emergency unit. Specially trained nurses will assist the cardiologist throughout the procedures. They are instructed, well trained, often constituting of underestimated, poorly paid, highly competent professionals.

Conclusion

The introduction of intensive coronary care units (CCUs) have reduced the acute mortality risks of myocardial infarction in hospitalized patients to about half. At the same time, new surgery and catheterization techniques have been implemented. Much experience was gathered, which lead to the development of stents, a devise which is inserted into the coronary artery narrowing to keep it open and maintain blood flow. Third –and probably most important for survival – the introduction of efficient pharmacotherapy for prevention of death after an acute heart attack is perhaps the most effective measure.

Today virtually all post-AMI patients are taking preventative drugs every day, for the rest of their lives. First, the beta blockers were introduced on the market. They were shown to help against angina pain, reduce blood pressure and relieve symptoms of heart failure, and even postpone mortality (reference needed). Furthermore, coenzyme A reductase inhibitors – statins – were introduced in order to lower LDL cholesterol. But they were also found to have a substantial beneficial effect on all cause and heart disease-related mortality, which could not be explained by effects on LDL only (reference needed). In subsequent studies, statins were found to have antithrombotic effects which were more important than could be shown with any other drug (reference needed). In the recent SWITCHD study, it appears as if the statins might reinforce the effects of the cognitive stress reduction program (Orth-Gomer' et al. 2009).

What are the possible explanations for this finding? This finding could be based on patients' greater motivation and discipline when taking our cognitive stress-reducing program. But it could also be due to patients becoming more trustful and having more faith and being psychologically more receptive when taking the statins. This effect then would interact with the cognitive stress reduction program by strengthening its efficiency.

In women patients who had received both statins and CBT, mortality was less than 1 %, whereas in the other three groups, women who were taking only one –or none – of the two therapy options, mortality rates over 7 years were between 15 % and 20 %. Thus an interactive effect was noted between statins, the most potent of the pharmacological preventive therapies and CBT and the most potent of the psychosocial treatment modalities.

Altogether around 800 women patients have been followed for 20 years with the same psychosocial measures using QCA, we showed that low social support, depression, and exhaustion accelerate the atherosclerotic process in the coronary arteries, worsen prognosis, and seem to yield the best fit to the multivariate model

of disease progression (Orth-Gomér et al. 2015). Compelling evidence has accumulated for a wide range of psychosocial risk factors, which are now ready to be implemented in clinical practice.

References

Berkmann, L., & Syme, S. L. (1979). Social networks, host resistance and mortality. A nine year follow up of Alameda county residents. *American Journal of Epidemiology, 109*, 186–204.

Blazer, D. (1982). Social support and mortality in elderly community population. *American Journal of Epidemiology, 115*, 684–694.

Blom, M. (1997). Psychosocial finings in women with heart disease. Stress research report No 255 Karolinska Institutet.

De Backer, G., Ambrosioni, E., Borch-Johnsen, K., Brotons, C., Cifkova, R., Dallongeville, J., Ebrahim, S., Faergeman, O., Graham, I., Mancia, G., Manger Cats, V., Orth-Gomér, K., Perk, J., Pyörälä, K., Rodicio, J. L., Sans, S., Sansoy, V., Sechtem, U., Silber, S., Thomsen, T., Wood, D., & Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. (2003). European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *European Heart Journal, 24*(17), 1601–1610. No abstract available.

Henderson, S., Duncan-Jones, P., & Byrne, D. G. (1980). Measuring social relationships. The interview schedule for social interaction. *Psychological Medicine, 10*, 723–734.

Horsten, M., Mittleman, M. A., Wamala, S. P., Schenck-Gustafsson, K., & Orth-Gomér, K. (2000). Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. *European Heart Journal, 21*(13), 1072–1080.

House, J. S., Robbins, C., & Metzner, H. L. (1982). The association of social relationships and activity with mortality. Prospective evidence from the Tecumseh community health study. *American J. of Epidemiology, 116*, 123–140.

House, J. S., Landis, K. R., & Umberson, D. (1988). Social relationship and health. *Science, 41*, 40–45.

Janlert, U., Asplund, K., Weinehall, L., Orth-Gomér, K., & Undén, A. L. (1992). Men who never married. A socio-medical study in northern Sweden. *Arctic Medical Research, 51*(2), 72–80.

Kaplan, G. A., Salonen, I. T., Cohen, R. D., et al. (1988). Social connection and mortality from all causes, prospective evidence from eastern Finland. *American of Epidemiology, 128*, 170–180.

Orth-Gomér, K. (1987). A loose social network increases the risk of cardiovascular diseases. *Läkartidningen, 84*(43), 3474–3475. Swedish.

Orth-Gomér, K. (2012). Behavioral interventions for coronary heart disease patients. *Biopsychosoc Med, 6*(1), 5. doi:10.1186/1751-0759-6-5.

Orth-Gomér, K., & Undén, A. L. (1987). The measurement of social support in population surveys. *Social Science and Medicine, 24*(1), 83–94.

Orth-Gomér, K., Rosengren, A., & Wilhelmsen, L. (1993). Lack of social support and incidence of coronary heart disease in middle-aged Swedish men. *Psychosomatic Medicine, 55*(1), 37–43.

Orth-Gomér, K., Wamala, S. P., Horsten, M., Schenck-Gustafsson, K., Schneiderman, N., & Mittleman, M. A. (2000). Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study. *JAMA, 284*(23), 3008–3014.

Orth-Gomér, K., Horsten, M., Wamala, S. P., Mittleman, M. A., Kirkeeide, R., Svane, B., Rydén, L., & Schenck-Gustafsson, K. (1998). Social relations and extent and severity of coronary artery disease. *The Stockholm Female Coronary Risk Study*. *European Heart Journal, 19*(11), 1648–1656.

Orth-Gomér, K., Schneiderman, N., Wang, H. X., Walldin, C., Blom, M., Jernberg, T. (2009). Stress reduction prolongs life in women with coronary disease: The Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). *Circulation: Cardiovascular Quality and Outcomes*, *2*(1), 25–32.

Orth-Gomér, K., Schneiderman, N., Vaccarino, V., & Deter, H. C. (Eds.). (2015). *Psychosocial stress, and cardiovascular disease in women – concepts findings, future directions*. New York: Springer.

Rose, G. (1992). *The strategy of preventive medicine*. Oxford: Oxford University Press.

Ruberman, W., Weinblatt, E., Goldberg, J., et al. (1984). Psychosocial influences on mortality after myocardial infarction. *NEJM, 311*, 552–559.

Stamler, J. (1980). Preventive cardiology. In T. Cheng (Ed.), *Textbook of cardiology* (pp. 1237–1255). New York: Pergamon.

Unden, A. L. (1991). Academic thesis, Karolinska Institute.

Wang, H. X., Mittleman, M. A., & Orth-Gomer, K. (2005). Influence of social support on progression of coronary artery disease in women. *Social Science and Medicine, 60*(3), 599–607.

Yusuf, S., Hawken, S., Ounpuu, S., et al. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*(9438), 937–952.

Zapf, K. M. (2009). *Social work and the environment: Understanding people and place*. Toronto: Canadian Scholars Press, Toronto.

Mental Health and Cardiovascular Disease Risk in Refugees

Harry Minas

Contents

Abstract

In 2013 there were 51.2 million persons worldwide who had been forcibly displaced as a result of persecution, conflict, generalized violence, or human rights violations. 16.7 million persons, half of whom were children, were refugees. More than 80 % were living in refugee camps and other generally temporary although often long-lasting arrangements, in developing countries. From this massive population, only 98,000 were resettled in refugee-receiving countries. The prevalence of mental disorders, particularly post-traumatic stress disorder, depression, and anxiety, is greater in refugees than in non-refugees, although prevalence estimates vary greatly. As well as having poorer mental health, refugees are also more likely than non-refugee immigrants or host populations to experience poorer physical health, higher all-cause mortality, and higher cardiovascular mortality. Although the severe and persistent stress that is a central element of refugee experience is probably an independent risk factor for cardiovascular disease, it seems likely that the higher cardiovascular

H. Minas (✉)
Global and Cultural Mental Health Unit, Melbourne Refugee Studies Program, School of Population and Global Health, The University of Melbourne, Parkville, VIC, Australia
e-mail: h.minas@unimelb.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_34

risk is mediated by mental disorders, such as post-traumatic stress disorder and depression, which are common in refugees and are clearly associated with increased cardiovascular risk. In addition, refugees are less likely to have access to effective mental health and general health services, resulting in further avoidable risk of cardiovascular morbidity and mortality.

Keywords

Cardiovascular disease (CVD) and mental disorders • Cognitive behavioral therapy (CBT) • Heart rate variability (HRV) • Mental disorders • Post-traumatic stress disorder (PTSD) • Refugees • CVD risk factors; *see* Cardiovascular Disease (CVD) • UNHCR

Introduction

In 2013, the latest year for which comprehensive global data are available (United Nations High Commissioner for Refugees 2014), there were 51.2 million persons who had been forcibly displaced as a result of persecution, conflict, generalized violence, or human rights violations. 10.7 million persons were newly displaced in 2013, of whom 8.2 million were internally displaced within their own country. The other 2.5 million were new refugees, the largest number in a single year since 1994. 16.7 million persons were refugees, of whom 50 % were aged less than 18 years. There were 33.3 million internally displaced persons and 1.2 million asylum seekers.

More than half of all refugees worldwide came from three countries: Afghanistan (2.6 million), Syria (2.5 million), and Somalia (1.1. million), followed by Sudan, Democratic Republic of Congo, Myanmar, Iraq, Colombia, Vietnam, and Eritrea. The five top refugee-hosting countries were Pakistan (1.6 million), Iran (857,000), Lebanon (856,000), Jordan (642,000), and Turkey (610,000). Eighty-six percent of the world's refugees (compared to 70 % a decade previously) were being hosted in developing countries, and more than 5.4 million refugees were in countries with a GDP per capita of less than US$ 5000.

1.1 million persons submitted applications for asylum or refugee status in 2013. Only 98,000 refugees were resettled in countries, with the United States receiving the largest number (66,000). More than 400,000 returned to their country of origin, with most returning to Syria (141,000), Democratic Republic of Congo (68,000), and Iraq (61,000). This was the lowest level of refugee returns in 25 years (United Nations High Commissioner for Refugees 2014).

While these stark figures from UNHCR give an indication of the scale of the global problem of forced displacement, they cannot convey the depth of suffering experienced by asylum seekers and refugees who have fled their homes and countries as a result of threats to personal safety, livelihood, freedom, dignity, and an acceptable future for themselves and their children. Many have experienced violence and injury and sexual assault. A significant number have been subjected to persistent human rights abuses and state-sponsored torture. Most have witnessed destruction, violence, killings, assaults, and disappearances. Loss of home,

belongings, privacy and liberty, opportunity, and future prospects is commonplace, as are loss of dignity and hope. The world that was familiar is disrupted. Normal facilities and services, including vital health services and social functions and networks, have collapsed. It is unclear who can be trusted and few can be relied upon to provide vital help. Circumstances are unpredictable and there is little prospect of a return to order and stability. There may be insufficient water, food, and shelter.

During the period of flight and on arrival in some temporary places of relative safety, asylum seekers live in a state of chronic alarm, fear, and anxiety. In this fractured world, little is familiar. Privacy, choice, control, and planning become impossible. Loss of family, friends, and colleagues, separation from loved ones, and anxiety about those left behind are constant preoccupations. As well as anxiety, grief, and helplessness, there may also be guilt and shame because of things done and things not done. While many people in these circumstances display remarkable resilience, it may be expected that there would be high rates of mental disorder, particularly depression, anxiety, and post-traumatic stress disorder (PTSD), an expectation that is confirmed by the available evidence.

Mental Disorders

The World Health Organization's World Mental Health Survey has generated estimates of lifetime prevalence and age-of-onset distributions of anxiety, mood disorders, and substance use disorders from a combined 85,052 participants in 17 countries in Africa, Asia, the Americas, Europe, and the Middle East (Kessler et al. 2007). Median lifetime prevalence estimates are anxiety disorders 4.8–31.0 %, mood disorders 3.3–21.4 %, substance use disorders 1.3–15.0 %, and any disorder 12.0–47.4 %. Median age of onset is very early for some anxiety disorders (7–14 years) and impulse control disorders (7–15 years). The age-of-onset distribution is later for mood disorders (29–43 years), other anxiety disorders (24–50 years), and substance use disorders (18–29 years).

The authors suggest three possible biases that may have resulted in the underestimation of prevalence. The first is that people with mental illness are less likely than others to participate in surveys, because of sample frame exclusions (e.g., excluding homeless people), differential mortality, or greater reluctance to participate. It is suggested that the wide variation in estimates across countries may be due to variation in the magnitude of such underestimation across countries. A second possible bias is that lifetime prevalence is sometimes underreported because of respondent reluctance to admit mental illness, which is also likely to vary across countries. The third is possible interviewer error, with under-detection resulting from rushing through interviews due to being paid by the hour. Although it is possible that the estimates may be too high because thresholds for the presence of mental disorder may have been too low, clinical reappraisal studies in some of the countries with the highest prevalence estimates found no evidence of such bias.

Reviewing 174 surveys across 63 countries estimating population estimates of the prevalence of mental disorders, Steel and colleagues report a combined 12-month prevalence of 17.6 % and 29.2 % lifetime prevalence for common mental disorders (Steel et al. 2014).

Although the ranges for estimated prevalence and median age of onset are very wide, it is clear that mental disorders are common and that many mental disorders have their onset in adolescence and early adulthood.

Mental Disorders in Refugees

A systematic review of population-based studies published from 1990 to 2007 reporting prevalence rates of depression and anxiety in immigrant and refugee adults, with a combined sample of 24,051 refugees, identified 35 studies in 37 immigrant and refugee populations. Combined prevalence rates for depression were 20 % among immigrants and 44 % among refugees. For anxiety the combined estimates were 21 % among immigrants and 40 % among refugees (Lindert et al. 2009).

Several systematic reviews of studies reporting prevalence of PTSD and depression have been carried out. Vu et al. (2014) reported prevalence of 8–37.2 % for PTSD and 28.3–75 % for depression among community samples of resettled Iraqi refugees. Iraqi refugees continue to represent one of the largest groups being resettled worldwide. A systematic review of prevalence surveys focusing on PTSD, depression, and psychotic illnesses (Al Kasseh et al. 2014) identified 20 eligible studies, with a total study population of 6743 adult refugees from seven countries. One in 10 adult refugees resettled in western countries had PTSD, 1 in 20 had major depression, and 1 in 25 had an anxiety disorder. While the prevalence of depression is about the same as in non-refugee general populations, PTSD was about ten times more common in refugees than in general populations.

Porter and Haslam reviewed 56 studies that investigated a refugee group and a non-refugee comparison group and reported quantitative group comparisons on measures of psychopathology (Porter and Haslam 2005). Refugees had worse outcomes and, importantly, both pre-displacement and post-displacement conditions moderated mental health outcomes.

The available evidence suggests that mental disorders, particularly PTSD, depression, and anxiety, are more prevalent in refugees than in immigrants and host populations. Most mental disorders have their onset in childhood or adolescence and early adulthood. Most asylum seekers and refugees are young – 50 % of the refugee population is children below 18 years – and many of the rest are young adults (United Nations High Commissioner for Refugees 2014). This is important, because the onset of mental disorder is most likely to occur in the context of a life – age and stage of development – that is already in turmoil because of asylum seeker or refugee status, complicating everything. For more than four out of five refugees globally who are in marginal circumstances in developing countries (United Nations High Commissioner for Refugees 2014), this means little or no access to

even basic health and social services let alone skilled mental health services. Emerging mental disorders are likely to be undetected and untreated, with negative consequences for the mentally ill refugee and her/his family.

CVD Risk Factors

The major modifiable risk factors for CVD are well known and will be discussed here only insofar as they may be relevant to refugees. There are consistent findings of greater exposure to CVD risks and higher rates of CVD among refugees than in host populations.

Chronic stresshas been identified as a significant risk factor for CVD. Among the circumstances that give rise to chronic stress among refugees are exposure to violence and more specifically sexual violence and torture. Refugee women are particularly vulnerable to sexual violence in situations of conflict and displacement. A systematic review yielding 19 eligible studies reported an estimate of prevalence of sexual violence of 21.4 %. The authors considered this an underestimate because of the substantial barriers to disclosure (Vu et al. 2014). In a review of 161 articles reporting results from a combined total of 81,866 refugees and other conflict-affected persons from 40 countries, Steel et al. (2009) reported the prevalence of PTSD ranging from 0 % to 99 % and the prevalence of depressions ranging from 3 % to 85.5 %. This remarkable variation in estimates was attributed to methodological factors, such as nonrandom sampling, small sample sizes, and self-report questionnaires, and to variations in substantive population risk factors. Among the substantive risks reported, torture emerged as the strongest factor associated with PTSD, followed by the level of exposure to traumatic events, time since conflict, and assessed level of political terror (Steel et al. 2009).

While gender-based violence is known to be a common and disturbing refugee experience, an attempt to carry out a systematic review of studies of strategies for prevention and treatment of gender-based violence or to address the physical and mental health consequences of gender-based violence, among refugees, yielded no eligible studies. The authors found not a single article evaluating prevention, treatment, or management of gender-based violence and its health consequences in displaced populations that met the systematic review inclusion criteria. Although there were many expert recommendations and guidelines from international organizations that presented specific strategies to prevent and/or treat the health consequences of gender-based violence, none was supported by primary research on displaced populations (Asgary et al. 2013).

There are few rigorous studies of the prevalence of torture among refugees. Experience of torture varies greatly among different country-of-origin groups and among different cohorts from the same country. A study of Iraqi refugees in the USA found that 56 % had been subjected to torture and that torture is associated with the presence of both mental and physical symptoms on the post-arrival health screen (Willard et al. 2014).

There is clear evidence of PTSD being associated with increased risk of CVD and with increased CVD morbidity and mortality. While there are many methodological challenges in studying PTSDand CVD in refugees, some methodologically rigorous work that has been done with US military veterans can be instructive in relation to refugees, since PTSD is a very common diagnosis in both groups.

A substantial follow-up project of 15,288 US Army veterans (Boscarino 2006a) examined the link between PTSD and survival time and cause of death 30 years after military service. The large sample size, the excellent sampling frame enabled by military records, and the high participation rate by veterans in the study enable some firm conclusions to be drawn. Thirty years postwar, mortality hazard ratios were all-cause (HR = 2.2) and cardiovascular (HR = 1.7), cancer (HR = 1.9), and external (including motor vehicle accidents, accidental poisonings, suicides, homicides, and injuries of undetermined intent) (HR = 2.3) causes of death (Boscarino 2006b).

Factors that may increase vulnerability to obesity and cardiovascular disease among refugees include both dietary changes and limited physical activity (Drummond et al. 2011; Sundquist et al. 2010). Sub-Saharan refugees in Australia have been found to be at risk of obesity and diabetes (Renzaho et al. 2011), and Bosnian refugee women in Sweden have been found to have CVD risk profile lipids and obesity (Sundquist et al. 1999).

The available evidence, although still limited, suggests that risk factors for CVD may be substantially higher among refugees than among immigrants and host populations, resulting in higher rates of cardiovascular morbidity and mortality.

Mental Disorders and CVD

A population-based cohort study of mental disorders and all-cause and cause-specific mortality among 86,395 immigrants and refugees in Sweden found that immigrants and refugees had poorer mental health than native Swedes, refugees of most origins had a higher likelihood of poor mental health than non-refugees of the same origin, and refugee men had a significantly higher risk than immigrants of cardiovascular mortality (hazard ratio 1.53) and death from external causes (hazard ratio 1.59) (Hollander et al. 2012; Hollander 2013). Socioeconomic factors did not significantly influence overall risk. Female refugees had higher risk of cardiovascular mortality, with a hazard ratio similar to that for men. Because of smaller numbers in the sample, no conclusions could be drawn about deaths from external causes for women.

Depression is the most intensively studied mental disorder in relation to cardiovascular disease. A recent scientific statement by the American Heart Association concluded that “Despite the heterogeneity of published studies included in this review, the preponderance of evidence supports the recommendation that the American Heart Association should elevate depression to the status of a risk factor for adverse medical outcomes in patients with acute coronary syndrome” (Lichtman et al. 2014).

Depression is a robust risk factor for the development of CVD in healthy populations and is associated with negative outcomes such as myocardial infarction and death among populations with preexisting cardiovascular disease (Clark and Mytton 2007). Post-myocardial infarction depression is associated with an increased risk of all-cause mortality, cardiac mortality, and increased cardiac events (Robinson et al. 2008). This link may be mediated through low heart rate variability (HRV) which is found in many studies in both depression and anxiety and through behavioral risk factors, including physical inactivity, medication nonadherence, and smoking (Stein et al. 2000; Carney et al. 2001, 2005; Clark and Mytton 2007; Martens et al. 2008). Among persons with major depression, the strongest link to CVD is the link between depression and myocardial infarction (Kessler et al. 2007). The presence of depression in persons with coronary artery disease has been reported to be associated with increased risk of further cardiac events (Nielsen et al. 2013) and increased mortality. It is possible that this link is mediated by reduced HRV in depression, a known risk factor for CVD. In patients with stable coronary heart disease, some studies have not found evidence of an association between depression and HRV (Gehi et al. 2005).

Although much less research has been done on the links between other specific mental disorders and CVD, and the evidence concerning other mental disorders is less compelling than that for depression, there is a body of evidence suggesting that schizophrenia (Ringen et al. 2014), bipolar disorder (Kessler et al. 2007; Callaghan and Khizar 2010), and PTSD (Boscarino 2006b) are associated with greater risk of developing CVD and increased CVD morbidity and mortality. While tuberculosis was the commonest cause of death in people with schizophrenia a century ago, suicide remains a common cause of death in young people with schizophrenia, and CVD is now the commonest cause of death among older people with schizophrenia (Callaghan et al. 2009; Healy et al. 2012).

Although several possible mechanisms for the association of mental disorders with cardiovascular risk and outcomes have been proposed, including the behavioral risk factors mentioned above, it is clear they are likely to include multiple systems and pathways (Bouzinova et al. 2014) including the central and autonomic nervous systems, the neuroendocrine system, the immune system, and the vascular and hematologic systems. Potentially relevant pathophysiologic factors include "homeostatic imbalance between the sympathetic and the parasympathetic systems with loss of heart rate variability in depression, sympathoadrenal activation, hypothalamic-pituitary-adrenal axis activation resulting in hypercortisolemia, immune system dysregulation with release of pro-inflammatory cytokines and chemokines, platelet activation and hypercoagulability" (Halaris 2013). All of the above abnormalities have been demonstrated in people with major depressive disorder. A likely common factor in the comorbidity between cardiovascular pathology and depression is chronic stress, which results in "sustained sympathetic overdrive and diminished vagal tone. Diminished vagal tone contributes to a pro-inflammatory status which affects neurotransmitter regulation, specifically serotonergic transmission" (Halaris 2013). Chronic stress is particularly important in persons with PTSD, but is clearly also a major factor in all mental disorders,

particularly as a result of the stigma and discrimination and the daily humiliations experienced by people with mental disorders, long-term poverty even in rich countries, lack of access to safe housing and decent work, and the mental distress that is a central experience of mental disorders.

It has also been suggested that mental disorders such as depression may be directly related to increased arterial stiffness and abnormal endothelial function even when compared with blood pressure-matched controls and that a possible mechanism linking PTSD to arterial stiffness and cardiovascular disease is inflammation, which has been shown to promote both conditions, with evidence suggesting that PTSD may induce chronic low-level inflammation (Tomlinson and Cockcroft 2011).

There is continuing disagreement concerning the question of whether effective treatment of depression results in decreased risk of CVD and improved CVD outcomes (Fernandez-San-Martin et al. 2014; Gierisch et al. 2014). In particular, it has been suggested that effective treatment of depression may reduce CVD risks (Halaris 2013) by, for example, increasing HRV, thereby reducing mortality after acute myocardial infarction (Carney et al. 2005; Martens et al. 2008). A study of treatment of depression with cognitive behavioral therapy (CBT) demonstrated reduced heart rate and increased short-term HRV, suggesting that such treatment may reduce the risk of cardiac events and mortality in depressed patients with coronary heart disease (Carney et al. 2000).

Health Services

Immigrants, asylum seekers, and refugees face many obstacles in getting access to effective culturally appropriate primary care (Bellamy et al. 2015), mental health (Minas et al. 2013; Colucci et al. 2015), and general health services (Hollifield et al. 2002), even in countries with high levels of health resources and highly developed health systems. These problems are multiplied many times for the great majority of refugees who are living in refugee camps and other less than adequate settings in developing countries. Asylum seekers and refugees are also often not reached by and do not benefit from national and local health promotion campaigns, most commonly because of communication difficulties and also because the campaigns are designed for the dominant cultural group. Even when refugees do get access to health services, despite the high rates of mental disorders and CVD (Yun et al. 2012) and complex health service needs (Renzaho et al. 2011, 2014), refugees often receive suboptimal treatment (Tomlinson and Cockcroft 2011).

Because of this many authors have suggested that routine screening for depression among people with CVD would result in better detection, more appropriate assessment, and better CVD outcomes (Callaghan et al. 2009; Callaghan and Khizar 2010; Yun et al. 2012), and this has been supported by the American Heart Association. Despite the many calls for screening, several authors have expressed doubt about the value of routine screening for depression among people with CVD. Thombs et al. (2013) have concluded that, while there is evidence that

treatment of depression results in modest improvement in depressive symptoms in post-MI and stable CHD patients, there is still no evidence that routine screening for depression improves depression or cardiac outcomes. They add that American Heart Association Science Advisory (Bigger and Glassman 2010) on depression screening should be revised to reflect this lack of evidence (Rossi et al. 2012). While acknowledging that depression in patients with CVD is extremely common and is associated with increased risk of morbidity and mortality, Huffman et al. (2013) suggest that in patients who have had a myocardial infarct, routine assessment for depression is still only indicated if there is a clear pathway by which positive-screen patients can obtain formal assessment, initiation of treatment, and longitudinal care (Huffman et al. 2013). Whether successful treatment of depression is associated with a reduction in cardiac morbidity and mortality remains unknown (MacDuff et al. 2011).

Conclusions

Refugees are more likely than non-refugees to develop cardiovascular disease and have increased prevalence of anxiety and mood disorders and greatly increased prevalence of PTSD. It would appear that central elements of the refugee experience – anxiety and chronic stress – may constitute a direct risk for CVD and cardiovascular morbidity and premature mortality. It is probable, however, that the main pathway between refugee experience and CVD is through mental disorders. The American Heart Association has recognized depression as an independent risk factor for coronary artery disease, although the quality of evidence underlying this decision has been questioned.

In addition, there is accumulating evidence that both refugee status and the presence of mental disorder are associated with reduced likelihood of early detection of CVD and appropriate treatment, resulting in avoidable cardiovascular morbidity and mortality. It is not yet possible to draw confident conclusions about the value of alertness by clinicians and health services to the increased risk for CVD or of routine screening for CVD among refugees and when mental disorder is present. However, until equitable and effective mental health and general health services are available for refugees, particularly refugees with mental disorder, it would seem prudent to encourage such alertness and screening and to further evaluate whether this produces improved detection and reduced CVD morbidity and mortality.

Finally, refugee research presents many methodological and practical challenges. The quantity and the quality of refugee research, and the level of support for such research, are not consistent with the scale of the global refugee issue, the possibility that the number of refugees globally may continue to increase, and the population health and economic burden of unrecognized and ineffectively treated mental disorders and cardiovascular disease in refugees. This issue of health system inadequacy is particularly important in the context that the great majority of refugees live in countries with underdeveloped health systems and that many

refugee-receiving countries with the health system capacity to do better than is now the case are developing increasingly restrictive and sometimes punitive asylum seeker and refugee policies.

Asylum seeker and refugee research, and more effective health system responses to the needs of refugees, must become clearer priorities and more prominent components of global health and global mental health programs and of global disaster risk reduction programs.

References

Al Kasseh, A. S., Zaki, N. M., Aljeesh, Y. I., & Soon, L. K. (2014). Risk factors of gestational diabetes mellitus in the refugee population in Gaza strip: A case-control study. *Eastern Mediterranean Health Journal, 19*(Suppl 3), S12–S18.

Asgary, R., Emery, E., & Wong, M. (2013). Systematic review of prevention and management strategies for the consequences of gender-based violence in refugee settings. *International Health, 5*(2), 85–91.

Bellamy, K., Ostini, R., Martini, N., & Kairuz, T. (2015). Access to medication and pharmacy services for resettled refugees: A systematic review. *Australian Journal of Primary Health, 21*(3). doi:10.1071/PY14121.

Bigger, J. T. & Glassman, A. H. (2010). The American Heart Association science advisory on depression and coronary heart disease: an exploration of the issues raised. *Cleve Clin J Med, 77*(Suppl 3), S12–19.

Boscarino, J. A. (2006a). Posttraumatic stress disorder and mortality among U.S. Army veterans 30 years after military service. *Annals of Epidemiology, 16*(4), 248–256.

Boscarino, J. A. (2006b). External-cause mortality after psychologic trauma: The effects of stress exposure and predisposition. *Comprehensive Psychiatry, 47*(6), 503–514.

Bouzinova, E. V., Wiborg, O., Aalkjaer, C., & Matchkov, V. V. (2014). The role of peripheral vascular resistance for the association between major depression and cardiovascular disease. *Journal of Cardiovascular Pharmacology, 65*(4), 299–307.

Callaghan, R. C., & Khizar, A. (2010). The incidence of cardiovascular morbidity among patients with bipolar disorder: A population-based longitudinal study in Ontario, Canada. *Journal of Affective Disorders, 122*(1–2), 118–123.

Callaghan, R. C., Boire, M. D., Lazo, R. G., McKenzie, K., & Cohn, T. (2009). Schizophrenia and the incidence of cardiovascular morbidity: A population-based longitudinal study in Ontario, Canada. *Schizophrenia Research, 115*(2–3), 325–332.

Carney, R. M., Freedland, K. E., Stein, P. K., Skala, J. A., Hoffman, P., & Jaffe, A. S. (2000). Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. *Psychosomatic Medicine, 62*(5), 639–647.

Carney, R. M., Blumenthal, J. A., Stein, P. K., Watkins, L., Catellier, D., Berkman, L. F., Czajkowski, S. M., O'Connor, C., Stone, P. H., & Freedland, K. E. (2001). Depression, heart rate variability, and acute myocardial infarction. *Circulation, 104*(17), 2024–2028.

Carney, R. M., Blumenthal, J. A., Freedland, K. E., Stein, P. K., Howells, W. B., Berkman, L. F., Watkins, L. L., Czajkowski, S. M., Hayano, J., Domitrovich, P. P., & Jaffe, A. S. (2005). Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Archives of Internal Medicine, 165*(13), 1486–1491.

Clark, R. C., & Mytton, J. (2007). Estimating infectious disease in UK asylum seekers and refugees: A systematic review of prevalence studies. *Journal of Public Health (Oxford, England), 29*(4), 420–428.

Colucci, E., Minas, H., Szwarc, J., Guerra, C., & Paxton, G. (2015). In or out? Barriers and facilitators to refugee-background young people accessing mental health services. *Transcultural Psychiatry, 52*, 766–790.

Drummond, P. D., Mizan, A., Burgoyne, A., & Wright, B. (2011). Knowledge of cardiovascular risk factors in West African refugee women living in Western Australia. *Journal of Immigrant and Minority Health, 13*(1), 140–148.

Fernandez-San-Martin, M. I., Martin-Lopez, L. M., Masa-Font, R., Olona-Tabuena, N., Roman, Y., Martin-Royo, J., Oller-Canet, S., Gonzalez-Tejon, S., San-Emeterio, L., Barroso-Garcia, A., Vinas-Cabrera, L., & Flores-Mateo, G. (2014). The effectiveness of lifestyle interventions to reduce cardiovascular risk in patients with severe mental disorders: Meta-analysis of intervention studies. *Community Mental Health Journal, 50*(1), 81–95.

Gehi, A., Mangano, D., Pipkin, S., Browner, W. S., & Whooley, M. A. (2005). Depression and heart rate variability in patients with stable coronary heart disease: Findings from the heart and soul study. *Archives of General Psychiatry, 62*(6), 661–666.

Gierisch, J. M., Nieuwsma, J. A., Bradford, D. W., Wilder, C. M., Mann-Wrobel, M. C., McBroom, A. J., Hasselblad, V., & Williams, J. W., Jr. (2014). Pharmacologic and behavioral interventions to improve cardiovascular risk factors in adults with serious mental illness: A systematic review and meta-analysis. *The Journal of Clinical Psychiatry, 75*(5), e424–e440.

Halaris, A. (2013). Co-morbidity between cardiovascular pathology and depression: Role of inflammation. *Modern Trends in Pharmacopsychiatry, 28*, 144–161.

Healy, D., Le Noury, J., Harris, M., Butt, M., Linden, S., Whitaker, C., Zou, L., & Roberts, A. P. (2012). Mortality in schizophrenia and related psychoses: Data from two cohorts, 1875–1924 and 1994–2010. *BMJ Open, 2*(5), e001810.

Hollander, A. C. (2013). Social inequalities in mental health and mortality among refugees and other immigrants to Sweden – Epidemiological studies of register data. *Global Health Action, 6*, 21059.

Hollander, A. C., Bruce, D., Ekberg, J., Burstrom, B., Borrell, C., & Ekblad, S. (2012). Longitudinal study of mortality among refugees in Sweden. *International Journal of Epidemiology, 41*(4), 1153–1161.

Hollifield, M., Warner, T. D., Lian, N., Krakow, B., Jenkins, J. H., Kesler, J., Stevenson, J., & Westermeyer, J. (2002). Measuring trauma and health status in refugees: A critical review. *JAMA, 288*(5), 611–621.

Huffman, J. C., Celano, C. M., Beach, S. R., Motiwala, S. R., & Januzzi, J. L. (2013). Depression and cardiac disease: Epidemiology, mechanisms, and diagnosis. *Cardiovascular Psychiatry and Neurology, 2013*, 695925.

Kessler, R. C., Angermeyer, M., Anthony, J. C., De Graaf, R., Demyttenaere, K., Gasquet, I., de Girolamo, G., Gluzman, S., Gureje, O., Haro, J. M., Kawakami, N., Karam, A., Levinson, D., Medina Mora, M. E., Oakley Browne, M. A., Posada-Villa, J., Stein, D. J., Adley Tsang, C. H., Aguilar-Gaxiola, S., Alonso, J., Lee, S., Heeringa, S., Pennell, B. E., Berglund, P., Gruber, M. J., Petukhova, M., Chatterji, S., & Ustun, T. B. (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry, 6*(3), 168–176.

Lichtman, J. H., Froelicher, E. S., Blumenthal, J. A., Carney, R. M., Doering, L. V., Frasure-Smith, N., Freedland, K. E., Jaffe, A. S., Leifheit-Limson, E. C., Sheps, D. S., Vaccarino, V., Wulsin, L., American Heart Association Statistics Committee of the Council on Epidemiology and Prevention, & Council on Cardiovascular and Stroke Nursing. (2014). Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: Systematic review and recommendations: A scientific statement from the American Heart Association. *Circulation, 129*(12), 1350–1369.

Lindert, J., Ehrenstein, O. S., Priebe, S., Mielck, A., & Brahler, E. (2009). Depression and anxiety in labor migrants and refugees – A systematic review and meta-analysis. *Social Science & Medicine, 69*(2), 246–257.

MacDuff, S., Grodin, M. A., & Gardiner, P. (2011). The use of complementary and alternative medicine among refugees: A systematic review. *Journal of Immigrant and Minority Health, 13*(3), 585–599.

Martens, E. J., Nyklicek, I., Szabo, B. M., & Kupper, N. (2008). Depression and anxiety as predictors of heart rate variability after myocardial infarction. *Psychological Medicine, 38*(3), 375–383.

Minas, H., Kakuma, R., Too, L. S., Vayani, H., Orapeleng, S., Prasad-Ildes, R., Turner, G., Procter, N., & Oehm, D. (2013). Mental health research and evaluation in multicultural Australia: Developing a culture of inclusion. *International Journal of Mental Health Systems, 7*(1), 23.

Nielsen, T. J., Vestergaard, M., Christensen, B., Christensen, K. S., & Larsen, K. K. (2013). Mental health status and risk of new cardiovascular events or death in patients with myocardial infarction: A population-based cohort study. *British Medical Journal Open, 3*(8):e003045

Porter, M., & Haslam, N. (2005). Predisplacement and postdisplacement factors associated with mental health of refugees and internally displaced persons: A meta-analysis. *JAMA, 294*(5), 602–612.

Renzaho, A. M., Nowson, C., Kaur, A., Halliday, J. A., Fong, D., & Desilva, J. (2011). Prevalence of vitamin D insufficiency and risk factors for type 2 diabetes and cardiovascular disease among African migrant and refugee adults in Melbourne: A pilot study. *Asia Pacific Journal of Clinical Nutrition, 20*(3), 397–403.

Renzaho, A. M., Bilal, P., & Marks, G. C. (2014). Obesity, type 2 diabetes and high blood pressure amongst recently arrived Sudanese refugees in Queensland, Australia. *Journal of Immigrant and Minority Health, 16*(1), 86–94.

Ringen, P. A., Engh, J. A., Birkenaes, A. B., Dieset, I., & Andreassen, O. A. (2014). Increased mortality in schizophrenia due to cardiovascular disease – A non-systematic review of epidemiology, possible causes, and interventions. *Frontiers in Psychiatry, 5*, 137.

Robinson, R. G., Spalletta, G., Jorge, R. E., Bassi, A., Colivicchi, F., Ripa, A., & Caltagirone, C. (2008). Decreased heart rate variability is associated with poststroke depression. *The American Journal of Geriatric Psychiatry, 16*(11), 867–873.

Rossi, C., Shrier, I., Marshall, L., Cnossen, S., Schwartzman, K., Klein, M. B., Schwarzer, G., & Greenaway, C. (2012). Seroprevalence of chronic hepatitis B virus infection and prior immunity in immigrants and refugees: A systematic review and meta-analysis. *PloS One, 7*(9), e44611.

Steel, Z., C. Marnane, C. Iranpour, T. Chey, J. W. Jackson, V. Patel & D. Silove (2014). The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. *Int J Epidemiol, 43*(2), 476–493.

Steel, Z., Chey, T., Silove, D., Marnane, C., Bryant, R. A., & van Ommeren, M. (2009). Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement: A systematic review and meta-analysis. *JAMA, 302*(5), 537–549.

Stein, P. K., Carney, R. M., Freedland, K. E., Skala, J. A., Jaffe, A. S., Kleiger, R. E., & Rottman, J. N. (2000). Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *Journal of Psychosomatic Research, 48*(4–5), 493–500.

Sundquist, J., Cmelic-Eng, M., & Johansson, S. E. (1999). Body mass index and distribution of body fat in female Bosnian refugees – A study in primary health care. *Public Health, 113*(2), 89–93.

Sundquist, J., Hagstromer, M., Johansson, S. E., & Sundquist, K. (2010). Effect of a primary health-care-based controlled trial for cardiorespiratory fitness in refugee women. *BMC Family Practice, 11*, 55.

Thombs, B. D., M. Roseman, J. C. Coyne, P. de Jonge, V. C. Delisle, E. Arthurs, B. Levis & R. C. Ziegelstein (2013). Does evidence support the American Heart Association's recommendation to screen patients for depression in cardiovascular care? An updated systematic review. *PLoS One 8*(1):e52654.

Tomlinson, L. A., & Cockcroft, J. R. (2011). Post-traumatic stress disorder: Breaking hearts. *European Heart Journal, 32*(6), 668–669.

United Nations High Commissioner for Refugees. (2014). *War's human cost: UNHCR Global Trends 2013*. Geneva: United Nations High Commissioner for Refugees.

Vu, A., Adam, A., Wirtz, A., Pham, K., Rubenstein, L., Glass, N., Beyrer, C., & Singh, S. (2014). The prevalence of sexual violence among female refugees in complex humanitarian emergencies: A systematic review and meta-analysis. *PLOS Currents Disasters, 6* Edition 1. doi: 10.1371/currents.dis.835f10778fd80ae031aac12d3b533ca7

Willard, C. L., Rabin, M., & Lawless, M. (2014). The prevalence of torture and associated symptoms in United States Iraqi refugees. *Journal of Immigrant and Minority Health, 16*(6), 1069–1076.

Yun, K., Hebrank, K., Graber, L. K., Sullivan, M. C., Chen, I., & Gupta, J. (2012). High prevalence of chronic non-communicable conditions among adult refugees: Implications for practice and policy. *Journal of Community Health, 37*(5), 1110–1118.

Social Disadvantage and Cardiovascular Disease Risk

Steinar Krokstad, Erik R. Sund, Linda Ernstsen, and Jostein Holmen

Contents

S. Krokstad (✉) • E.R. Sund • J. Holmen
Department of Public Health and General Practice, HUNT Research Centre, Norwegian University of Science and Technology, Levanger, Norway
e-mail: steinar.krokstad@ntnu.no; erik.r.sund@ntnu.no; jostein.holmen@ntnu.no

L. Ernstsen
Faculty of Health and Social Sciences, Department of Nursing Sciences, Norwegian University of Science and Technology, Trondheim, Norway
e-mail: linda.ernstsen@ntnu.no

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_35

Abstract

In western societies there is a persistent social patterning of cardiovascular disease (CVD) risk. Social disadvantaged (SD) people are at greater risk of CVD than people in more advantageous positions. Both individual and contextual risk factors are of importance. Several models have been put forward to understand the relationship between social disadvantage and CVD risk. The concept psychosocial reflects psychological processes that are linked to the social environment and directs attention to both behavioral and endogenous biological responses to human interactions. The physical and social environment shapes health behaviors as health behaviors are observed socially patterned. Today, one must expect that clinicians are aware of the fact that SD increases CVD risk and thus manage to think beyond traditional individual-based CVD risk assessment.

Keywords

Disadvantage • Cardiovascular diseases • Risk factors • Socioeconomic status

Social Disadvantage, CVD Morbidity, and Mortality

Introduction

In western societies there is a persistent social patterning of cardiovascular disease (CVD) risk (Diez Roux 2005). *Social disadvantaged* (SD) people are at greater risk of CVD than people in more advantageous positions. These disparities are found across multiple social categories like: gender, ethnicity, marital status, and socioeconomic position (SEP), but in this chapter, the focus is on the latter.

Whether SEP is defined according to income, occupation, or education, the relationship is consistent, and the nature is graded whereby each step-up of the socioeconomic ladder reduces the propensity for cardiovascular morbidity (Kaplan and Keil 1993) and mortality (Mackenbach et al. 2000). Socioeconomic gradients in CVD are preventable, avoidable, and unjust – and the potential to improve population health by narrowing such gradients is large.

The occurrence of CVDs mirrors a society's stage of economic development, and during the earliest stages of the epidemic CVD was a disease of affluence (Kawachi and Marmot 1998). As death rates from coronary heart disease (CHD) started to decline in the mid-1960s, the burden of disease gradually shifted to those at the lower end of the socioeconomic hierarchy. Partly as a consequence, SEP gradients in CVD mortality vary between countries. In some countries they seem to be widening, whereas in others they seem to be narrowing depending on whether these measures of inequality are judged on an absolute or relative scale (Mackenbach et al. 2014).

Socioeconomic Position: Disadvantaged Individuals and Disadvantaged Places

Societies are stratified in a number of ways which lead to varying degrees of advantages and disadvantages (Galobardes et al. 2006). These systems of social stratification, whether they are economic, political, social, or cultural, constitute important mechanisms through which societal resources and goods are distributed to different groups in the population. Socioeconomic position can be used as a generic term referring to those social and economic factors that influence which position individuals will hold within the same social structure.

Commonly used measures of socioeconomic position in western societies are some form of occupational status ranking, level of education, or income level, and they each cover a different aspect of social stratification (Chandola and Marmot 2010). Income may be considered a resource-based measure, whereas an occupational status ranking may be more prestige based. In general these proxies for SEP are utilized as indicators for some form of disadvantage for individuals or families.

Place of residence, whether it is the local neighborhood or a larger geographical area, may also be considered rankable according to some marker of SEP. There is a large literature on deprived places and regions, especially from the UK, and there has been a renewed interest in the study of additional health effects from contextual features associated with place of residence (Bingenheimer and Raudenbush 2004; Diez Roux 2000; Subramanian et al. 2003). *Place deprivation* constitutes such a feature and refers to poor access to locationally specific goods and services, areas with pollution, noise, poverty, and high rates of crime. In contrast, *people deprivation* means that individuals in a specific location are deprived by virtue of the class-based position they occupy in the broader socioeconomic system. These individuals may live in a certain part of a city as a result of their low income and the workings of the housing market, but their income is not low because of where they live. Place deprivation thus refers to a contextual feature associated with a certain place, while people deprivation is a compositional feature (Smith 1977).

CVD epidemiology has been considered the paradigm of risk factor epidemiology with its focus on individual-level behavioral and biological risk factors (Diez Roux 2003). More recent research has also added contextual features associated with place of residence to their explanatory framework – and thus highlighting multilevel influences on individual CVD risk (Diez Roux et al. 2001).

Measurement of Health Inequalities: Relative and Absolute Measures

There has been considerable debate in health inequality research surrounding what measures should be utilized to present health differences between social groups. There is consensus on the importance of choice of measure, but less consensus on which measure – absolute or relative – should be reported and interpreted (Houweling et al. 2007). The controversy applies in particular in cross-country

comparisons and monitoring and can be summarized as follows: In a situation where the overall level of the outcome falls through time, increasing relative inequalities (e.g., rate ratio) are nearly inevitable. Conversely, utilizing absolute measures of inequality in the same situation (e.g., rate difference) will most likely lead to the conclusion that inequalities are getting smaller. Based on considerations of ethical, conceptual, and pragmatic issues, it is generally recommended that both absolute and relative measures should be reported in scientific papers (Harper and Lynch 2006). The measurement of health inequalities is by no means a value-neutral process (Harper et al. 2010).

Socioeconomic Gradients in CVD Risk Factors

There is substantial evidence for an association between SEP and CVD morbidity (Kaplan and Keil 1993) and mortality (Mackenbach et al. 2000). Similarly, there are numerous studies demonstrating associations between SEP and risk factors for CVD like: body mass index, cholesterol, systolic blood pressure, smoking, and diabetes (Ernstsen et al. 2012; Strand and Tverdal 2006). In general, many behavioral and modifiable risk factors for CVD have a clear SEP gradient (Pampel et al. 2010). While there is considerable disagreement in terms of the importance of behavior for SEP inequalities in morbidity and mortality (Strand and Tverdal 2004), there is a clear potential for improved population health by the elimination or reduction of CVD risk factors. Trends in SEP inequalities for many classical CVD risk factors are equivocal and are also dependent on country (Stringhini et al. 2011) as well as methodological issues (Lynch et al. 2006; Singh-Manoux et al. 2008).

How To Understand the Relationship Between Social Disadvantage and CVD Risk

Social Disadvantage and Social Position

Social disadvantage may be defined as being subjected to racial or ethnic prejudice or cultural bias because of identity as members of a group. However, relevant literature shows that there is a gradient in health throughout the population, depending on people's social position (Marmot 2004). It is important to underline that SD refers to a gradient and not to a dichotomy between poor versus nonpoor and that different social positions possess different degrees of social disadvantage.

Social disadvantage must however arise from circumstances beyond personal control. But very few are in such a privileged position that they can freely choose education, occupation, or income. In practice, then, a person's social position is a result of social structures and coincidences, but the consequences for health are apparent – at mean group level.

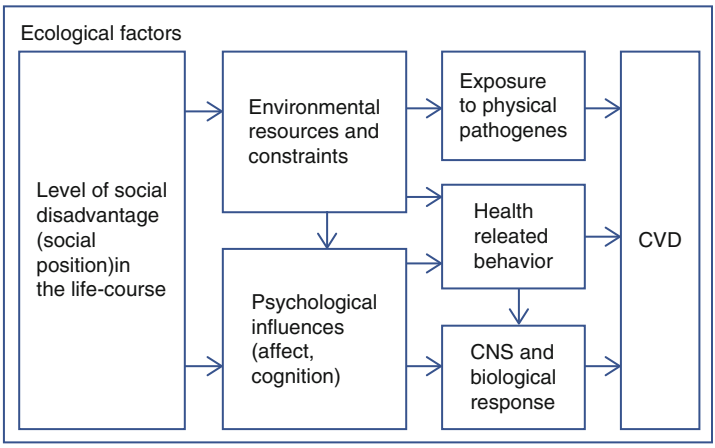


Fig. 1 A model to understand the relationship between social disadvantage and CVD risk (Krieger 2001; Adler and Ostrove 1999)

The terms inequity and inequality are closely related in origin and in some of their secondary definitions, but there are distinct differences between them. Inequality refers primarily to the condition of being unequal, and it tends to relate to things that can be expressed in numbers. Inequity, in its main sense, is a close synonym of injustice and unfairness, so it usually relates to more qualitative matters (Whitehead 1992). As this chapter is about social disadvantage, differences in CVD risk by SD are largely interpreted in terms of inequity.

The majority of diseases accumulate to a larger extent in groups with a low SEP. However, some risk conditions and diseases show less distinct or opposite patterns (Clegg et al. 2009). This may have implications for the hypotheses that evolve in terms of disease causation. The larger the inequalities in health by social position, the more likely it is that diseases can be caused by socioeconomic disadvantages.

How Can Social Disadvantage Influence Risk Factors for CVD?

Adler and Ostrove suggested a model to explain how SEP can influence risk factor levels and health integrated in Fig. 1 (Adler and Ostrove 1999). SEP is important to health not only for those in poverty but at all levels of SEP below the top level. On average, the more disadvantaged individuals are, the worse their health. The threshold model, i.e., the idea that only the most SD or poor people suffer or have worse health than all the other, was challenged forcefully by the Whitehall study (Marmot et al. 1978). In virtually all socioepidemiological studies, a gradient pattern emerges. However, reversed causation might cause some health inequalities, most likely for diseases with early onset with profound effects on life trajectories (e.g., schizophrenia). But here is overwhelming evidence that increasing SD contributes to health differences.

One pathway from low SEP or SD to increased risk factor levels is through exposure to different environments and adaptations to these environments. One aspect of environments is differential exposure to physical pathogens, like tobacco smoke polluted air. More important are probably the social and interpersonal factors in the environments, particularly exposure to threats and stress in both the work and the private environment. With increasing SD, decreasing levels of control and decreasing degree of emotional and instrumental support will be experienced, and exposure to conflict and threats increase.

The social and physical environments people experience, different levels of demands and supports, shape patterns of psychological responses. Individuals that experience SD are more likely to develop a sense of helplessness, low self-esteem, hostility, and distrust than others.

The physical and social environment also shapes health behaviors. Health behaviors are clearly socially patterned, and this might be caused by fewer opportunities for exercise and less access to nutritious foods. The combination of individual characteristics, formed by the social background and the environmental factors, will affect the likelihood of enacting health-related behaviors such as tobacco use, alcohol use, exercise, and dietary practice.

Ecosocial Theory

These suggested causal pathways are of course oversimplified. The pathways by which SD can influence CVD risk factors are likely to be influenced by feedback loops and interaction effects. Mechanisms on all levels, from societal to subcellular level, may be involved (Fig. 1). Ecosocial and other multilevel epidemiologic frameworks seek to integrate social and biological factors and a dynamic, historical, and ecological perspective to develop new insights into why SD influences health (Krieger 2001).

Neo-material Theory

In research, only selected aspects or pathways may be explored in observational studies. The neo-material interpretation argues that SD affects health through differential accumulation of exposures and experiences originating in the material world. It is a combination of negative exposures and lack of resources held by socially deprived individuals, along with systematic underinvestment across a wide range of human, physical, health, and social infrastructure where socially deprived people live (Lynch et al. 2000).

Psychosocial Explanation

But if the neo-material alone explained the relationship between SD and CVD risk, giving every family enough money to have enough food and a house, deal with air pollution, and provide a physically safe environment should solve the problem. But this is obviously insufficient. The psychosocial effects of relative deprivation involving control over life, insecurity, anxiety, social isolation, socially

problematic environments, bullying, and depression still remain. Evidence shows that these factors influence health and that their prevalence is affected by the socioeconomic structure and by people's degree of SD (Marmot and Wilkinson 2001).

One relevant theory of how social disadvantage may affect CVD risk is about learned helplessness. The effects may be mediated by psychobiological mechanisms related to stress physiology. The stress response occurs whenever an individual is faced with a challenge, and a period of recovery is necessary to rebalance and to manage new demands. Individuals with SD have more environmental challenges and less psychosocial resources. This may lead to negative outcomes, loss of coping ability, strain, hopelessness, and chronic stress and influence both health-related behavior and CNS, endocrine, immune, and cardiovascular systems (Kristenson et al. 2004).

Health-Related Behavior

An individualistic paradigm has influenced thinking and practice regarding management of health lifestyles in several disciplines, but this approach neglects the structural dimensions and has limited applicability to understand the challenge. A tendency to focus on individual behavioral patterns that affect CVD is observed, thereby neglecting the collective (structural) characteristics. However, all theories of social life suggest that something (structure) exists beyond the individual to give rise to habits and patterns of behavior. People are linked together through social relationships, such as family ties, work, religion, and politics. Their shared norms, values, ideals, and social perspectives constitute intersubjective communities where behavior varies systematically (Cockerham 2005).

Life-Course Perspective

It may be hard to understand how relatively small socioeconomic differences in modern societies affect risk factor levels and health as observed in the socioeconomic gradients (Marmot et al. 1978). However, the life-course perspective refers to how risk factors and health status at any given age, for a given birth cohort or an individual, reflect not only contemporary conditions but are embodiments of prior living circumstances, in utero onward (Corna 2013). In such a perspective, when the accumulation of the effects of SD over time is taken into account, understanding of the health effects may be easier.

The Fundamental Cause

Link and Phelan developed a theory of fundamental causes to explain the relationship between SD and mortality. SD may influence an array of resources negatively, such as knowledge, prestige, power, money, and social connections. All these factors may be associated with CVD risk no matter what mechanisms are relevant at any given time (Phelan et al. 2010).

Social Disadvantage, Psychosocial Factors, and Health-Related Behavior

Social Disadvantage, Psychosocial Exposure, and CVD Risk

While social factors include general factors at the societal and structural level that affect individuals, psychological factors include individual-level processes that influence mental state and emotions. The concept psychosocial reflects psychological processes that are linked to the social environment and directs attention to both behavioral and endogenous biological responses to human interactions (Stansfeld and Marmot 2002). The health-damaging potential of psychological stress is generated by the imbalance between exposure to adverse conditions (daily hassles, acute or chronic stress) and psychosocial resources (social support, personality factors, coping strategies, resilience) (Hjemdahl et al. 2012). Beside the physiological responses on psychological stress, individuals may use certain behaviors (e.g., smoking, drinking, overeating) to cope with stress and reduce unpleasant arousal.

In the INTERHEART study, a standardized case–control study of acute myocardial infarction (including 29,972 participants from Asia, Europe, the Middle East, Africa, Australia, North America, and South America), psychosocial stress was assessed by questions about stress at work and at home, financial stress, major life events in the past year, and feelings of depression. The psychosocial factors increased the odds of first myocardial infarction by approximately threefold and accounted for 33 % of the population-attributable risk for the development of myocardial infarction (Yusuf et al. 2004). A large body of research supports that emotional factors such as anxiety, depression, psychosocial work characteristics, and low social support are independently involved in the etiology and prognosis of coronary heart disease (Kuper et al. 2002; Van der Kooy et al. 2007). Several studies also support that workplace-related stress, defined by high demands and low control and/or by effort-reward imbalance, elicits sustained stress reactions with negative long-term consequences for cardiovascular health (Siegrist and Marmot 2004).

Empirical evidence indicates that socioeconomic position is adversely associated with psychosocial factors linked to CVD risk (Gallo and Matthews 2003; Skodova et al. 2008). In the literature, the leading candidate psychosocial pathways connecting social disparities and CVD risk are through stress and emotions (Gallo and Matthews 2003). A number of studies have also shown a dose–response relation between social position and depression (Andersen et al. 2009; Lorant et al. 2003; Melchior et al. 2013).

If psychosocial factors represent a causal pathway between social disparities and health, studies should evaluate and support mediation, but several studies find that psychosocial factors such as anxiety and depression do not mediate the association between social position and CVD risk (Kittleson et al. 2006; Thurston et al. 2006).

In a recent progress report on psychosocial mediators of SEP-health associations, Matthews et al. (2010) conclude that the evidence is insufficient to draw strong conclusion about the hypothesized pathway and that the limited existing

literature has produced mixed findings (Matthews et al. 2010). Opposite to the mediator (causal) pathway, psychosocial factors may moderate the association between social position and CVD which means that the effects of any psychosocial variable are dependent (increase or decrease) upon social position. A recent prospective study of 6,070 men free from previous history of CHD and stroke at baseline found that the effect from job strain on risk of coronary heart disease is higher in blue-collar workers compared to white-collar workers (Torén et al. 2014). The results are in line with another recent prospective study of 66,500 participants free of CVD and cancer at baseline, which suggested that the harmful effect of psychological distress (measured by the 12-item General Health Questionnaire) on mortality from coronary heart disease and stroke is significantly higher in lower occupational grades (Lazzarino et al. 2013).

Social Disadvantage and Health Behavior

The vast majority of observational studies on social disparities conclude that even if health-related behaviors do not explain all social difference, it makes an important contribution to the social gradient in cardiovascular morbidity and mortality (Beauchamp et al. 2010), especially smoking (Jha et al. 2006; Mackenbach 2011) and physical inactivity (Ernstsen et al. 2010). Different measures of social disparities (education, income, occupation, gender, poverty) represent different theoretical bases. For example, in studies that define social position as occupational position, health-related behavior often contributes less to inequalities in CVD than studies using education or prestige-based measures. The main explanation for this is that behavior to a great extent reflects "exposure" through culture and norms that are established in relatively early in life (Marmot and Bartely 2002). Recent results from several different data sets from the USA and the UK suggest that income, health insurance, and family background explain about 30 % of the educational gradient in health behaviors, while knowledge and cognitive ability account for an additional 30 %. Social networks account for 10 % of the gradient, while self-esteem, sense of control, stress, depression, and anxiety do not appear to mediate the association between education and health behavior (Cutler and Lleras-Muney 2010).

A growing body of literature investigates associations between neighborhood social environments and coronary heart disease. It is *hypothesized* that neighborhood social interactions affect a wide set of affective, cognitive, and relational experiences which in turn influence the cognitive-emotional antecedents of behavior which is the end shape health behavior (Chaix 2009). In a recent study on CVD risk factors, the authors found that Black Americans in the US Virgin Islands had better cardiovascular health profiles and healthier lifestyles than their counterparts residing in 50 US states, despite having lower education, and that CVD differences were largely unchanged after accounting for health behaviors or social position (Lee et al. 2013). The authors suggest that there may be contextual factors, both social and physical, that influence these differences in health behaviors and CVD

outcomes among Black people living in different continents. Health behavior also differs between ethnic groups. In a systematic review of racial/ethnic disparities in CVD risk factors, the authors found that Mexican Americans had a significantly lower prevalence of smoking than Whites and Blacks and that American Indians/Alaskan Natives (AIANs) had significantly higher prevalence of smoking compared to Whites. Mexican Americans had the highest prevalence of no leisure-time physical activity, followed by AIANs and Blacks (Kurian and Cardarelli 2007). Despite the fact that health behaviors are strongly associated with CVD mortality, their contribution to socioeconomic differences in mortality differs by their social patterning. This was recently illustrated in a prospective study where the contribution of health behaviors in explaining the social gradient in mortality by SEP was assessed in the British Whitehall II study and the French GAZEL study. The association between socioeconomic factors and mortality and that between health behaviors and mortality were similar in both cohorts, but behaviors attenuated the association of social position with mortality by 75 % in the Whitehall II study and only 19 % in the GAZEL study (Stringhini et al. 2011). The authors propose three explanations for their findings. Firstly, they suggest that smoking, eating, and drinking habits are more linked to cultural norms in Southern European regions compared to the Northern European regions. Secondly, the social distribution of unhealthy behavior may represent the epidemiologic transition from behaviors of "affluence" to behaviors of "the poor," especially smoking, and that this transition is at different stages in the two countries. Thirdly, country-specific factors such as welfare policies, bans on smoking, and taxes are likely to influence behavior.

Based on a recent review of broad literatures in sociology, economics, and public health, Pampel et al. (2010) classified explanations of higher smoking, lower exercise, poorer diet, and excess weight among low-SEP persons into nine broad groups (including deprivation, inequality, and stress) that specify related but conceptually distinct mechanisms. The authors (Pampel et al. 2010) found no clear support for any one explanation and concluded that the literature on social disparities in health and health behaviors should do more to design studies that better test for the importance of the varied mechanisms involved.

Social Disadvantage and Clinical Risk Factors

Traditional Clinical CVD Risk Assessment

According to recommendations (Mancia et al. 2013), CVD risk assessment should include blood pressure, heart rate, lipids (total cholesterol, LDL (Low Density Lipoprotein), HDL (High Density Lipoprotein), triglycerides), BMI (Body Mass Index), waist/hip circumferences, glucose, creatinine, MA (microalbuminuria), and CRP (C-reactive protein) in addition to information about food habits, smoking, alcohol use, physical activity, and family history. A growing body of literature has demonstrated that the CVD risk profile is generally unfavorable in people in low-SEP groups compared to people in high-SEP groups. This occurs in all

industrialized countries and involves all relevant CVD risk factors (Al-Qaoud et al. 2011; Franks et al. 2011; Jenkins and Ofstedal 2014; Schumann et al. 2011; Subramanyam et al. 2013; Tamayo et al. 2012).

High-Risk Strategy and Population Strategy (Strategies of CVD Prevention)

The prevailing practice in most countries is the high-risk strategy, i.e., identifying high-risk individuals, assessing the risk by clinical examinations and laboratory tests, and initiating treatment accordingly. The treatment is often lifestyle intervention in combination with drug treatment, like antihypertensive drugs and statins. Such treatment should be continued for years, probably for rest of the life.

However, not only the CVD risk profile but also the healthcare is often unfavorable to the low-SEP groups. "The inverse care law," stated by Hart in 1971 (Hart 1971), still seems to operate (Grintsova et al. 2014), resulting in increased gap between SEP groups (Eggen et al. 2014). Rose addressed this issue already in 1985, arguing for a population strategy in preventive health work (Rose 2001), and this debate is still ongoing. In 2006 Manuel and coauthors revisited Rose (Manuel et al. 2006), arguing that "population health strategies that target the majority of the population (people at low coronary heart disease risk) have little effect on population outcomes because the population risk is low in this group" and concluding that "medicine has developed analytical tools, such as the Framingham risk algorithms which use multiple factors to better characterize baseline risk of health outcomes. The result is a much improved effectiveness and efficiency of drug treatment for improving coronary heart disease." This is a controversial area, and Manuel et al. were criticized for having greatly underestimated the effect of population strategies by including patient with established CVD, inflating the numbers in the "high-risk" group, assuming that effectiveness in routine clinical practice equaled efficacy in RCTs (randomized controlled trials) and ignoring undertreatment and poor long-term adherence. Secondly, they systematically underestimated the contribution of population strategies (Capewell and Graham 2010). According to Capewell and Graham, there is increasing evidence that inequalities in risk factors can widen when effects are mediated through individual-level changes in knowledge, motivation, and behavior. High-risk intervention, which requires mobilization of an individual's resources, whether material or psychological, generally favors those with more resources, thus leading to increased social inequalities. Disadvantage can occur at every stage of the process, from the person's beliefs about health and disease, and actual health behavior, to presentation, screening, risk assessment, negotiation, participation, program persistence, and treatment adherence (Capewell and Graham 2010). Consequently, it is referred to substantial socioeconomic gradients in statins use, both in the UK and in Denmark. Likewise, inequalities in antihypertensive therapy have been reported. Long-term adherence (compliance) with primary prevention medications barely reaches 50 %, and is

often worse in deprived groups. Furthermore, inequalities in adherence have been specifically reported for both statins and antihypertensive medications. The authors suggest that combining population-based and high-risk approaches might be more effective and refer to a Swedish study practicing a combined strategy, where the predicted CVD mortality risk was reduced by 36 % in the intervention area compared to 1 % in a control community. Socioeconomically less privileged group benefited more from the program (Weinehall et al. 2001).

Kones (2011) recognizes that "even though the original belief that prevention was cost-ineffective has now been disproven, at least for cardiovascular applications, there has been disappointing progress in effecting successful population-based primordial prevention. For truly effective improvements in cardiovascular risk, primordial prevention appears necessary as an adjunct to the high-risk strategy traditionally offered to individual patients." "Given the lack of success and resistance to primordial prevention, population-wide pharmacological reduction of risk, previously rejected because of expense and potential side effects, is being reevaluated as a cost-effective maneuver. If one restricts evidence-based cardiovascular risk reduction to statins, the question reduces to what segments of the population will be eligible for how much of what statin or polypill" (Kones 2011). His answer is therefore more use of statins.

Population-Wide Reductions in Dietary Salt

Instead of recommending intensifying pharmacological treatment, Bibbins-Domingo and coauthors analyzed the effect (in the USA) of population-wide reductions in dietary salt up to three grams per day (Bibbins-Domingo et al. 2010). The result predicted reduction of the annual number of new cases of CHD by 60,000–120,000, stroke by 32,000–66,000, and myocardial infarction by 54,000–99,000 and to reduce the annual number of deaths from any cause by 44,000–92,000. All segments of the population would benefit, with Blacks benefiting proportionately more, women benefiting particularly from stroke reduction, older adult from reductions in CHD events, and younger adults from lower mortality rates. The cardiovascular benefits of reduced salt intake are on par with the benefits of population-wide reduction in tobacco use, obesity, and cholesterol levels. Such an intervention would be cost saving even if only a modest reduction of 1 gram per day was achieved gradually between 2010 and 2019 and would be more cost-effective than using medications to lower blood pressure in all persons with hypertension (Bibbins-Domingo et al. 2010).

As Blacks generally have a higher CVD risk profile, have a higher prevalence of CVD, and are less privileged than Whites in the US community, this is a good example of a population-based intervention with potential of decreasing the gap between the SEP groups. However, population-based interventions are hard to achieve and require strong political will and concerted cross-sectorial efforts both at local, regional, and national level.

Clinical Implications

Today, one should expect that clinicians are aware of the association between SD and CVD risk and thus manage to think beyond traditional individual-based CVD risk assessment that include blood pressure, heart rate, lipids, BMI, waist/hip circumferences, glucose, creatinine, MA, and CRP in addition to information about food habits, smoking, alcohol use, physical activity, and family history. The SEP of the patient must be taken into account. In the health services, it is important to be aware of the inverse care law and the tendency to provide the best services for those who need it least and thus have a reduced cost-effectiveness. Finally, it is important to be aware of the health services' limitations in terms of reducing CVD in the population because it only uses individual-based high-risk strategies. Healthcare workers should contribute to the understanding of the potential of population-based prevention strategies in society, to both reduce social inequalities in CVD risk and reduce CVD risk in total population.

Conclusion

In western societies there is a persistent social patterning of CVD risk (Diez Roux 2005). Social disadvantaged people are at greater risk of CVD than people in more advantageous positions. Social disadvantage may be defined as being subjected to racial or ethnic prejudice or cultural bias because of identity as members of a group. However, it is not only the most vulnerable groups that have poorer health than others. Different social positions possess different degrees of social disadvantage. Relevant literature shows that there is a gradient in CVD risk throughout the population, depending on people's SP (Marmot 2004). The health services have serious limitations in terms of reducing CVD and SEP inequities in CVD in the population. In addition to individual-based high-risk preventive strategies applied in clinics, population-based prevention strategies are necessary (Rose 2001).

References

Adler, N. E., & Ostrove, J. M. (1999). Socioeconomic status and health: What we know and what we don't. *Annals of the New York Academy of Sciences, 896*, 3–15.

Al-Qaoud, T. M., et al. (2011). Socioeconomic status and reduced kidney function in the Whitehall II study: Role of obesity and metabolic syndrome. *American Journal of Kidney Diseases, 58*, 389–397.

Andersen, I., Thielen, K., Nygaard, E., & Diderichsen, F. (2009). Social inequality in the prevalence of depressive disorders. *Journal of Epidemiology and Community Health, 63*, 575–581.

Beauchamp, A., Peeters, A., Wolfe, R., Turrell, G., Harriss, L. R., Giles, G. G. et al. (2010). Inequalities in cardiovascular disease mortality: The role of behavioural, physiological and social risk factors. *Journal of Epidemiology and Community Health, 64*, 542–548.

Bibbins-Domingo, K., et al. (2010). Projected effect of dietary salt reductions on future cardiovascular disease. *New England Journal of Medicine, 362*, 590–599.

Bingenheimer, J. B., & Raudenbush, S. W. (2004). Statistical and substantive inferences in public health: Issues in the application of multilevel models. *Annual Review of Public Health, 25*, 53–77.

Capewell, S., & Graham, H. (2010). Will cardiovascular disease prevention widen health inequalities? *PLoS Medicine, 7*(8):e1000320

Chaix, B. (2009). Geographic life environments and coronary heart disease: A literature review, theoretical contributions, methodological updates, and a research agenda. *Annual Review of Public Health, 30*, 81–105.

Chandola, T., & Marmot, M. G. (2010). Socio-economic position and health. In A. Steptoe (Ed.), *Handbook of behavioral medicine*. New York: Springer.

Clegg, L. X., Reichman, M. E., Miller, B. A., Hankey, B. F., Singh, G. K., Lin, Y. D., et al. (2009). Impact of socioeconomic status on cancer incidence and stage at diagnosis: Selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. *Cancer Causes and Control, 20*, 417–435.

Cockerham, W. C. (2005). Health lifestyle theory and the convergence of agency and structure. *Journal of Health and Social Behavior, 46*, 51–67.

Corna, L. M. (2013). A life course perspective on socioeconomic inequalities in health: A critical review of conceptual frameworks. *Advances in Life Course Research, 18*, 150–159.

Cutler, D. M., & Lleras-Muney, A. (2010). Understanding differences in health behaviors by education. *Journal of Health Economics, 29*, 1–28.

Diez Roux, A. V. (2000). Multilevel analysis in public health research. *Annual Review of Public Health, 21*, 171–192.

Diez Roux, A. V. (2003). Residential environments and cardiovascular risk. *Journal of Urban Health, 80*, 569–589.

Diez Roux, A. V. (2005). Persistent social patterning of cardiovascular risk: Rethinking the familiar. *Circulation, 111*, 3020–3021.

Diez Roux, A. V., Merkin, S. S., Arnett, D., Chambless, L., Massing, M., Nieto, F. J., et al. (2001). Neighborhood of residence and incidence of coronary heart disease. *New England Journal of Medicine, 345*, 99–106.

Eggen, A. E., Mathiesen, E. B., Wilsgaard, T., Jacobsen, B. K., & Njølstad, I. (2014). Trends in cardiovascular risk factors across levels of education in a general population: Is the educational gap increasing? The Tromsø study 1994–2008. *Journal of Epidemiology & Community Health, 68*, 712–719.

Ernstsen, L., Bjerkeset, O., & Krokstad, S. (2010). Educational inequalities in ischaemic heart disease mortality in 44,000 Norwegian women and men: The influence of psychosocial and behavioural factors. The HUNT Study. *Scandinavian Journal of Public Health, 38*, 678–685.

Ernstsen, L., Strand, B. H., Nilsen, S. M., Espnes, G. A., & Krokstad, S. (2012). Trends in absolute and relative educational inequalities in four modifiable ischaemic heart disease risk factors: Repeated cross-sectional surveys from the Nord-Trondelag Health Study (HUNT) 1984–2008. *BMC Public Health, 12*, 266.

Franks, P., Winters, P. C., Tancredi, D. J., & Fiscella, K. A. (2011). Do changes in traditional coronary heart disease risk factors over time explain the association between socio-economic status and coronary heart disease? *BMC Cardiovascular Disorders, 11*, 28.

Gallo, L. C., & Matthews, K. A. (2003). Understanding the association between socioeconomic status and physical health: Do negative emotions play a role? *Psychological Bulletin, 129*, 10–51.

Galobardes, B., Shaw, M., Lawlor, D. A., Smith, G. D., & Lynch, J. (2006). Indicators of socioeconomic position. In J. M. Oakes & J. S. Kaufman (Eds.), *Methods in social epidemiology*. San Francisco: Jossey-Bass.

Grintsova, O., Maier, W., & Mielck, A. (2014). Inequalities in health care among patients with type 2 diabetes by individual socio-economic status (SES) and regional deprivation: A systematic literature review. *International Journal for Equity in Health, 13*, 43.

Harper, S., & Lynch, J. W. (2006). Measuring health inequalities. In J. M. Oakes & J. S. Kaufman (Eds.), *Methods in social epidemiology*. San Francisco: Jossey-Bass.

Harper, S., King, N. B., Meersman, S. C., Reichman, M. E., Breen, N., & Lynch, J. W. (2010). Implicit value judgements in the measurement of health inequalities. *The Milbank Quarterly, 88*, 4–29.

Hart, J. T. (1971). The inverse care law. *Lancet, 297*, 405–412.

Hjemdahl, P., Steptoe, A., & Rosengren, A. (2012). Introduction to cardiovascular disease, stress and adaption. In P. Hjemdal, A. Steptoe, & A. Rosengren (Eds.), *Stress and cardiovascular disease*. London: Springer London.

Houweling, T. A., Kunst, A. E., Huisman, M., & Mackenbach, J. P. (2007). Using relative and absolute measures for monitoring health inequalities: Experiences from cross-national analyses on maternal and child health. *International Journal for Equity in Health, 6*, 15.

Jenkins, K. R., & Ofstedal, M. B. (2014). The association between socioeconomic status and cardiovascular risk factors among middle-aged and older men and women. *Women and Health, 54*, 15–34.

Jha, P., Peto, R., Zatonski, W., Boreham, J., Jarvis, M. J., & Lopez, A. D. (2006). Social inequalities in male mortality, and in male mortality from smoking: Indirect estimation from national death rates in England and Wales, Poland, and North America. *Lancet, 368*, 367–370.

Kaplan, G. A., & Keil, J. E. (1993). Socioeconomic factors and cardiovascular disease: A review of the literature. *Circulation, 88*, 1973–1998.

Kawachi, I., & Marmot, M. G. (1998). Commentary: What can we learn from studies of occupational class and cardiovascular disease? *American Journal of Epidemiology, 148*, 160–163.

Kittleson, M. M., Meoni, L. A., Wang, N., Chu, A. Y., Ford, D. E., & Klag, M. J. (2006). Association of childhood socioeconomic status with subsequent coronary heart disease in physicians. *Archives of Internal Medicine, 166*, 2356–2361.

Kones, R. (2011). Primary prevention of coronary heart disease: Integration of new data, evolving views, revised goals, and role of rosuvastatin in management. A comprehensive survey. *Drug Design, Development and Therapy, 5*, 325–380.

Krieger, N. (2001). Theories for social epidemiology in the 21st century: An ecosocial perspective. *International Journal of Epidemiology, 30*, 668–677.

Kristenson, M., Eriksen, H. R., Sluiter, J. K., Starke, D., & Ursin, H. (2004). Psychobiological mechanisms of socioeconomic differences in health. *Social Science and Medicine, 58*, 1511–1522.

Kuper, H. H., Marmot, M. M., & Hemingway, H. H. (2002). Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. *Seminars in Vascular Medicine, 2*, 267–314.

Kurian, A. K., & Cardarelli, K. M. (2007). Racial and ethnic differences in cardiovascular disease risk factors: A systematic review. *Ethnicity and Disease, 17*, 143–152.

Lazzarino, A. I., Hamer, M., Stamatakis, E., & Steptoe, A. (2013). Low socioeconomic status and psychological distress as synergistic predictors of mortality from stroke and coronary heart disease. *Psychosomatic Medicine, 75*, 311–316.

Lee, H., Kershaw, K. N., Hicken, M. T., Abdou, C. M., Williams, E. S., Rivera-O'Reilly, N., & Jackson, J. S. (2013). Cardiovascular disease among Black Americans: Comparisons between the U.S. Virgin Islands and the 50 U.S. States. *Public Health Reports, 128*, 170–178.

Lorant, V., Deliege, D., Eaton, W., Robert, A., Philippot, P., & Ansseau, M. (2003). Socioeconomic inequalities in depression: A meta-analysis. *American Journal of Epidemiology, 157*, 98–112.

Lynch, J. W., Davey Smith, G., Kaplan, G. A., & House, J. S. (2000). Income inequality and mortality: Importance to health of individual income, psychosocial environment, or material conditions. *BMJ, 320*, 1200–1204.

Lynch, J., Davey Smith, G., Harper, S., & Bainbridge, K. (2006). Explaining the social gradient in coronary heart disease: Comparing relative and absolute risk approaches. *Journal of Epidemiology & Community Health, 60*, 436–441.

Mackenbach, J. P. (2011). What would happen to health inequalities if smoking were eliminated? *BMJ, 342*, d3460.

Mackenbach, J. P., Cavelaars, A. E., Kunst, A. E., & Groenhof, F. (2000). Socioeconomic inequalities in cardiovascular disease mortality; an international study. *European Heart Journal, 21*, 1141–1151.

Mackenbach, J. P., Kulhanova, I., Menvielle, G., Bopp, M., Borrell, C., Costa, G., et al. (2014). Trends in inequalities in premature mortality: A study of 3.2 million deaths in 13 European countries. *Journal of Epidemiology & Community Health*. doi:10.1136/jech-2014-204450.

Mancia, G., et al. (2013). ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Journal of Hypertension, 31*, 1281–1357.

Manuel, D. G., Lim, J., Tanuseputro, P., Anderson, G. M., Alter, D. A., Laupacis, A., & Mustard, C. A. (2006). Revisiting Rose: Strategies for reducing coronary heart disease. *BMJ, 332*, 659–662.

Marmot, M. (2004). *Status syndrome. How your social standing directly affects your health and life expectancy*. London: Bloomsbury.

Marmot, M., & Bartely, M. (2002). Social class and coronary heart disease. In S. Stansfeld & M. Marmot (Eds.), *Stress and the heart: Psychosocial pathways to coronary heart disease*. London: BMJ Books.

Marmot, M., & Wilkinson, R. G. (2001). Psychosocial and material pathways in the relation between income and health: A response to Lynch et al. *BMJ, 322*, 1233–1236.

Marmot, M., Rose, G., Shipley, M. J., & Hamilton, P. J. S. (1978). Employment grade and coronary heart disease in British civil servants. *Journal of Epidemiology & Community Health, 32*, 244–249.

Matthews, K. A., Gallo, L. C., & Taylor, S. E. (2010). Are psychosocial factors mediators of socioeconomic status and health connections? A progress report and blueprint for the future. *Annals of the New York Academy of Sciences, 1186*, 146–173.

Melchior, M., Chastang, J. F., Head, J., Goldberg, M., Zins, M., Nabi, H., & Younes, N. (2013). Socioeconomic position predicts long-term depression trajectory: A 13-year follow-up of the GAZEL cohort study. *Molecular Psychiatry, 18*, 112–121.

Pampel, F. C., Krueger, P. M., & Denney, J. T. (2010). Socioeconomic disparities in health behaviors. *Annual Review of Sociology, 36*, 349–370.

Phelan, J. C., Link, B. G., & Tehranifar, P. (2010). Social conditions as fundamental causes of health inequalities: Theory, evidence, and policy implications. *Journal of Health and Social Behavior, 51*(Suppl), S28–S40.

Rose, G. (2001). Sick individuals and sick populations. *Bulletin of the World Health Organization, 79*, 990–996.

Schumann, B., Kluttig, A., Tiller, D., Werdan, K., Haerting, J., & Greiser, K. H. (2011). Association of childhood and adult socioeconomic indicators with cardiovascular risk factors and its modification by age: The CARLA study 2002–2006. *BMC Public Health, 11*, 289.

Siegrist, J., & Marmot, M. (2004). Health inequalities and the psychosocial environment – Two scientific challenges. *Social Science & Medicine, 58*, 1463–1473.

Singh-Manoux, A., Nabi, H., Shipley, M., Gueguen, A., Sabia, S., Dugravot, A., et al. (2008). The role of conventional risk factors in explaining social inequalities in coronary heart disease: The relative and absolute approaches to risk. *Epidemiology, 19*, 599–605.

Skodova, Z., Nagyova, I., van Dijk, J., Sudzinova, A., Vargova, H., Studencan, M., & Reijneveld, S. (2008). Socioeconomic differences in psychosocial factors contributing to coronary heart disease: A review. *Journal of Clinical Psychology in Medical Settings, 15*, 204–213.

Smith, D. (1977). *Human geography: A welfare approach*. London: Edward Arnold.

Stansfeld, S. A., & Marmot, M. (2002). 1: Introduction. In S. A. Stansfeld & M. Marmot (Eds.), *Stress and the heart: Psychosocial pathways to coronary heart disease*. London: BMJ Books.

Strand, B. H., & Tverdal, A. (2004). Can cardiovascular risk factors and lifestyle explain the educational inequalities in mortality from ischaemic heart disease and from other heart diseases? 26 year follow up of 50,000 Norwegian men and women. *Journal of Epidemiology & Community Health, 58*, 705–709.

Strand, B. H., & Tverdal, A. (2006). Trends in educational inequalities in cardiovascular risk factors: A longitudinal study among 48,000 middle-aged Norwegian men and women. *European Journal of Epidemiology, 21*, 731–739.

Stringhini, S., Dugravot, A., Shipley, M., Goldberg, M., Zins, M., Kivimaki, M., et al. (2011). Health behaviours, socioeconomic status, and mortality: Further analyses of the British Whitehall II and the French GAZEL prospective cohorts. *PLoS Medicine, 8*, e1000419.

Subramanian, S. V., Jones, K., & Duncan, C. (2003). Multilevel methods for public health research. In I. Kawachi & L. F. Berkman (Eds.), *Neighborhoods and health*. Oxford: Oxford University Press.

Subramanyam, M. A., James, S. A., Diez-Roux, A. V., Hickson, D.A., Sarpong, D., Sims, M., et al. (2013). Socioeconomic status, John Henryism and blood pressure among African-Americans in the Jackson Heart Study. *Social Science and Medicine, 93*, 139–146.

Tamayo, T., Jacobs, D. R. Jr, Strassburger, K., Giani, G., Seeman, T. E., Matthews, K., et al. (2012). Race- and sex-specific associations of parental education with insulin resistance in middle-aged participants: The CARDIA study. *European Journal of Epidemiology, 27*, 349–355.

Thurston, R. C., Kubzansky, L. D., Kawachi, I., & Berkman, L. F. (2006). Do depression and anxiety mediate the link between educational attainment and CHD? *Psychosomatic Medicine, 68*, 25–32.

Torén, K., Schiöler, L., Giang, W. K., Novak, M., Söderberg, M., & Rosengren, A. (2014). A longitudinal general population-based study of job strain and risk for coronary heart disease and stroke in Swedish men. *BMJ Open, 4*(3):e004355.

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. *International Journal of Geriatric Psychiatry, 22*, 613–626.

Weinehall, L., Hellsten, G., Boman, K., Hallmans, G., Asplund, K., & Wall, S. (2001). Can a sustainable community intervention reduce the health gap? 10-year evaluation of a Swedish community intervention program for the prevention of cardiovascular disease. *Scand J Public Health Suppl, 56*, 59–68.

Whitehead, M. (1992). The concepts and principles of equity and health. *International Journal of Health Services, 22*, 429–445.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., & Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*, 937–952.

Part IV

Psychology and Cardiovascular Biology: The Linking Mechanisms

Role of the Sympathetic Nervous System in Cardiovascular Disease

Gavin Wiliam Lambert and Murray Esler

Contents

G.W. Lambert (✉)
Human Neurotransmitters Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Faculty of Medicine, Nursing Health Sciences, Monash University, Melbourne, VIC, Australia
e-mail: gavin.lambert@bakeridi.edu.au

M. Esler
Human Neurotransmitters Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia
e-mail: murray.esler@bakeridi.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_36

Abstract

The sympathetic nervous system is pivotal in both circulatory and metabolic control. While acute activation of the sympathetic nervous system is important during regular daily activities in order to maintain homeostasis or in times of stress in order to initiate a fight or flight response, chronic activation of the sympathetic nervous system is associated with disease development and end-organ dysfunction. Of particular importance is the role of the sympathetic nervous system in the initiation and maintenance of hypertension and the development of left ventricular hypertrophy, diastolic dysfunction, and insulin resistance. Given the undoubted role of the sympathetic nervous system in generating cardio-metabolic illness, inhibition of the sympathetic nervous system seems a logical choice in order to alleviate disease burden associated with these conditions. Lifestyle changes involving diet, exercise, and cognitive-based therapies as well as pharmacological and device-based interventions directly targeting the sympathetic nervous system are likely to be of benefit.

Keywords

Autonomic nervous system • Stress • Metabolic syndrome • Depression • Hypertension • Noradrenaline • Insulin resistance • Obesity

Introduction

The role of the sympathetic nervous system in cardiovascular control is well recognized. Indeed, with the advent of beta-blocker therapy being associated with improved survival in patients with heart failure and the development and implementation of radiofrequency ablation of the renal sympathetic nerves for the treatment of resistant hypertension, the sympathetic nervous system has remained at center stage in cardiovascular medicine. What is perhaps less readily appreciated is that the sympathetic nervous system also exerts substantial effects on metabolism and hence may be an important player in the pathology underpinning the growing burden of obesity-related illness. While sympathetic nervous activation is of course desirable in stressful situations as part of the fight or flight response, sustained and unfettered sympathetic activation can result in adverse cardiovascular and metabolic consequences. Importantly, with common comorbid conditions, the degree of sympathetic nervous activation is often further augmented, accelerating end dysfunction. Sympathetic nervous activation is an important determinant of survival in patients with chronic heart failure (Kaye et al. 1995; Petersson et al. 2005) or renal disease (Zoccali et al. 2002) and may underpin the elevated cardiac risk in patients with depression (Barton et al. 2007) or be linked with the metabolic consequences of obesity. An understanding of the mechanisms involved in sympathetic regulation may pave the way for the development of novel treatment strategies in a variety of clinically important conditions.

Mechanisms of Sympathetic Nervous Activation

Central Determinants and Reflex Control

A number of brain regions, including the ventromedial and rostral ventrolateral medulla, caudal raphe nuclei, A5 noradrenergic cell group, and paraventricular nucleus of the hypothalamus, have been shown to influence sympathetic preganglionic outflow at all thoracolumbar levels (Guyenet 2006). Efferent sympathetic nervous activity is influenced by, among other things, changes in blood pressure, temperature, and circulating glucose levels. Pressure-sensitive sympathetic nerves are influenced directly by the arterial baroreflex and are responsible for short- and long-term blood pressure control. The activity of these sympathetic nerves is regulated largely, but not exclusively, by the neurons of the nucleus of the solitary tract, rostroventrolateral medulla, and hypothalamus. While limbic, cortical, and midbrain regions are generally responsible for changes in sympathetic activity that relate to behavior, it is important to appreciate that hemodynamic and behavioral pathways/responses are not mutually exclusive. For instance, cardiopulmonary volume receptor afferents do project to the noradrenergic nuclei of the locus coeruleus, and the firing rate of locus coeruleus neurons is changed by alterations in cardiopulmonary pressures (Elam et al. 1984, 1985). Functionally, the locus coeruleus and its hypothalamic and amygdala projections are also closely linked with behavioral responses involving autonomic activation (Foote et al. 1983).

Insulin

While the peripheral action of insulin is fundamental in maintaining appropriate control of glucose via direct effects on the liver to reduce glycogenolysis (Sindelar et al. 1998) and through indirect effects, including inhibition of lipolysis and reduction in glucagon, insulin also exerts a central effect and influences hypothalamic signaling. Obici et al. demonstrated that the targeted reduction of insulin receptors in the medial area of the arcuate nucleus is associated with hyperphagia, increased fat mass, and the development of hepatic insulin resistance (Obici et al. 2002a). Stimulation of hypothalamic insulin signaling results in an approximately 40 % inhibition of glucose production (Obici et al. 2002b). The central effect of insulin is likely mediated, at least in part, via inhibition of neuropeptide Y (NPY) neurons in the arcuate nucleus of the hypothalamus (Porte et al. 2005; van den Hoek et al. 2004). Studies in mice have demonstrated that intracerebroventricular infusion of NPY leads to the development of insulin resistance of endogenous glucose production via activation of sympathetic drive to the liver (van den Hoek et al. 2008). In humans, hyperinsulinemia is associated with elevation of the muscle sympathetic outflow (Gudbjornsdottir et al. 1996; Vollenweider et al. 1994), with the response being blunted in obese subjects (Vollenweider et al. 1994).

Obesity and Increased Body Fat

There is now a substantial body of evidence that sympathetic nervous activity is elevated in obese individuals. Indeed, fat is a major determinant of the degree of activation of muscle sympathetic nerve activity (Randin et al. 1994), with visceral fat in the abdomen being the prime adipose tissue depot linking obesity with increased sympathetic drive (Alvarez et al. 2002). Factors produced by and secreted from fat such as non-esterified fatty acids (NEFAs) and leptin may influence sympathetic activation. Antigens derived from perivascular fat surrounding the aorta may promote the infiltration of leukocytes and T cells into the aorta, kidney, and CNS and lead to sympathetic activation and hypertension development (Guzik et al. 2007; Harrison et al. 2011; Vinh et al. 2010; Zubcevic et al. 2011). Adding further support for some interaction between circulating lipids and sympathetic regulation, studies in both humans and animals have shown that the use of statins to lower cholesterol is associated with a reduction in sympathetic nervous outflow (Gomes et al. 2010; Pliquett et al. 2003).

Obstructive Sleep Apnea

The repetitive bouts of hypoxia that occur during sleep in patients with obstructive sleep apnea are associated with a pronounced increase in muscle sympathetic nerve activity (Somers et al. 1995), most likely as a result of stimulation of peripheral chemoreceptors (Narkiewicz et al. 1999b) coupled with an impairment of the arterial baroreflex (Parati et al. 1997). Treatment of OSA with continuous positive airway pressure reduces sympathetic activity (Hedner et al. 1995; Narkiewicz et al. 1999a) and is associated with an improvement in insulin sensitivity, blood pressure, and plasma lipids in patients with OSA and the metabolic syndrome (Dorkova et al. 2008; Harsch et al. 2004).

Stress and Hypothalamic-Pituitary-Adrenal Axis Activation

Mental stress is associated with increased sympathetic nervous activity and activation of both the adrenomedullary and adrenocortical systems. In fact, laboratory mental stress is associated with a specific activation of the cardiac sympathetic outflow (Esler et al. 1989). Glucocorticoid levels are elevated in response to stress and have been associated with the development of hyperinsulinemia, insulin resistance, glucose intolerance, increased blood lipids and visceral fat (Bjorntorp 1995), and hypertension (Esler et al. 2008). Longitudinal data from the Whitehall II study shows that both the HPA axis and the sympathetic nervous system are activated in subjects with the metabolic syndrome, with psychosocial factors being associated with the increased normetanephrine levels observed in these subjects (Brunner et al. 2002). Moreover, work-related stress has been demonstrated to be related to metabolic syndrome development (Brunner et al. 2007).

Depression

Approximately one third of patients with major depressive disorder have substantially elevated sympathetic nervous activity (Barton et al. 2007). Depression has also been associated with activation of the HPA axis (Gold and Chrousos 2002) and increased inflammatory cytokine production (Alesci et al. 2005). Data from the longitudinal Health, Aging, and Body Composition Study demonstrated that the presence of depressive symptoms on entry to the study was associated with a subsequent increase in abdominal obesity (Vogelzangs et al. 2008). Recent investigations have shown an association between depression and the metabolic syndrome (McCaffery et al. 2003; Skilton et al. 2007), with the number of components of the metabolic syndrome being increased in proportion to the degree of depression. Previous reports have also demonstrated an association between depression and insulin resistance, one of the hallmarks of metabolic syndrome development (Timonen et al. 2007). The use of serotonin specific reuptake inhibitors is associated with a reduction in sympathetic activity in some patients with depression (Barton et al. 2007) and improves glucose control in men with abdominal obesity (Ljung et al. 2001).

Consequences of Sympathetic Nervous Activation

Hypertension

The sympathetic nervous system is pivotal in the initiation and maintenance of high blood pressure. Activation of the sympathetic outflows to the heart, kidneys, and skeletal muscle is evident in lean patients with hypertension. Hypertension frequently occurs in subjects with hyperinsulinemia, insulin resistance, and elevated lipids (Ford et al. 2002). This pattern is consistent with the observation that around 70 % of the risk for the development of hypertension is linked to overweight and obesity (Garrison et al. 1987; Must et al. 1999). Importantly, sympathetic nervous activation, as has been shown in the longitudinal studies of Timio and colleagues (Timio et al. 1997, 1988), is associated with elevated blood pressure and increased all-cause and cardiovascular-related mortality. While the effect of hypertension on cardiovascular disease, stroke, and kidney disease development is readily acknowledged, evidence supporting a link between uncontrolled high blood pressure, particularly in mid-life, and subsequent cognitive decline and dementia development has emerged. Examination of the association between cognitive function and blood pressure in subjects aged less than 70 at enrollment (range 35–70) indicated significantly lower cognitive performance, or a more rapid decline of cognitive function, in those with higher blood pressure (Staessen et al. 2007). Although data from randomized clinical trials detailing the possible protective effect of blood pressure control in alleviating the progression of dementia is perhaps equivocal (Skoog et al. 1996), a number of observational studies have reported that antihypertensive drug treatment is

associated with a lower risk of cognitive decline, with the degree of improvement being proportional to the duration of therapy and the degree of blood pressure control (Peila et al. 2006).

Cardiac Structure and Function

Activation of the cardiac sympathetic outflow is associated with the development of diastolic dysfunction (Fici et al. 2012) and left ventricular hypertrophy (Schlaich et al. 2003), not only in patients with established hypertension but also in young overweight or obese individuals with mildly elevated blood pressure (Lambert et al. 2010). The cardiac sympathetic nerves are preferentially stimulated in severe heart failure (Hasking et al. 1986). Interestingly, the degree of both cardiac (Kaye et al. 1995) and renal (Petersson et al. 2005) sympathetic activity in patients with heart failure has been demonstrated to be a major determinant of prognosis, with those patients, with the highest cardiac or renal sympathetic activity having greatly reduced survival. The importance of renal sympathetic drive in this context perhaps reflects the activation of renal afferent nerves by the diseased kidney, with renal afferent stimulation of the hypothalamus leading to activation of the sympathetic nervous system (Hausberg et al. 2002).

Renal Damage

Regional sympathetic activation, with evidence of increased sympathetic nervous outflow to the kidneys (Esler et al. 2006; Rumantir et al. 1999), is evident in both lean and obese individuals and in patients with hypertension. The persistent neurohumoral activation and increased blood pressure leads to the prolongation of glomerular hyperfiltration and metabolic changes that may initiate further renal injury. In subjects with the metabolic syndrome, in whom sympathetic nervous activation is evident, an increased prevalence of microalbuminuria (Palaniappan et al. 2003) and diminished renal function (Chen et al. 2004; Shinohara et al. 2002) has been described. The presence of proteinuria and the progressive development of renal dysfunction in obese individuals may occur even in the absence of hypertension and diabetes (Henegar et al. 2001; Morales et al. 2003).

Hyperglycemia

Electrical stimulation of nerves innervating the liver leads to an increase in activity of liver glycogen phosphorylase and glucose-6-phospahatase activities in the rabbit (Shimazu 1967; Shimazu and Fukuda 1965) and a rapid elevation in blood glucose levels in man (Jarhult et al. 1979) and dog (Edwards and Silver 1972). Indicative of the possible CNS pathways involved in this process, stimulation of the hypothalamus leads to an increase in noradrenaline overflow (Takahashi et al. 1997) and

glucose production (Shimazu and Ogasawara 1975; Takahashi et al. 1997) by the liver. Previous studies in dogs indicated that the hepatic sympathetic nerves inhibit liver glucose uptake and that hepatic sympathetic denervation is associated with an increase in net hepatic glucose uptake in response to hyperglycemia (Dicostanzo et al. 2006). Impaired glucose tolerance and insulin resistance are often found in patients with liver cirrhosis (Petrides and DeFronzo 1989; Proietto et al. 1980). Following liver transplantation, these metabolic impairments are improved (Merli et al. 1999).

Insulin Resistance

The possible involvement of the sympathetic nervous system in the development of insulin resistance is complicated. Hyperinsulinemia may drive an increase in sympathetic nervous activity through stimulation of the hypothalamus or via a reflex response to insulin's vasodilation; alternatively, sympathetic vasoconstriction may antagonize insulin's effect on glucose uptake via an influence on skeletal muscle blood flow (Jamerson et al. 1993; Laakso et al. 1990). Data derived from prospective trials with between 10- and 18-year follow-up has shown that sympathetic activation precede the subsequent increase in body weight and development of insulin resistance (Flaa et al. 2008; Masuo et al. 1997, 2003).

Conclusion

A large body of evidence emphasizes the importance of the sympathetic nervous system in the development and progression of cardiovascular and cardio-metabolic disease. Inhibition of the sympathetic nervous system should be considered as part of the therapeutic approach to combat these conditions. Lifestyle changes involving diet, exercise, and cognitive-based therapies as well as pharmacological and device-based interventions directly targeting the sympathetic nervous system are likely to be of benefit.

References

Alesci, S., Martinez, P. E., Kelkar, S., Ilias, I., Ronsaville, D. S., Listwak, S. J., Ayala, A. R., Licinio, J., Gold, H. K., Kling, M. A., Chrousos, G. P., & Gold, P. W. (2005). Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: Clinical implications. *Journal of Clinical Endocrinology and Metabolism, 90*(5), 2522–2530. doi:10.1210/jc.2004-1667.

Alvarez, G. E., Beske, S. D., Ballard, T. P., & Davy, K. P. (2002). Sympathetic neural activation in visceral obesity. *Circulation, 106*(20), 2533–2536.

Barton, D. A., Dawood, T., Lambert, E. A., Esler, M. D., Haikerwal, D., Brenchley, C., Socratous, F., Kaye, D. M., Schlaich, M. P., Hickie, I., & Lambert, G. W. (2007). Sympathetic activity in

major depressive disorder: Identifying those at increased cardiac risk? *Journal of Hypertension, 25*(10), 2117–2124. doi:10.1097/HJH.0b013e32829baae7.

Bjorntorp, P. (1995). Endocrine abnormalities of obesity. *Metabolism, 44*(9 Suppl 3), 21–23.

Brunner, E. J., Chandola, T., & Marmot, M. G. (2007). Prospective effect of job strain on general and central obesity in the Whitehall II study. *American Journal of Epidemiology, 165*(7), 828–837. doi:10.1093/aje/kwk058.

Brunner, E. J., Hemingway, H., Walker, B. R., Page, M., Clarke, P., Juneja, M., Shipley, M. J., Kumari, M., Andrew, R., Seckl, J. R., Papadopoulos, A., Checkley, S., Rumley, A., Lowe, G. D., Stansfeld, S. A., & Marmot, M. G. (2002). Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: Nested case-control study. *Circulation, 106*(21), 2659–2665.

Chen, J., Muntner, P., Hamm, L. L., Jones, D. W., Batuman, V., Fonseca, V., Whelton, P. K., & He, J. (2004). The metabolic syndrome and chronic kidney disease in U.S. adults. *Annals of Internal Medicine, 140*(3), 167–174. doi: 140/3/167 [pii].

Dicostanzo, C. A., Dardevet, D. P., Neal, D. W., Lautz, M., Allen, E., Snead, W., & Cherrington, A. D. (2006). Role of the hepatic sympathetic nerves in the regulation of net hepatic glucose uptake and the mediation of the portal glucose signal. *American Journal of Physiology Endocrinology and Metabolism, 290*(1), E9–E16. doi:10.1152/ajpendo.00184.2005.

Dorkova, Z., Petrasova, D., Molcanyiova, A., Popovnakova, M., & Tkacova, R. (2008). Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. *Chest, 134*(4), 686–692. doi:10.1378/chest.08-0556.

Edwards, A. V., & Silver, M. (1972). Comparison of the hyperglycaemic and glycogenolytic responses to catecholamines with those to stimulation of the hepatic sympathetic innervation in the dog. *Journal of Physiology, 223*(2), 571–593.

Elam, M., Svensson, T. H., & Thoren, P. (1985). Differentiated cardiovascular afferent regulation of locus coeruleus neurons and sympathetic nerves. *Brain Research, 358*(1–2), 77–84.

Elam, M., Yao, T., Svensson, T. H., & Thoren, P. (1984). Regulation of locus coeruleus neurons and splanchnic, sympathetic nerves by cardiovascular afferents. *Brain Research, 290*(2), 281–287.

Esler, M., Eikelis, N., Schlaich, M., Lambert, G., Alvarenga, M., Kaye, D., El-Osta, A., Guo, L., Barton, D., Pier, C., Brenchley, C., Dawood, T., Jennings, G., & Lambert, E. (2008). Human sympathetic nerve biology: Parallel influences of stress and epigenetics in essential hypertension and panic disorder. *Annals of the New York Academy of Sciences, 1148*, 338–348. doi:10.1196/annals.1410.064.

Esler, M., Jennings, G., & Lambert, G. (1989). Measurement of overall and cardiac norepinephrine release into plasma during cognitive challenge. *Psychoneuroendocrinology, 14*(6), 477–481.

Esler, M., Straznicky, N., Eikelis, N., Masuo, K., Lambert, G., & Lambert, E. (2006). Mechanisms of sympathetic activation in obesity-related hypertension. *Hypertension, 48*(5), 787–796.

Fici, F., Ural, D., Tayfun, S., Kozdag, G., Facchetti, R., Brambilla, G., Dell'oro, R., Grassi, G., & Mancia, G. (2012). Left ventricular diastolic dysfunction in newly diagnosed untreated hypertensive patients. *Blood Pressure, 21*(6), 331–337. doi:10.3109/08037051.2012.686179.

Flaa, A., Aksnes, T. A., Kjeldsen, S. E., Eide, I., & Rostrup, M. (2008). Increased sympathetic reactivity may predict insulin resistance: An 18-year follow-up study. *Metabolism, 57*(10), 1422–1427. doi:10.1016/j.metabol.2008.05.012.

Foote, S. L., Bloom, F. E., & Aston-Jones, G. (1983). Nucleus locus ceruleus: New evidence of anatomical and physiological specificity. *Physiological Reviews, 63*(3), 844–914.

Ford, E. S., Giles, W. H., & Dietz, W. H. (2002). Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. *JAMA, 287*(3), 356–359.

Garrison, R. J., Kannel, W. B., Stokes, J., 3rd, & Castelli, W. P. (1987). Incidence and precursors of hypertension in young adults: The Framingham offspring study. *Preventive Medicine, 16*(2), 235–251. doi: 0091-7435(87)90087-9 [pii].

Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. *Molecular Psychiatry, 7*(3), 254–275. doi:10.1038/sj.mp.4001032.

Gomes, M. E., Lenders, J. W., Bellersen, L., Verheugt, F. W., Smits, P., & Tack, C. J. (2010). Sympathoinhibitory effect of statins in chronic heart failure. *Clinical Autonomic Research, 20* (2), 73–78. doi:10.1007/s10286-009-0041-2.

Gudbjornsdottir, S., Elam, M., Sellgren, J., & Anderson, E. A. (1996). Insulin increases forearm vascular resistance in obese, insulin-resistant hypertensives. *Journal of Hypertension, 14*(1), 91–97.

Guyenet, P. G. (2006). The sympathetic control of blood pressure. *Nature Review Neuroscience, 7* (5), 335–346. doi:10.1038/nrn1902.

Guzik, T. J., Hoch, N. E., Brown, K. A., McCann, L. A., Rahman, A., Dikalov, S., Goronzy, J., Weyand, C., & Harrison, D. G. (2007). Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *Journal of Experimental Medicine, 204*(10), 2449–2460. doi:10.1084/jem.20070657.

Harrison, D. G., Guzik, T. J., Lob, H. E., Madhur, M. S., Marvar, P. J., Thabet, S. R., Vinh, A., & Weyand, C. M. (2011). Inflammation, immunity, and hypertension. *Hypertension, 57*(2), 132–140. doi:10.1161/HYPERTENSIONAHA.110.163576.

Harsch, I. A., Schahin, S. P., Radespiel-Troger, M., Weintz, O., Jahreiss, H., Fuchs, F. S., Wiest, G. H., Hahn, E. G., Lohmann, T., Konturek, P. C., & Ficker, J. H. (2004). Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine, 169*(2), 156–162. doi:10.1164/rccm.200302-206OC.

Hasking, G. J., Esler, M. D., Jennings, G. L., Burton, D., Johns, J. A., & Korner, P. I. (1986). Norepinephrine spillover to plasma in patients with congestive heart failure: Evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation, 73*(4), 615–621.

Hausberg, M., Kosch, M., Harmelink, P., Barenbrock, M., Hohage, H., Kisters, K., Dietl, K. H., & Rahn, K. H. (2002). Sympathetic nerve activity in end-stage renal disease. *Circulation, 106* (15), 1974–1979.

Hedner, J., Darpo, B., Ejnell, H., Carlson, J., & Caidahl, K. (1995). Reduction in sympathetic activity after long-term CPAP treatment in sleep apnoea: Cardiovascular implications. *European Respiratory Journal, 8*(2), 222–229.

Henegar, J. R., Bigler, S. A., Henegar, L. K., Tyagi, S. C., & Hall, J. E. (2001). Functional and structural changes in the kidney in the early stages of obesity. *Journal of the American Society of Nephrology, 12*(6), 1211–1217.

Jamerson, K. A., Julius, S., Gudbrandsson, T., Andersson, O., & Brant, D. O. (1993). Reflex sympathetic activation induces acute insulin resistance in the human forearm. *Hypertension, 21* (5), 618–623.

Jarhult, J., Falck, B., Ingemansson, S., & Nobin, A. (1979). The functional importance of sympathetic nerves to the liver and endocrine pancreas. *Annals of Surgery, 189*(1), 96–100.

Kaye, D. M., Lefkovits, J., Jennings, G. L., Bergin, P., Broughton, A., & Esler, M. D. (1995). Adverse consequences of high sympathetic nervous activity in the failing human heart. *Journal of the American College of Cardiology, 26*(5), 1257–1263. doi:10.1016/0735-1097(95)00332-0.

Laakso, M., Edelman, S. V., Brechtel, G., & Baron, A. D. (1990). Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man. A novel mechanism for insulin resistance. *Journal of Clinical Investigation, 85*(6), 1844–1852. doi:10.1172/JCI114644.

Lambert, E., Sari, C. I., Dawood, T., Nguyen, J., McGrane, M., Eikelis, N., Chopra, R., Wong, C., Chatzivlastou, K., Head, G., Straznicky, N., Esler, M., Schlaich, M., & Lambert, G. (2010). Sympathetic nervous system activity is associated with obesity-induced subclinical organ damage in young adults. *Hypertension, 56*(3), 351–358. doi:10.1161/HYPERTENSIONAHA.110.155663.

Ljung, T., Ahlberg, A. C., Holm, G., Friberg, P., Andersson, B., Eriksson, E., & Bjorntorp, P. (2001). Treatment of abdominally obese men with a serotonin reuptake inhibitor: A pilot study. *Journal of Internal Medicine, 250*(3), 219–224.

Masuo, K., Kawaguchi, H., Mikami, H., Ogihara, T., & Tuck, M. L. (2003). Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. *Hypertension, 42*(4), 474–480. doi:10.1161/01.HYP.0000091371.53502.D3.

Masuo, K., Mikami, H., Ogihara, T., & Tuck, M. L. (1997). Sympathetic nerve hyperactivity precedes hyperinsulinemia and blood pressure elevation in a young, nonobese Japanese population. *American Journal of Hypertension, 10*(1), 77–83.

McCaffery, J. M., Niaura, R., Todaro, J. F., Swan, G. E., & Carmelli, D. (2003). Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute twin study. *Psychosomatic Medicine, 65*(3), 490–497.

Merli, M., Leonetti, F., Riggio, O., Valeriano, V., Ribaudo, M. C., Strati, F., Tisone, G., Casciani, C. U., & Capocaccia, L. (1999). Glucose intolerance and insulin resistance in cirrhosis are normalized after liver transplantation. *Hepatology, 30*(3), 649–654. doi:10.1002/hep.510300306.

Morales, E., Valero, M. A., Leon, M., Hernandez, E., & Praga, M. (2003). Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *American Journal of Kidney Diseases, 41*(2), 319–327. doi:10.1053/ajkd.2003.50039. S0272638602691413 [pii].

Must, A., Spadano, J., Coakley, E. H., Field, A. E., Colditz, G., & Dietz, W. H. (1999). The disease burden associated with overweight and obesity. *JAMA, 282*(16), 1523–1529. doi: joc81719 [pii].

Narkiewicz, K., Kato, M., Phillips, B. G., Pesek, C. A., Davison, D. E., & Somers, V. K. (1999a). Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation, 100*(23), 2332–2335.

Narkiewicz, K., van de Borne, P. J., Pesek, C. A., Dyken, M. E., Montano, N., & Somers, V. K. (1999b). Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. *Circulation, 99*(9), 1183–1189.

Obici, S., Feng, Z., Karkanias, G., Baskin, D. G., & Rossetti, L. (2002a). Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. *Nature Neuroscience, 5*(6), 566–572. doi:10.1038/nn861. nn861 [pii].

Obici, S., Zhang, B. B., Karkanias, G., & Rossetti, L. (2002b). Hypothalamic insulin signaling is required for inhibition of glucose production. *Nature Medicine, 8*(12), 1376–1382. doi:10.1038/nm798. nm798 [pii].

Palaniappan, L., Carnethon, M., & Fortmann, S. P. (2003). Association between microalbuminuria and the metabolic syndrome: NHANES III. *American Journal of Hypertension, 16*(11 Pt 1), 952–958. doi: S0895706103010094 [pii].

Parati, G., Di Rienzo, M., Bonsignore, M. R., Insalaco, G., Marrone, O., Castiglioni, P., Bonsignore, G., & Mancia, G. (1997). Autonomic cardiac regulation in obstructive sleep apnea syndrome: Evidence from spontaneous baroreflex analysis during sleep. *Journal of Hypertension, 15*(12 Pt 2), 1621–1626.

Peila, R., White, L. R., Masaki, K., Petrovitch, H., & Launer, L. J. (2006). Reducing the risk of dementia: Efficacy of long-term treatment of hypertension. *Stroke, 37*(5), 1165–1170. doi:10.1161/01.STR.0000217653.01615.93.

Petersson, M., Friberg, P., Eisenhofer, G., Lambert, G., & Rundqvist, B. (2005). Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. *European Heart Journal, 26*(9), 906–913. doi:10.1093/eurheartj/ehi184.

Petrides, A. S., & DeFronzo, R. A. (1989). Glucose metabolism in cirrhosis: A review with some perspectives for the future. *Diabetes/Metabolism Reviews, 5*(8), 691–709.

Pliquett, R. U., Cornish, K. G., Peuler, J. D., & Zucker, I. H. (2003). Simvastatin normalizes autonomic neural control in experimental heart failure. *Circulation, 107*(19), 2493–2498. doi:10.1161/01.CIR.0000065606.63163.B9.

Porte, D., Jr., Baskin, D. G., & Schwartz, M. W. (2005). Insulin signaling in the central nervous system: A critical role in metabolic homeostasis and disease from C. elegans to humans. *Diabetes, 54*(5), 1264–1276. doi: 54/5/1264 [pii].

Proietto, J., Alford, F. P., & Dudley, F. J. (1980). The mechanism of the carbohydrate intolerance of cirrhosis. *Journal of Clinical Endocrinology and Metabolism, 51*(5), 1030–1036.

Randin, D., Vollenweider, P., Tappy, L., Jequier, E., Nicod, P., & Scherrer, U. (1994). Effects of adrenergic and cholinergic blockade on insulin-induced stimulation of calf blood flow in humans. *American Journal of Physiology, 266*(3 Pt 2), R809–R816.

Rumantir, M. S., Vaz, M., Jennings, G. L., Collier, G., Kaye, D. M., Seals, D. R., Wiesner, G. H., Brunner-La Rocca, H. P., & Esler, M. D. (1999). Neural mechanisms in human obesity-related hypertension. *Journal of Hypertension, 17*(8), 1125–1133.

Schlaich, M. P., Kaye, D. M., Lambert, E., Sommerville, M., Socratous, F., & Esler, M. D. (2003). Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation, 108*(5), 560–565. doi:10.1161/01.CIR.0000081775.72651.B6.

Shimazu, T. (1967). Glycogen synthetase activity in liver: Regulation by the autonomic nerves. *Science, 156*(3779), 1256–1257.

Shimazu, T., & Fukuda, A. (1965). Increased activities of glycogenolytic enzymes in liver after splanchnic-nerve stimulation. *Science, 150*(3703), 1607–1608.

Shimazu, T., & Ogasawara, S. (1975). Effects of hypothalamic stimulation on gluconeogenesis and glycolysis in rat liver. *American Journal of Physiology, 228*, 1787–1793.

Shinohara, K., Shoji, T., Emoto, M., Tahara, H., Koyama, H., Ishimura, E., Miki, T., Tabata, T., & Nishizawa, Y. (2002). Insulin resistance as an independent predictor of cardiovascular mortality in patients with end-stage renal disease. *Journal of the American Society of Nephrology, 13*(7), 1894–1900.

Sindelar, D. K., Chu, C. A., Venson, P., Donahue, E. P., Neal, D. W., & Cherrington, A. D. (1998). Basal hepatic glucose production is regulated by the portal vein insulin concentration. *Diabetes, 47*(4), 523–529.

Skilton, M. R., Moulin, P., Terra, J. L., & Bonnet, F. (2007). Associations between anxiety, depression, and the metabolic syndrome. *Biological Psychiatry, 62*(11), 1251–1257. doi:10.1016/j.biopsych.2007.01.012.

Skoog, I., Lernfelt, B., Landahl, S., Palmertz, B., Andreasson, L. A., Nilsson, L., Persson, G., Oden, A., & Svanborg, A. (1996). 15-year longitudinal study of blood pressure and dementia. *Lancet, 347*(9009), 1141–1145.

Somers, V. K., Dyken, M. E., Clary, M. P., & Abboud, F. M. (1995). Sympathetic neural mechanisms in obstructive sleep apnea. *Journal of Clinical Investigation, 96*(4), 1897–1904. doi:10.1172/JCI118235.

Staessen, J. A., Richart, T., & Birkenhager, W. H. (2007). Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. *Hypertension, 49*(3), 389–400. doi:10.1161/01.HYP.0000258151.00728.d8.

Takahashi, A., Ishimaru, H., Ikarashi, Y., Kishi, E., & Maruyama, Y. (1997). Effects of ventromedial hypothalamus stimulation on glycogenolysis in rat liver using in vivo microdialysis. *Metabolism, 46*, 897–901.

Timio, M., Lippi, G., Venanzi, S., Gentili, S., Quintaliani, G., Verdura, C., Monarca, C., Saronio, P., & Timio, F. (1997). Blood pressure trend and cardiovascular events in nuns in a secluded order: A 30-year follow-up study. *Blood Pressure, 6*(2), 81–87.

Timio, M., Verdecchia, P., Venanzi, S., Gentili, S., Ronconi, M., Francucci, B., Montanari, M., & Bichisao, E. (1988). Age and blood pressure changes. A 20-year follow-up study in nuns in a secluded order. *Hypertension, 12*(4), 457–461.

Timonen, M., Salmenkaita, I., Jokelainen, J., Laakso, M., Harkonen, P., Koskela, P., Meyer-Rochow, V. B., Peitso, A., & Keinanen-Kiukaanniemi, S. (2007). Insulin resistance and depressive symptoms in young adult males: Findings from Finnish military conscripts. *Psychosomatic Medicine, 69*(8), 723–728. doi:10.1097/PSY.0b013e318157ad2e.

van den Hoek, A. M., van Heijningen, C., Schroder-van der Elst, J. P., Ouwens, D. M., Havekes, L. M., Romijn, J. A., Kalsbeek, A., & Pijl, H. (2008). Intracerebroventricular administration of neuropeptide Y induces hepatic insulin resistance via sympathetic innervation. *Diabetes, 57* (9), 2304–2310. doi:10.2337/db07-1658. db07-1658 [pii].

van den Hoek, A. M., Voshol, P. J., Karnekamp, B. N., Buijs, R. M., Romijn, J. A., Havekes, L. M., & Pijl, H. (2004). Intracerebroventricular neuropeptide Y infusion precludes inhibition of glucose and VLDL production by insulin. *Diabetes, 53*(10), 2529–2534. doi: 53/10/2529 [pii].

Vinh, A., Chen, W., Blinder, Y., Weiss, D., Taylor, W. R., Goronzy, J. J., Weyand, C. M., Harrison, D. G., & Guzik, T. J. (2010). Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. *Circulation, 122*(24), 2529–2537. doi:10.1161/CIRCULATIONAHA.109.930446.

Vogelzangs, N., Kritchevsky, S. B., Beekman, A. T., Newman, A. B., Satterfield, S., Simonsick, E. M., Yaffe, K., Harris, T. B., & Penninx, B. W. (2008). Depressive symptoms and change in abdominal obesity in older persons. *Archives of General Psychiatry, 65*(12), 1386–1393. doi:10.1001/archpsyc.65.12.1386.

Vollenweider, P., Randin, D., Tappy, L., Jequier, E., Nicod, P., & Scherrer, U. (1994). Impaired insulin-induced sympathetic neural activation and vasodilation in skeletal muscle in obese humans. *Journal of Clinical Investigation, 93*(6), 2365–2371. doi:10.1172/JCI117242.

Zoccali, C., Mallamaci, F., Parlongo, S., Cutrupi, S., Benedetto, F. A., Tripepi, G., Bonanno, G., Rapisarda, F., Fatuzzo, P., Seminara, G., Cataliotti, A., Stancanelli, B., & Malatino, L. S. (2002). Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation, 105*(11), 1354–1359.

Zubcevic, J., Waki, H., Raizada, M. K., & Paton, J. F. (2011). Autonomic-immune-vascular interaction: An emerging concept for neurogenic hypertension. *Hypertension, 57*(6), 1026–1033. doi:10.1161/HYPERTENSIONAHA.111.169748.

Sympathetic Nerve Activity, Stress, and Cardiovascular Risk

Yrsa Bergmann Sverrisdóttir

Contents

Abstract

Recent discoveries supporting a functional and structural link between the brain and the heart emphasize the importance of understanding the cross talk for cardio- and cerebrovascular health. Stress has been shown to play a crucial role in the generation of cardiovascular diseases and has a major impact on neurodegenerative diseases and mental disorders presumably through activation of the sympathetic branch of the autonomic nervous system. It is well established that overactivity of the sympathetic nervous system plays a central role in the development of cardiovascular disease and constitutes an important risk factor for cardiovascular morbidity and mortality. Further, increasing evidence suggests the

Y.B. Sverrisdóttir (✉)
Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK

Nuffield Department of Surgical Sciences, Department of Functional Neurosurgery, John Radcliffe Hospital, University of Oxford, Oxford, UK
e-mail: Yrsa.sverrisdottir@dpag.ox.ac.uk; Yrsa.sverrisdottir@nds.ox.ac.uk

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_37

overactivity of the sympathetic branch is a common phenomenon linking major cardiac pathologies seen in association with several primarily neurological conditions, such as cerebral infarction and subarachnoid hemorrhage. Modulating brain activity in humans for otherwise treatment resistant disorders has been demonstrated to affect cardiovascular parameters. Direct electrical stimulation of specific midbrain areas in humans for pain relief regulates human cardiovascular reflex control and can evoke panic and anxiety, by modulating the activity of the autonomic nervous system.

This chapter examines the connection between the brain and the heart the autonomic nervous system provides. Evidence of a linking between emotional stresses and cardiovascular risk is explored, more specifically, stress-induced cardiomyopathy and a plausible explanation for the female predisposition of the condition.

Keywords
Sympathetic nervous system • Mental stress • Cardiovascular disease • Women

Introduction

Cardio- and cerebrovascular health is based on a complex relationship between the heart and the brain, with the sympathetic division of the autonomic nervous system (ANS) being the key regulator. In 1932 Walter Cannon suggested that two of the ANS principal divisions, the sympathetic and parasympathetic nervous systems, had a primary role in regulating our internal environment (*milieu interieur*, Claude Bernard 1878) by means of negative feedback. He also introduced the term *homeostasis* to describe the tendency toward stability in the body and portrayed the ANS as central to its regulation. Although the whole brain is more or less involved in the maintenance of homeostasis, the control is governed by an area comprising less than 1 % of its total volume, the hypothalamus. Despite its modest size, the hypothalamus controls cardiovascular functions, respiration, metabolism, and temperature regulation and mobilizes our fight and flight and defeat reaction by regulating and modifying autonomic output and endocrine function to face a challenge and restore homeostasis. Cannon showed that when an animal is strongly aroused, the sympathetic division of the ANS "mobilizes the animal for an emergency response of fight or flight. The sympathico-adrenal system orchestrates changes in blood supply, sugar availability, and the blood's clotting capacity in a marshaling of resources keyed to the violent display of energy." The key regulator in the finely tuned beat-to-beat orchestration of normal cardiovascular function from quiet rest to extreme activation is the sympathetic nervous system (SNS). It has been known for well over a century that the brain exerts a powerful effect over sympathetic outflow. It is therefore of pivotal importance to be able to measure sympathetic nervous function and its response to changes in the internal environment posed by external and internal physiological perturbations, when investigating the complex relationship between the brain and heart.

Assessing Human Sympathetic Nervous Function

With the aid of modern techniques to assess SNS activity, we now have better understanding of how the SNS maintains normal cardiovascular function on a beat-to-beat basis. In contrast to somatic motor nerves, sympathetic nerves are shown to be tonically active (Adrian et al. 1932), so all innervated blood vessels remain under some degree of continuous constriction. By rapidly regulating the level of activity, the degree of vasoconstriction in the blood vessels of many key organs around the body is altered. As the SNS plays such an important role in peripheral vascular resistance and shows a close relation to baroreceptor function, its involvement in the development of cardiovascular diseases has been vastly studied.

The different components in sympathetic nervous control of the cardiovascular system have provided a basis for various techniques for assessing sympathetic cardiovascular control in humans. These techniques are complimentary rather than competing methodologies and provide different aspects of sympathetic nervous function.

Microneurography: This electrophysiological technique, developed in Uppsala, Sweden, in the early 1960s, by Hagbarth and Vallbo (Vallbo et al. 1979), provides direct measure of sympathetic nerve firing from efferent postganglionic unmyelinated "C" nerve fibers in limb nerves of awake, unanesthetized humans. Postganglionic sympathetic nerves are composed of hundreds to thousands of unmyelinated fibers whose individual contributions to the recorded signal are exceedingly small. However, accumulation of these thinnest of all human nerve fibers makes it possible to lodge the tip of an electrode in their vicinity and record their ongoing activity. Virtually any human mixed nerve is accessible to the recording electrode, but studies have been confined mainly to the peroneal, tibial, or median nerves. Though visceral sympathetic and parasympathetic activity is still inaccessible, two sympathetic subdivisions are accessible, which are those to the skin vascular bed (SSNA) made up of a mixture of sudomotor and vasomotor impulses and to the muscle vascular bed (MSNA) which is dominated by vasoconstrictor impulses. The marked differences in temporal patterns of sympathetic activity in human skin and muscle nerves have challenged the concept of a "common sympathetic tonus," as the findings indicate that there are different populations of sympathetic neurons subjected to their own homogenous supraspinal drive which may be different from that of other populations.

The noradrenaline spillover measurements: The methodology, which was introduced by Murray Esler and colleagues in Melbourne, Australia, in 1979, is based on the use of a radiotracer (radiolabeled noradrenaline (NA)) employed to measure the rates of turnover of tissue NA and organ-specific spillover of NA to plasma. The method has aided insight into the sympathetic neuronal outflow to internal organs, the inaccessibility of which has been a limitation in cardiovascular research (Esler et al. 1979, 1988, 1990).

Power spectral analysis of circulatory rhythms: With this method, which is based on mathematical partitioning, individual, superimposed rhythms producing cyclical variations in heart rate or arterial pressure can be separated and quantified (Pagani et al. 1986). The variability in heart rate, which is largely attributable to the influence of the autonomic nervous system, can be divided into high (0.3 Hz) and low (0.1 Hz) frequency components, proposed to reflect the vagal parasympathetic and cardiac

sympathetic drive, respectively. While the high frequency component is shown to be a good marker for vagal activity, the low frequency component is not regarded a reliable measure of sympathetic activity (Kingwell et al. 1994).

The Sympathetic Nervous System and Stress

Clinical observations in patients with various primarily neurological conditions such as stroke, subarachnoid hemorrhage, epilepsy, traumatic brain injury, or central nervous system infections, with concomitant ECG abnormalities and in some cases cardiac pathology with wall motion abnormalities as in neurogenic stress cardiomyopathy (NSC), support the connection between the brain and the heart (Mazzeo et al. 2014).

These cardiac abnormalities in acute neurological conditions are mediated by the autonomic nervous system.

Acute mental stress can induce myocardial ischemia in patients with coronary artery disease and induce cardiac electrical instability leading to life-threatening arrhythmias (Kop et al. 2004).

While a flight and flight response to an external stressor is vital for survival, psychological distress, such as intense emotions, anger, and mental stress, can trigger acute coronary syndromes and sudden cardiac death (Samuels 2007).

Dysregulation of the autonomic nervous system, resulting in sympathetic activation and/or parasympathetic withdrawal, is the major pathophysiological mechanism of mental stress-induced cardiac events. Whether our lifestyle or responsiveness to emotional or other stimuli plays a mechanistic role is somewhat uncertain and remains to be elucidated. It is however shown that sympathetic nerve activity and blood pressure tend to increase in emotionally stressful environments (white coat hypertension), while staying stable over time in populations (cloistered nuns) living in secluded and unchanging environments (Timio et al. 2001).

Sudden Cardiac Events Associated with Increased Sympathetic Activity

It is well established that acute coronary syndromes and sudden cardiac death can be triggered by acute psychological distress, such as intense emotions, anger, and mental stress (Samuels 2007). The SNS is known to be active in sudden cardiovascular death. Though not fully understood by which mechanism increased SNS activity to different organs can lead to such events, the parallel increase in SNS activity and morning peaks in acute MI, transient ischemia, and stroke indicates that increased SNS activity may be a trigger for sudden cardiovascular events.

The interaction between central and autonomic nervous system responses may have implications for further investigations of the brain-heart associations and mechanisms by which acute and chronic psychological distress increase the risk of myocardial infarction, cardiac arrhythmias, and sudden cardiac death.

Deep Brain Stimulation, Sympathetic Outflow, and Cardiovascular Function

The main central nervous system components associated with autonomic regulation constitute the Central Autonomic Network (CAN). This is a functional network of cortical and subcortical central nervous system structures that receive information from humoral, visceral, and environmental sources and integrates these inputs to generate preganglionic autonomic, neuroendocrine, and behavioral outputs essential for survival (Benarroch 1993).

The primary brain areas involved in the autonomic modulation of the brain-heart association are the insula, medial prefrontal cortex, and cerebellum. Other areas involved in stress-induced autonomic modulation are the (anterior) cingulate cortex, parietal cortex, somatomotor cortex/precentral gyrus, and temporal cortex.

One of the main structures of the central autonomic network is the subcortical periaqueductal gray (PAG), a complex midbrain region involved in regulating bodily as well as behavioral functions and which is routinely used to treat chronic neuropathic pain. Electrical stimulation of this area has been shown to have cardiovascular effects in humans (Pereira et al. 2010; Green et al. 2005). The PAG contains four longitudinal columns, referred to as the dorsomedial (dmPAG), dorsolateral (dlPAG), lateral (lPAG), and ventrolateral (vlPAG) subdivisions, which collectively have a pivotal role in integrating behavioral and physiological responses to external stressors as well as other functions. Activation of the vlPAG column produces a reduction in cardiovascular activity, while activation of the dlPAG column, believed to be an important component of the central mechanisms that generate the defensive response to acute psychological stressors, is associated with an increased cardiovascular activation (Dampney et al. 2013). The dorsolateral, lateral, and ventrolateral columns of the PAG have distinct reciprocal connections with autonomic centers of the lower brainstem and hypothalamus that differentially regulate activity in neurons of the peripheral autonomic pathways (Bandler et al. 2000).

In the early twentieth century, development of techniques aimed to electrically stimulate specific areas of the brain provided a vital tool to illuminate the role of the brain in regulating autonomic function. With more widespread use of deep brain stimulation (DBS) for otherwise treatment-resistant disorders, reports of autonomic side effects became an area of attention and interest, providing a unique insight into central autonomic regulation and pathophysiology. In rats stimulation of the dlPAG was shown to evoke flight behavior and autonomic changes characteristic of panic (Yardley and Hilton 1986); in humans, DBS at midbrain sites for treating neuropathic pain reported the procedure often evoked intolerable side effects, which resembled the symptoms of panic (Kumar et al. 1997; Nashold et al. 1969; Richardson and Akil 1977). In a recent study by Sverrisdóttir and colleagues (2014), stimulation of the dorsolateral PAG in patients with neuropathic pain was shown to result in a distinctive sympathetic nerve firing pattern previously reported in conditions associated with anxiety and mental stress (Wilkinson et al. 1998; Donadio et al. 2002). An active coping response ("fight and flight") occurs when an individual encounters a threatening stimulus that may be harmful or cause pain. This defense

pattern is represented in the dmPAG and dlPAG and is classically associated with endogenous non-opioid analgesia, increased arterial blood pressure, and heart rate, although recent evidence in humans suggests that it may in fact be opioid-mediated (Pereira et al 2013, Wang et al.). In the absence of an external threat, Sverrisdóttir and co-workers showed that by directly stimulating the midbrain region where the defense pattern is orchestrated, the nerve firing pattern and cardiovascular response resemble that of anxiety, mental stress, and fight and flight response.

While emotional stress and emotion have long been associated with ventricular arrhythmias and sudden cardiac death, in the past decade, cases and conditions have been identified in which severe mental distress has resulted in physical changes to the heart muscle, resulting in a spectrum of stress-related neurogenic cardiomyopathy syndromes, which includes the takotsubo or broken heart syndrome.

Takotsubo Stress Cardiomyopathy or Broken Heart Syndrome: When an Emotion Changes the Shape of Your Heart

The English artist Walter Langley's emotional painting from 1894, which title arises from Tennyson's poem *In Memoriam*, is about loss and heart break. The painting portrays a young woman being comforted by an older woman as she holds her head in her hands and cries. The turmoil of human emotions displayed is in direct

Never morning wore to evening but some heart did break

contrast to the flat calm sea in the background; it is the calm after the storm which took the life of the young woman's beloved and broke her heart.

The idea of the heart as the vulnerable locus of emotion is as old as time. Irish mythology has Deirdre of the Sorrows and her lover Naoise; Greek mythology has the tragedy of Apollo and Daphne, Wagner's opera of Tristan and Isolde, and Shakespeare's Romeo and Juliet. Tales of death from a broken heart feature throughout history and are as genuine today as they were yesterday.

Sympathetic Outflow in Stress-Induced Cardiomyopathy

Takotsubo cardiomyopathy, a particular stress-induced cardiomyopathy, was first described by the Japanese in the early 1990s. They reported baffling cases of patients with cardiac failure presenting signs and symptoms of acute coronary syndrome without evidence of obstructive coronary artery disease recovering spontaneously within days or weeks. This reversible cardiomyopathy was most prevalent in postmenopausal women following a strong emotional or physical stressor such as death of a loved one or other catastrophic news. Angiograms showed that the heart had changed shape. The stunned organ, constricted at the top, ballooned at the bottom, resembled more an octopus trap (takotsubo in Japanese) than a normal heart. The physical change in the shape of the heart, triggered by a powerful emotional stressor, strongly suggests that mental stress can cause cardiovascular disease.

Though the definite pathophysiology of takotsubo stress-induced cardiomyopathy (SIC) remains to be identified, increased plasma levels of catecholamine have been found (Wittstein et al. 2005). Hence, exaggerated SNS activation is proposed to be a major contributor to the pathogenesis and forms the basis for treatment of this medical entity. In a recent study, SNS activity, recorded with microneurography, was found to be lower in women in the acute and chronic phase of SIC as compared to healthy controls (Sverrisdóttir et al. 2012). While the findings of a reduced SNA activity in SIC compared to healthy controls may seem contradictory to findings of increased plasma catecholamine, they may instead reflect the different phases of the condition. As portrayed in Langley's painting, an initial intense sympathetic storm in the acute phase of SIC may cause excessive catecholamine release over the atria and distension of the ventricles. A reflex sympatho-inhibition, as demonstrated in direct nerve recordings, follows as a consequence of the storm and leaves behind a broken heart.

How would this come about? The left ventricular myocardium contains unmyelinated afferents with receptors that are excited both by mechanical and chemical stimuli. It has been proposed that in myocardial distress, these intracardiac receptors may function as protective nociceptors, which when activated can inhibit cardiac contraction and decrease peripheral resistance (Warltier et al. 2003). A distension of the ventricular myocardium, due to excessive catecholamine release over the atria in the acute phase, could increase the rate of discharge of these unmyelinated cardiac c-fiber afferents, resulting in reflex vagal bradycardia and widespread sympathetic inhibition (Folkow 1979). Due to such a reflex mechanism, even though SNS

activity is recorded in the acute phase, it would not capture the early acute catecholamine release as the reflex would already have "kicked in."

Why the Female Predisposition?

The underlying cause for the evident female predisposition of SIC is unknown, but may be related to gender differences in vulnerability to emotional stress (Orth-Gomér et al. 2000) and myocardial sensitivity to catecholamine toxicity (Kneale et al. 2000). That SIC seems to predominantly occur in postmenopausal women indicates that their declining levels of estrogen in the absence of testosterone may also explain their greater vulnerability to SIC (Zhou et al. 2010). In postmenopausal women, estradiol and estrogen levels are closer to those of healthy adult men than those of premenopausal women. Estradiol reduces the response to vasoconstrictors in both male and female arteries. Increasing estrogen levels by means of transdermal estrogen replacement therapy has been shown to decrease SNS activity in postmenopausal women (Vongpatanasin et al. 2001).

Equally, the lower incidence of SIC in healthy males suggests that androgens may play a protective regulatory role in the pathophysiology of SIC.

A big man with a broken heart. In a recent clinical observation of a takotsubo stress-induced cardiomyopathy in a morbidly obese man (Zhou et al. 2010), free testosterone level was found to be lower and estrogen level higher than for an adult male, probably due to aromatization of androgens to estrogens; hence the protective role of androgens may be lost in obese men.

The Midbrain Periaqueductal Gray (PAG), Estrogen, and Emotional Stress

Depression and panic disorders are more common in women than in men and occur at times of extreme hormonal change, such as the premenstrual period, following pregnancy, and during the menopause (Lovick 2014). In mammals, 17β-estradiol (E2) has powerful effects on numerous central neural networks, reduces the response of vasoconstrictors in both male and female arteries, and can modulate pain, anxiety, depression, and cognitive function (García-Villalón et al. 1996).

There exists a reciprocal relationship between the hypothalamic-pituitary-adrenal (HPA) stress axis and the hypothalamic-pituitary-gonadal (HPG) hormonal axes. Both testosterone and estrogen can modulate the response of the stress axis, whereas activation of the stress axis inhibits estrogen and testosterone secretion (Toufexis et al. 2014).

The dorsolateral part of the periaqueductal gray, where the fight and flight reaction resides, is shown to be dense with estrogen receptors. Whether the decline in estrogen levels associated with the menopause affects the function and density of estrogen receptors in the dlPAG is not known. However, one may speculate that without the protective shield of estrogen, a change in estrogen receptor function and

density might affect women's response to emotional stress, rendering them more vulnerable and defenseless in the event of a sympathetic storm.

Conclusion

This chapter has taken a closer look at the link the autonomic nervous system provides between the brain and the heart, serving as a "telephone line" between the two and forming a basis for the connection. Evidence of a linking between emotional stresses and cardiovascular risk has been explored and more specifically, stress-induced cardiomyopathy and a plausible explanation for the female predisposition of the condition have been discussed.

References

Adrian, E. D., et al. (1932). Discharges in mammalian sympathetic nerves. *The Journal of Physiology, 74*(2), 115–133.

Bandler, R., et al. (2000). Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. *Brain Research Bulletin, 53*(1), 95–104.

Benarroch, E. E. (1993). The central autonomic network: Functional organization, dysfunction, and perspective. *Mayo Clinic Proceedings, 68*(10), 988–1001.

Dampney, R. A. L., Furlong, T. M., Horiuchi, J., Iigaya, K. (2013). Role of dorsolateral periaqueductal grey in the coordinated regulation of cardiovascular and respiratory function. *Autonomic Neuroscience, 175*, 17–25.

Donadio, V., et al. (2002). Interindividual differences in sympathetic and effector responses to arousal in humans. *The Journal of Physiology, 544*(1), 293–302.

Esler, M., Jackman, G., Bobik, A., Kelleher, D., Jennings, G., Leonard, P., Skews, H., & Korner, P. (1979). Determination of norepinephrine apparent release rate and clearance in humans. *Life Science, 25*, 1461–1470.

Esler, M., Jennings, G., Korner, P., Willett, I., Dudley, F., Hasking, G., Anderson, W., & Lambert, G. (1988). Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension, 11*, 3–20.

Esler, M., Jennings, G., Lambert, G., Meredith, I., Horne, M., & Eisenhofer, G. (1990). Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. *Physiological Reviews, 70*, 963–985.

García-Villalón, A. L., et al. (1996). Sex differences in the effects of 17β-estradiol on vascular adrenergic responses. *European Journal of Pharmacology, 314*(3), 339–345.

Green, A. L., et al. (2005). Deep brain stimulation can regulate arterial blood pressure in awake humans. *NeuroReport, 16*(16), 1741–1745.

Kingwell, B. A., Thompson, J. M., Kaye, D. M., McPherson, G. A., Jennings, G. L., & Esler, M. D. (1994). Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. *Circulation, 90*, 234–240.

Kneale, B. J., et al. (2000). Gender differences in sensitivity to adrenergic agonists of forearm resistance vasculature. *Journal of the American College of Cardiology, 36*(4), 1233–1238.

Kop, W. J., et al. (2004). Effects of acute mental stress and exercise on T-wave alternans in patients with implantable cardioverter defibrillators and controls. *Circulation, 109*(15), 1864–1869.

Kumar, K., Toth, C., & Nath, R. K. (1997). Deep brain stimulation for intractable pain: a 15 year experience. *Neurosurgery, 40*, 736–746.

Lovick, T. A. (2014). "Sex determinants of experimental panic attacks." *Neuroscience & Biobehavioral Reviews, 46*, 465–471.

Mazzeo, A. T., et al. (2014). Brain–heart crosstalk: The many faces of stress-related cardiomyopathy syndromes in anaesthesia and intensive care. *British Journal of Anaesthesia, 112*(5), 803–815.

Nashold, B. S., Wilson, W. P., & Slaughter, D. G. (1969). Sensations evoked by stimulation in the midbrain of man. *Journal of Neurosurgery, 30*, 14–24.

Orth-Gomér, K., et al. (2000). Marital stress worsens prognosis in women with coronary heart disease: The Stockholm female coronary risk study. *JAMA, 284*(23), 3008–3014.

Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'Orto, S., Piccaluga, E., Turiel, M., Baselli, G., Cerutti, S., & Malliani, A. (1986). Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circulation Research, 59*, 178–193.

Pereira, E. A. C., et al. (2010). Sustained reduction of hypertension by deep brain stimulation. *Journal of Clinical Neuroscience, 17*(1), 124–127.

Pereira, E. A. C., et al. (2013). Elevated gamma band power in humans receiving naloxone suggests dorsal periaqueductal and periventricular gray deep brain stimulation produced analgesia is opioid mediated. *Experimental Neurology, 239*(0), 248–255.

Richardson, D. E., & Akil, H. (1977). Pain reduction by electrical brain stimulation in man. Part 1: acute administration in periaqueductal and periventricular sites. *Journal of Neurosurgery, 47*, 178–183.

Samuels, M. A. (2007). The brain–heart connection. *Circulation, 116*(1), 77–84.

Sverrisdóttir, Y., et al. (2012). Sympathetic nerve activity in stress-induced cardiomyopathy. *Clinical Autonomic Research, 22*(6), 259–264.

Sverrisdóttir, Y. B., et al. (2014). Differentiated baroreflex modulation of sympathetic nerve activity during deep brain stimulation in humans. *Hypertension, 63*(5), 1000–1010.

Timio, M., et al. (2001). A link between psychosocial factors and blood pressure trend in women. *Physiology & Behavior, 73*(3), 359–363.

Toufexis, D., et al. (2014). Stress and the reproductive axis. *Journal of Neuroendocrinology, 26*(9), 573–586.

Vallbo, A. B., et al. (1979). Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. *Physiological Reviews, 59*(4), 919–957.

Vongpatanasin, W., et al. (2001). Transdermal estrogen replacement therapy decreases sympathetic activity in postmenopausal women. *Circulation, 103*(24), 2903–2908.

Warltier, D. C., et al. (2003). Clinical relevance of the Bezold–Jarisch reflex. *Anesthesiology, 98*(5), 1250–1260.

Wilkinson, D., Thompson, J. M., Lambert, G. W., et al. (1998). Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. *Archives of General Psychiatry, 55*(6), 511–520.

Wittstein, I. S., et al. (2005). Neurohumoral features of myocardial stunning due to sudden emotional stress. *New England Journal of Medicine, 352*(6), 539–548.

Yardley, C. P., & Hilton, S. M. (1986). The hypothalamic and brainstem areas from which the cardiovascular and behavioural components of the defence reaction are elicited in the rat. *Journal of the Autonomic Nervous System, 15*, 227–244.

Zhou, J. Q., et al. (2010). A big man with a broken heart: Stress-induced cardiomyopathy in a morbidly obese man. *Mayo Clinic Proceedings, 85*(9), 864–865.

Immunology, Inflammation, Mental Disorders, and Cardiovascular Risk

Bernhard T. Baune

Contents

Abstract

The clinical relationship between mental disorders and cardiovascular disease and risk factors is highly important with serious consequences for morbidity and mortality. A key biological mechanism in this complex and bidirectional relationship is related to immune dysregulation and inflammation in particular. This review critically evaluates the existing literature on the bidirectional nature of this relationship, the contributing clinical factors, and the role of inflammation in prevalent risk factors for both mental disorders and cardiovascular disease including obesity, endothelial dysfunction, and diabetes mellitus type 2. This chapter outlines the lines of biological mechanisms in the bidirectional relationship between mental disorders and cardiovascular disease by exemplifying this

B.T. Baune (✉)
Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, SA, Australia
e-mail: bernhard.baune@adelaide.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_39

using depression as a common disorder. This focus on the role of immune dysregulation and inflammation in these risk factors and comorbid disease suggests new avenues for identifying and possibly treating early patients at risk, but also it opens up novel and preventive treatments such as the use of anti-inflammatories for both types of conditions.

Keywords
Inflammation • Obesity • Mental disorders • Depression • Cardiovascular disorders • Diabetes mellitus type 2

Introduction

The association between cardiovascular diseases (CVDs) and mental disorders has long been recognized. Early reports go back to the first half of the twentieth century when Benjamin Malzberg noticed in 1937 that institutionalized psychiatric patients had a higher mortality rate than the general population. In his seminal report, he described that the age-adjusted mortality rate among patients with involutional melancholia was almost eight times higher than that of the population with "diseases of the heart" accounting for almost 40 % of these deaths (Malzberg 1937).

In the following decades, the comorbidity of depression and CVDs has been rigorously investigated in many cross-sectional and longitudinal studies. Current literature suggests that the relationship between CVD and depression is bidirectional. Numerous clinical and epidemiological studies investigating the association between depression and cardiovascular disease have suggested that depression increases the risk of subsequent CVD by 1.5-fold on average (Grippo and Johnson 2002; Thombs et al. 2006; Lippi et al. 2009; Nicholson et al. 2006) and that patients with coronary artery disease and depression have a two- to threefold increased risk of future nonfatal and fatal cardiac events compared to those cardiac patients without depression (Goldston and Baillie 2008; Kooy et al. 2007; Rudisch and Nemeroff 2003; Frasure-Smith and Lesperance 2010). Moreover, depression has been found to be an independent predictor of a poorer outcome after an ischemic event (Barth et al. 2004; Nicholson et al. 2006; Meijer et al. 2011). The behavioral and biological mechanisms by which cardiovascular disease and mental disorders and depression specifically are linked are manyfold. A more recently developed theory places immune response and inflammation specifically at the center of this discussion. Inflammation has classically shown to be related to cardiovascular diseases, to depression, and to numerous comorbidities such as obesity and diabetes mellitus that increase the risk for depression and cardiovascular disease independently. The complexity of the role of immune dysregulation and inflammation specifically in cardiovascular disease and mental disorders with a focus on depression and common risk factors such as diabetes, obesity, stress, and endothelial dysfunction will form the main focus of this chapter.

Clinical Relationship Between Mental Disorders and Cardiovascular Risk Factors and Disease

Clinical depression characteristics such as disease duration, age at first onset, symptom severity, and number of depressive episodes are generally regarded as important determinants of treatment and long-term disease outcome. The most frequently reported depression characteristic influencing the depression-CVD relationship is symptom severity (Baune et al. 2012). It appears to have a dose-response relationship where more severe depressive symptoms have a large effect or risk, respectively, for both new-onset CVDs and a poorer post-event prognosis. The majority of longitudinal studies on the depression-CVD relationship utilized depression scales as their primary measure, suggesting that these studies have disease severity data available. It is surprising, however, that in many of these studies the potential mediating effect of disease severity data was not analyzed or reported. If these data are available, modeling depressive symptoms according to grades of severity may improve the understanding of the relationship between the two comorbid conditions.

A small number of studies have reported on the association between the number and duration of depressive episodes and their impact on cardiovascular risk (Jones et al. 2003; Scherrer et al. 2003; Surtees et al. 2008; Herbst et al. 2007; Kendler et al. 2009; Matthews et al. 2010; Seldenrijk et al. 2011; Agatisa et al. 2005). Their findings support an effect for the number of depressive episodes on the magnitude of the association between depression and CVDs. However, the importance of the mean duration of these episodes remains unclear. Future research into this comorbidity should include assessment of episode duration from a lifetime perspective, e.g., as an index for the cumulative exposure to biological correlates of the depressive illness.

The relationship between age at onset of depressive illness and its effects on cardiovascular risk has been the subject of only few studies (Surtees et al. 2008; Smith et al. 2009; Janszky et al. 2010; Seldenrijk et al. 2011). The available results support the hypothesis that older age at onset of depression may be a marker of a "vascular depression" subtype which is associated with greater cardiovascular risk (factors) (Alexopoulos et al. 1997). No longitudinal studies have yet found an association between older age at onset of depressive illness and subsequent cardiovascular risk. This makes it unclear whether this putative "vascular depression" subgroup has an etiologically relevant specific high risk for CVDs or simply serves as a marker of subclinical CVD.

Although the relationship between depression and CVDs is suggested to be bidirectional (Aben et al. 2003; Garcia-Fabela et al. 2009; Nicholson et al. 2006), only limited results that relate characteristics of CVDs, such as severity, age at onset, and number of events, to the risk of subsequent depression have been reported so far. It may be conceptualized that the strength of this association can vary across the spectrum of CVDs, i.e., hypertension may demonstrate a lower

degree of association with subsequent depression than angina pectoris, MI, or stroke. But no consistent pattern from the published literature has yet emerged. Furthermore, despite some evidence it is still inconclusive whether "severity" within categories of CVD such as the extent of MI as assessed by electrocardiographic features (i.e., the presence of Q waves or ST elevations) is independently associated with increased risk of post-event depression (Bush et al. 2001; Frasure-Smith et al. 1999; Lauzon et al. 2003; Shiotani et al. 2002; Smolderen et al. 2009; Sorensen et al. 2006). Similarly, the extent and location of stroke do not appear to be independently associated with risk of post-event depression (Snaphaan et al. 2009; Carson et al. 2000).

Subtypes of Depression Related to Cardiovascular Disease and Risk Factors

Many epidemiological and clinical studies examining biological models of the relationship between CVDs and depression classified depression dichotomously either as yes/no or restricted analyses to major depression only. However, more recent research has begun to differentiate depressive subtypes other than MD such as dysthymia, melancholic MD, with typical and atypical features (see description of subtypes in Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR); American Psychiatric Association 2000). While differences in the strength of the association between various depression subtypes and CVDs have been demonstrated (see Baune et al. 2006; Callaghan and Khizar 2010; Goldstein et al. 2009; Herbst et al. 2007; Larson et al. 2001; Maes et al. 1993a, b; Osby et al. 2001; Penninx et al. 2001; Rothermundt et al. 2001; Schlatter et al. 2001, 2004), first studies suggest that subtype-specific associations between depression and cardiovascular disease are caused by a subtype-specific biological correlate. As an overall finding, it is evident that differential systemic immune activation and HPA axis hyperactivity between CVD and depressive subtypes exist, though the pattern of these mechanisms is unclear at this stage (Stuart and Baune 2012).

Mechanisms of Immune Dysfunction, Mental Disorders, and Cardiovascular Risk and Disease

Research addressing the etiology and pathophysiology of the relationship between depression and CVD has primarily focused on biological mechanisms. Plausible models that might link these two conditions include the hypothalamic-pituitary-adrenal (HPA) axis, pro-inflammatory cytokines, changes in arterial vessel elasticity, and endothelial function (for reviews see Grippo and Johnson 2002; Rudisch and Nemeroff 2003; Dantzer et al. 2008; Goldston and Baillie 2008; Raison et al. 2006; Kop and Gottdiener 2005; Brown et al. 2004). These mechanisms have been related separately to mental disorders and cardiovascular disease as well

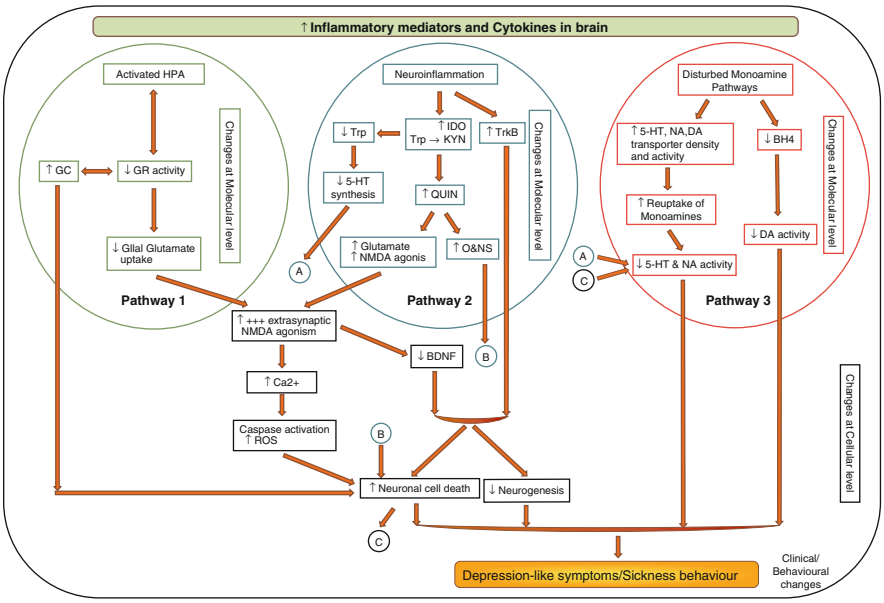


Fig. 1 Shared pathophysiology between mental disorders and cardiovascular risk and disease. *HPA* hypothalamic-pituitary-adrenal axis, *GC* glucocorticoids, *GR* glucocorticoid receptor, *IDO* indoleamine 2,3 diaoxygenase, *Trp* tryptophan, *KYN* kynurenine, *QUIN* quinolinic acid, *NMDA N*-methyl-D-aspartate, *5-HT* serotonin, *NA* noradrenaline, *DA* dopamine, *O&NS* oxidative and nitrosative stress, *ROS* reactive oxygen species, *BDNF* brain-derived neurotrophic factor, *TrkB* tyrosine kinase-B, *BH4* tetrahydrobiopterin. *A*, *B* and *C*: Connectors

as a shared pathophysiology between mental disorders and cardiovascular risk and disease as shown in Fig. 1. The following paragraphs investigate these mechanisms in more depth.

Immune System Dysregulation in Depression and CVD

Studies investigating immune system functioning in individuals with depression defined as either clinical depression or MDD, irrespective of depressive subtypes, have found that many of these individuals with depression have elevated inflammatory markers, particularly c-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) (Dowlati et al. 2010; Maes 2011). Accumulating evidence from both human and animal studies suggests that these markers may be relevant to both the pathogenesis and pathophysiology of depressive disorders (Dantzer et al. 2008; Raison et al. 2006). Furthermore, they are also implicated in the response to conventional pharmacological and electroconvulsive therapies for these disorders (Janssen et al. 2010; Fluitman et al. 2010). Currently, the literature associating depressive disorders

with activation of the immune system is limited by significant heterogeneity in study methodologies and a paucity of longitudinal studies.

Several authors have suggested that this association of depression and inflammatory markers may be a key biological link in the comorbidity of depression and CVD (Lippi et al. 2009; Rudisch and Nemeroff 2003; Kop and Gottdiener 2005). This may be mediated by interactions of inflammatory signaling cascades with several key processes implicated in the pathogenesis and pathophysiology of CVD. Key among these processes is atherosclerosis. It has been proposed that inflammatory mediators may accelerate the progression of atherosclerosis through several mechanisms including chemoattraction of leukocytes to atherosclerotic lesions, inducing endothelial activation and expression of adhesion molecules and stimulating the expression of vascular endothelial growth factors (see for review Hansson and Hermansson 2011). Furthermore, inflammatory signaling cascades may amplify and accelerate the process of coagulation and thrombus formation (Petaja 2011).

Correlation Between Severity of Depression and Inflammation

Severity of depressive symptoms has been found to be significantly associated with and predictive of CVD morbidity and CVD-related mortality among initially healthy individuals (Kendler et al. 2009; Lespérance et al. 2002) suggesting that the severity of depressive symptoms is an important factor in the development and progression of CVD in community samples and among those with a CVD. This has lead researchers to investigate the relationship between severity of depressive symptoms and the expression of immune markers to understand the link between depression and CVD.

Positive associations between severity of depressive symptoms and an overexpression of pro-inflammatory cytokines by LPS-stimulated blood monocytes have been observed. Research conducted by Suarez et al. (2003) examined the association between depressive symptom severity and IL-1α, IL-1β, TNF-α, CCL2, and IL-8 among healthy men. In this study, Beck Depression Inventory (BDI) total scores were positively and significantly correlated with LPS-stimulated expression of IL-1β, TNF-α, CCL2, IL-8, and IL-1α after controlling for factors. These findings suggest that depressive symptoms are significantly associated with monocyte-associated overexpression of pro-inflammatory cytokines and chemokines among men with low to moderate levels of depressive symptoms who do not meet a diagnosis of MDD (Suarez et al. 2003). These results for IL-1β are supported in a study by Thomas et al. (2005) which also demonstrated strong positive and significant correlations between IL-1β and current depressive symptom severity.

HPA Axis Dysregulation in Depression and CVD

The development of CVD is hastened by HPA axis hyperactivity. HPA axis hyperactivity is characterized by corticotropin-releasing hormone (CRH) hypersecretion; blunted corticotropin response to CRH; increased cortisol levels

in plasma, urine, and cerebrospinal fluid; exaggerated cortisol responses to corticotropin; cortisol non-suppression in response to dexamethasone (DEX), a synthetic glucocorticoid; increased adrenocorticotropic hormone (ACTH) concentrations; and enlarged pituitary and adrenal glands (Joynt et al. 2003; Daban et al. 2005; Barth et al. 2004). The HPA axis, a physiological feedback loop that consists of the hypothalamus, pituitary, adrenal glands, regulatory neural inputs, and releasing factors and hormones, activates in response to physical or psychological stress (Daban et al. 2005; Grippo and Johnson 2002). Research which has investigated HPA axis activation among patients with depression often demonstrates HPA axis hyperactivity in these individuals (Grippo and Johnson 2002; Joynt et al. 2003; Lippi et al. 2009; Lett et al. 2004; Raison and Miller 2003).

Processes that modulate HPA system activity and the biological effects of HPA axis hyperactivity are described elsewhere (Froger et al. 2004; Goldston and Baillie 2008; Grippo and Johnson 2002; Daban et al. 2005). Research suggests that the immune dysregulation observed in depressives may be mediated by this HPA axis dysregulation as the central nervous system and the immune system are suggested to be closely linked; interleukins stimulate the HPA axis, and the disruption of glucocorticoid receptor mediated negative feedback removes a key check against NF-κB-mediated inflammatory signaling (Kronfol 2002; Maes et al. 1993a, b; Brown et al. 1987; (Maletic et al. 2007; Pace et al. 2007; Raison and Miller 2003).

It has been suggested that the dysfunction of this system may also contribute to the pathogenesis of CVD (Joynt et al. 2003; Goldston and Baillie 2008). This contribution may be mediated, at least in part, by the loss of glucocorticoid receptor mediated negative feedback on inflammatory signaling which may contribute to atherosclerosis as discussed earlier. Additionally, dysregulation of the HPA axis may lead to sympathoadrenal hyperactivity via central pathways. This hyperactivity may lead to an increase in vasoconstrictive tone, heart rate, and platelet activation, each of which has been implicated in the progression to CVD (Malpas 2010; Joynt et al. 2003). Furthermore, excess sympathetic drive may result in reduced heart rate variability which may lead to arrhythmia (Kemp et al. 2010). This has been demonstrated to partially mediate the effects of depression of postinfarction survival rates (Carney et al. 2005).

Depression and cardiovascular consequences have also been studied in rodents exposed to chronic mild stress (CMS), an animal model that induces anhedonia in rodents through exposure to a chronic period of mild and unpredictable stressors (Grippo et al. 2003; Grippo 2009; Willner 2005). In a study by Grippo et al. (2005b), 4 weeks of CMS produced anhedonia and disrupted HPA axis activity evidenced by attenuated ACTH responses to 8-OH-DPAT (serotonin receptor agonist) administration in male and female rats. However, basal ACTH levels were not altered in CMS rats relative to controls. Rats exposed to CMS also showed slight but nonsignificant higher basal corticosterone levels relative to controls. Grippo et al. suggest that negative feedback in the HPA axis resulting from elevated corticosterone levels may have led to attenuated ACTH response to 8-OH-DPAT. However, disruption of the HPA axis was minor and may be more severe with a longer period of CMS (Grippo et al. 2005b). In a separate study,

Grippo and colleagues observed anhedonia, fatigue, elevated heart rate, reduced heart rate variability, and elevated sympathetic cardiac tone in rats exposed to CMS relative to controls (Grippo et al. 2003). Rats in the CMS group also showed significantly higher plasma corticosterone, circulating TNF-α, IL-1β, plasma renin activity, and aldosterone relative to controls (Grippo et al. 2005a). Additionally, cytokine levels were correlated with the degree on anhedonia in rats exposed to CMS (Grippo et al. 2005a).

Endothelial Dysfunction in Depression and CVD

Endothelial dysfunction is a recognized risk factor for CVD that is also often observed in patients with depression (Shimokawa 1999; Rybakowski et al. 2006; Bonetti et al. 2002; Cooper et al. 2011). In one study, Rajagopalan et al. (2001) demonstrated abnormal endothelial function in patients with MD on antidepressants without typical CAD risk factors relative to matched controls, while Sherwood et al. (2005) found abnormal endothelial function in depressives as measured by flow-mediation dilation relative to those without depression. However, these studies were limited in that they did not measure the severity of the depressive symptoms or differentiate between depressive subtypes to examine any associations between level of endothelial function and depressive severity and diagnosis.

Only one study has examined endothelial functioning and depressive symptom severity. Rybakowski et al. (2006) assessed arterial endothelial function among patients in the major depressive episode (MDE) of unipolar or bipolar disorders (BD) without medications for 7 or more days and CVD risk factors. The results indicated that patients with a mood disorder had impaired endothelial function. However, there were no significant correlations between endothelial function and duration of the mood disorder, age of illness onset, and duration of the current depressive episode. There also were no significant correlations between endothelial function and intensity of depression. Arterial endothelial dysfunction was also observed in patients in the remitted stage. The researchers suggested that arterial endothelial dysfunction may constitute a biological trait marker among those with these mood disorders and is a factor which increases their risk for cardiovascular diseases (Rybakowski et al. 2006).

Stress, Diabetes, and Obesity as Risk Factors for Inflammation in Comorbid Depression and Vascular Risk

A number of other risk factors such as stress, diabetes, and obesity exert immunological changes, often associated with inflammation that is a key mechanism of the biological relationship between mental disorders and cardiovascular risk and disease. The following paragraphs investigate these vascular risk factors for their ability to induce inflammation, thereby increasing vascular risk in addition to their risk to increase the likelihood of a mental disorder such as depression.

Stress and Inflammation

The implications of the above mechanisms for the pathogenesis of depression in patients with an infectious, autoimmune, or iatrogenic source of inflammatory stimulation are clear. However, inflammation may also contribute to the development of depression in the absence of a recognized inflammatory condition via the ability of stress to activate the immune system. It has been demonstrated in human and animal literature that both acute and chronic stress can cause activation of the immune system. For example, acute stress induced by two brief public speaking stressors (Trier social stress test) has been shown to induce elevations in levels of the cytokine IL-6 (von Kanel et al. 2005, 2006) and an increase in the activity of NF-κB (Wolf et al. 2009). Similarly, rats exposed to acute stress in the form of forced immobilization (Sotnikov et al. 2009) or exposed to a brightly lit open field (LeMay et al. 1990) have demonstrated elevations in cytokine levels, particularly IL-6 (LeMay et al. 1990; Soszynski et al. 1997). In humans, chronic stress from sources such as caring for a child with cancer (Miller et al. 2002) or a spouse with dementia (Kiecolt-Glaser et al. 2003) has been associated with elevations in cytokines and other inflammatory markers (Leonard and Myint 2009). These findings extend to animal models of depression also, as exposure to the chronic mild stress paradigm has also been associated with an increase in pro-inflammatory cytokine release (Grippo et al. 2005a).

Inflammation and Type 2 Diabetes

When studying the mechanisms and pathways of type 2 diabetes mellitus (T2DM), it is important to recognize that it is difficult to dissect this disease process from the construct of "metabolic syndrome." This syndrome consists of diabetes or elevated fasting glucose levels, abdominal obesity, dyslipidemia, and hypertension (Alberti et al. 2006), all of which are vascular risk factors. Of these components, obesity in particular may play a central role in mediating the relationship between inflammation and T2DM. Therefore while studies suggest a relationship both between diabetes and inflammation and obesity and inflammation, it is important to recognize that these comorbidities may share a similar pathogenetic process.

Diabetes Mellitus Type 2 Is Longitudinally Associated with Depression

The increase in pro-inflammatory mediators detailed above provides a plausible mechanistic link explaining the increased incidence of depression among patients with T2DM. It is important to note that T2DM is commonly associated with increased adiposity or obesity, a factor that has independently been associated with depression (Luppino et al. 2010). Given the existence of inflammatory pathways with the potential to interrelate these three conditions, it appears possible that these observed relationships may indeed be causal. A diabetes- and/or obesity-related increase in inflammatory markers, hyperglycemia, and possibly hyperinsulinemia may contribute to a net pro-inflammatory state in many tissues. Access of pro-inflammatory mediators to the CNS may then lead to an activation of the pathways leading to the development of depressive symptoms as reviewed above. An animal study demonstrated in the db/db mouse model of diabetes that

both the central and peripheral anti-inflammatory feedback responses to IL-1β or LPS were reduced in diabetic mice. This correlated with a significant extension of the "sickness behavior" responses in the diabetic mice (O'Connor et al. 2005). In addition, T2DM is associated with reduced volumes in areas of the brain implicated in depression such as the hippocampus and amygdala, providing strong support for the suggestion that T2DM does provide a true biological risk factor for depression (McIntyre et al. 2010a). Also, an animal model of T2DM (db/db mouse) has recently been found to exhibit a depressive phenotype in the forced swim test (Sharma et al. 2010). Although this review has focussed on the biological pathways between depression and T2DM, it is important to note that the psychosocial implications of diabetes and diabetic complications may also play a role in the later development of depression. It has been suggested that the stress of a diagnosis of diabetes may predispose to the onset of depression; however, several of the studies demonstrate an association of undiagnosed T2DM with depressive symptoms indicating that this alone is not sufficient to explain the relationship (Musselman et al. 2003).

Depression as a Precursor of Diabetes Mellitus Type 2

The epidemiological observation that depression increases the risk for a subsequent development of T2DM may also be explained through inflammatory pathways. An increase in the central synthesis of pro-inflammatory mediators, including IL-1β, TNF-α, and IL-6, may contribute to systemic inflammation as these cytokines are able to cross the BBB into the circulation (Banks et al. 1989; Gutierrez et al. 1993). These mediators have the potential to interact with insulin sensitivity and pancreatic β-cell function to contribute to the development of T2DM as detailed above. Indeed, an animal model of astrocyte-specific IL-6 overexpression found that when combined with a high fat diet these mice were more glucose intolerant than their wild-type littermates, although their body weight was not affected (Hidalgo et al. 2010). Individuals with obesity are at an increased risk of developing T2DM, and consistent with this notion, the interaction of mediators from the CNS with adipose tissue may contribute to an amplification of pro-inflammatory signaling from adipose tissue. TNF-α and IL-6 are both reliably correlated with depression and may also regulate the production of several adipokines (Dowlati et al. 2010; Rabe et al. 2008). In addition, depression is associated with high levels of glucocorticoid production and glucocorticoid resistance which may further contribute to an inflammatory state through a loss of suppression of immune cells. Glucocorticoids are also a key counter-regulatory hormone to the actions of insulin on glucose homeostasis, primarily through a stimulation of hepatic gluconeogenesis and inhibition of glucose uptake by tissues. It is unclear whether the glucocorticoid resistance commonly found in immune cells extends to these metabolic actions (Musselman et al. 2003). Beyond these biological mechanisms, it is again important to stress that psychosocial and behavioral effects of depression may contribute to the later development of T2DM. It is also particularly poignant at this point to note the literature that has found poorer outcomes and an increased risk of diabetic complications among patients with comorbid depression (Gendelman et al. 2009;

Katon et al. 2009; Koopmans et al. 2009; Le et al. 2006; Lin et al. 2010, 2010; Maraldi et al. 2007; Molife 2010; Musselman et al. 2003; Thaneerat et al. 2010; Winkley 2008). It is tempting to speculate that patients with comorbid depression may have a greater elevation in pro-inflammatory mediators than non-depressed patients with T2DM, thereby increasing vulnerability to complications; however, recent literature does not support this conclusion (Carnethon et al. 2007; Golden et al. 2008).

Alternatively, several other factors have been identified that may act as mediators of this relationship. These include poorer adherence to treatment and self-care activities (Yang et al. 2009), poorer metabolic control (Thaneerat et al. 2010), and exposure to the potential metabolic side effects of antidepressant medications. The use of antidepressant pharmacotherapy is frequently considered as a mediator of the relationship between depression and T2DM. Several studies have found that certain antidepressant medications are associated with long-term weight gain and suggested that this may represent a key biological factor; however, a recent meta-analysis found that the effects of antidepressants on glucose control remain ambiguous (van der Feltz-Cornelis et al. 2010). This may be due to significant heterogeneity in the pharmacological mechanisms of various antidepressant drugs (McIntyre et al. 2010b). Similarly, the effects of antidepressants on other aspects of metabolic disturbance such as weight gain and dyslipidemia appear to be closely related to the specific antidepressant evaluated in each study (McIntyre et al. 2010b; Serretti and Mandelli 2010). Although this body of literature does demonstrate an association of some antidepressant medications with the later onset of T2DM, this alone does not explain the observed association between the two conditions (Pyykkonen et al. 2011).

Obesity and Inflammation

Adipose tissue was formerly regarded as purely a storage site for excess fatty acids; however, a modern view suggests a far more complex role for this organ. Developments in recent years have uncovered an endocrine role for adipose tissue and its constituents, primarily through the release of adipokines, a collection of proteins with endocrine capabilities and the potential to influence metabolism, the immune system, and the vasculature. These adipokines are released from various cell types within the adipose tissue including vascular endothelium, resident macrophages, and the adipocytes themselves (Maury and Brichard 2010). The process leading to an inflammatory state in the adipose tissue is not completely understood and several possibilities have been raised. These include the increase in NF-κB and JNK activity by hypertrophied adipocytes, endoplasmic reticulum stress resulting in activation of the "unfolded protein response," hypoxic stress in adipose tissue, activation of toll-like receptor 4 (TLR4) by excess free fatty acids (FFA), or increased chylomicron-mediated transport of LPS from the gut lumen into circulation in a lipid-rich diet. A detailed discussion of these mechanisms is beyond the scope of this paper; however, several recent reviews are available on these topics (Donath and Shoelson 2011; Hotamisligil 2010; Maury and Brichard 2010).

After initiation of the inflammatory process, most likely through a combination of the above events, the potentiation of this response is primarily dependent on the actions of several cell types in adipose tissue and the liver. Larger adipocytes are

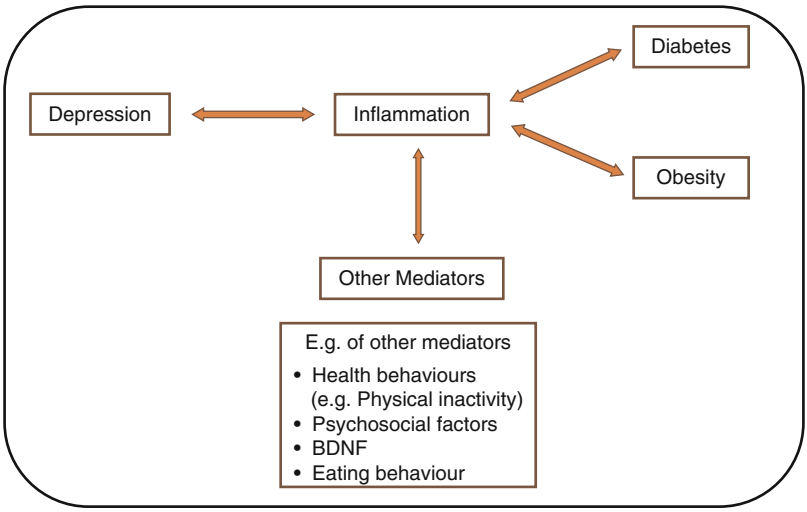


Fig. 2 The interrelationship between depression, diabetes and inflammation. *BDNF* brain derived neurotrophic factor

known to shift their secretory activity toward an increase in pro-inflammatory adipokines, including monocyte chemoattractant protein-1 (MCP-1) (Skurk et al. 2007). MCP-1 results in an influx of macrophages of a pro-inflammatory phenotype, also known as M1 or "classically activated." This influx skews the balance in adipose tissue away from the M2 or "alternatively activated," macrophages that also have the capability to secrete "anti-inflammatory" cytokines (Lumeng et al. 2008). The net increase in secretion of inflammatory molecules further stimulates the secretion of pro-inflammatory molecules by hypertrophied adipocytes (Maury et al. 2009). In obese people, this shift in M1/M2 balance, coupled with increased overall macrophage density, and secretion from hypertrophied adipocytes results in an increase in the levels of "pro-inflammatory" adipokines and a decrease in the levels of "anti-inflammatory" adipokines. This alteration in adipokine profile may contribute to the insulin resistance that is characteristic of T2DM (Antuna-Puente et al. 2008; Maury and Brichard 2010).

Circulating levels of several of these adipokines have been shown to correlate with obesity, and many appear to have a role in obesity-related insulin resistance. It is also relevant to note that many of these adipokines have been shown to have activity in the CNS or at the BBB in addition to their peripheral effects (see for review Pan and Kastin 2007).

In addition to adipose tissue, the primary tissues that are responsible for maintenance of glucose homeostasis in response to insulin are the liver and skeletal muscle. The establishment of a pro-inflammatory state in these three tissues may form the conditions for the systemic disruption of insulin sensitivity and glucose homeostasis that is characteristic of T2DM (Brun et al. 2007; Hijona et al. 2010; Varma et al. 2009).

Conclusions

Mental disorders and cardiovascular disease have long been described as comorbid conditions in a complex bidirectional relationship. A key biological mechanism that leads to support of a shared pathophysiology between mental disorders and CVDs includes alterations of the immune in general and of inflammation in particular. Inflammation has also been shown to be mechanistically linked to risk factors of both mental disorders and cardiovascular disease such as endothelial dysfunction, obesity, and diabetes mellitus type 2 which are regarded as independent risk factors for mental disorders such as depression and CVDs. The literature suggests that a biological model of the relationship between depression and CVDs should consider clinical-biological subtypes of depression and CVDs in favor of a generalized and possibly oversimplified global relationship between depressive symptoms and CVD risk factors and disease regardless of diagnostic subtypes. The presented approach enables a diagnostic classification of such subtypes based on inflammation, and novel treatments targeting the immune system and inflammation in particular might be clinically beneficial in treating and preventing the common comorbidity between mental disorders and CVDs.

References

Aben, I., Verhey, F., Strik, J., Lousberg, R., Lodder, J., & Honig, A. (2003). A comparative study into the one year cumulative incidence of depression after stroke and myocardial infarction. *Journal of Neurology, Neurosurgery and Psychiatry, 74*, 581–585.

Agatisa, P. K., Matthews, K. A., Bromberger, J. T., Edmundowicz, D., Chang, Y. F., & Sutton-Tyrrell, K. (2005). Coronary and aortic calcification in women with a history of major depression. *Archives of Internal Medicine, 165*, 1229–1236.

Alberti, K. G., Zimmet, P., & Shaw, J. (2006). Metabolic syndrome—a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabetic Medicine, 23*, 469–480.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular depression' hypothesis. *Archives of General Psychiatry, 54*, 915–922.

Antuna-Puente, B., Feve, B., Fellahi, S., & Bastard, J. P. (2008). Adipokines: The missing link between insulin resistance and obesity. *Diabetes & Metabolism, 34*, 2–11.

Association, A. P. (2000). *Diagnostic and statistical manual of mental disorders, Fourth edition, text revision*. Arlington: American Psychiatric Association.

Banks, W. A., Kastin, A. J., & Durham, D. A. (1989). Bidirectional transport of interleukin-1 alpha across the blood–brain barrier. *Brain Research Bulletin, 23*, 433–437.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine, 66*, 802–813.

Baune, B. T., Adrian, I., Arolt, V., & Berger, K. (2006). Associations between major depression, bipolar disorders, dysthymia and cardiovascular diseases in the general adult population. *Psychotherapy and Psychosomatics, 75*, 319–326.

Baune, B. T., Stuart, M., Gilmour, A., Wersching, H., Arolt, V., & Berger, K. (2012). Moderators of the relationship between depression and cardiovascular disorders: A systematic review. *General Hospital Psychiatry, 34*, 478–492.

Bonetti, P. O., Lerman, L. O., & Lerman, A. (2002). Endothelial dysfunction: A marker of atherosclerotic risk. *Arteriosclerosis, Thrombosis, and Vascular Biology, 22*, 1065–1074.

Brown, S., Smith, L., & Blalock, J. (1987). Interleukin 1 and interleukin 2 enhance proopiomelanocortin gene expression in pituitary cells. *Journal of Immunology, 139*, 3181–3183.

Brown, E. S., Varghese, F. P., & McEwen, B. S. (2004). Association of depression with medical illness: Does cortisol play a role? *Biological Psychiatry, 55*, 1–9.

Brun, P., Castagliuolo, I., Di Leo, V., Buda, A., Pinzani, M., Palu, G., & Martines, D. (2007). Increased intestinal permeability in obese mice: New evidence in the pathogenesis of nonalcoholic steatohepatitis. *American Journal of Physiology. Gastrointestinal and Liver Physiology, 292*, G518–G525.

Bush, D. E., Ziegelstein, R. C., Tayback, M., Richter, D., Stevens, S., Zahalsky, H., & Fauerbach, J. A. (2001). Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *The American Journal of Cardiology, 88*, 337–341.

Callaghan, R. C., & Khizar, A. (2010). The incidence of cardiovascular morbidity among patients with bipolar disorder: A population-based longitudinal study in Ontario, Canada. *Journal of Affective Disorders, 122*, 118–23.

Carnethon, M. R., Biggs, M. L., Barzilay, J. I., Smith, N. L., Vaccarino, V., Bertoni, A. G., Arnold, A., & Siscovick, D. (2007). Longitudinal association between depressive symptoms and incident type 2 diabetes mellitus in older adults: The cardio-vascular health study. *Archives of Internal Medicine, 167*, 802–807.

Carney, R. M., Blumenthal, J. A., Freedland, K. E., Stein, P. K., Howells, W. B., Berkman, L. F., Watkins, L. L., Czajkowski, S. M., Hayano, J., Domitrovich, P. P., & Jaffe, A. S. (2005). Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Archives of Internal Medicine, 165*, 1486–1491.

Carson, A. J., Machale, S., Allen, K., Lawrie, S. M., Dennis, M., House, A., & Sharpe, M. (2000). Depression after stroke and lesion location: A systematic review. *Lancet, 356*, 122–126.

Cooper, D. C., Tomfohr, L. M., Milic, M. S., Natarajan, L., Bardwell, W. A., Ziegler, M. G., & Dimsdale, J. E. (2011). Depressed mood and flow-mediated dilation: A systematic review and meta-analysis. *Psychosomatic Medicine, 73*, 360–369.

Daban, C., Vieta, E., Mackin, P., & Young, A. H. (2005). Hypothalamic-pituitary-adrenal axis and bipolar disorder. *Psychiatric Clinics of North America, 28*, 469–480.

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature, 9*, 46–57.

Donath, M. Y., & Shoelson, S. E. (2011). Type 2 diabetes as an inflammatory disease. *Nature Reviews Immunology, 11*, 98–107.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctot, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry, 67*, 446–457.

Fluitman, S. B., Heijnen, C. J., Denys, D. A., Nolen, W. A., Balk, F. J., & Westenberg, H. G. (2010). Electroconvulsive therapy has acute immunological and neuroendocrine effects in patients with major depressive disorder. *Journal of Affective Disorders, 131*, 388–92.

Frasure-Smith, N., & Lesperance, F. (2010). Depression and cardiac risk: Present status and future directions. *Heart, 96*, 173–176.

Frasure-Smith, N., Lesperance, F., Juneau, M., Talajic, M., & Bourassa, M. G. (1999). Gender, depression, and one-year prognosis after myocardial infarction. *Psychosomatic Medicine, 61*, 26–37.

Froger, N., Palazzo, E., Boni, C., Hanoun, N., Saurini, F., Joubert, C., Dutriez-Casteloot, I., Enache, M., Maccari, S., Barden, N., Cohen-Salmon, C., Hamon, M., & Lanfumey, L. (2004). Neurochemical and behavioral alterations in glucocorticoid receptor-impaired transgenic mice after chronic mild stress. *The Journal of Neuroscience, 24*, 2787–2796.

Garcia-Fabela, L., Melano-Carranza, E., Aguilar-Navarro, S., Garcia-Lara, J. M., Gutierrez-Robledo, L. M., & Avila-Funes, J. A. (2009). Hypertension as a risk factor for developing depressive symptoms among community-dwelling elders. *Revista de Investigación Clínica, 61*, 274–280.

Gendelman, N., Snell-Bergeon, J. K., McFann, K., Kinney, G., Paul Wadwa, R., Bishop, F., Rewers, M., & Maahs, D. M. (2009). Prevalence and correlates of depression in individuals with and without type 1 diabetes. *Diabetes Care, 32*, 575–579.

Golden, S. H., Lazo, M., Carnethon, M., Bertoni, A. G., Schreiner, P. J., Diez Roux, A. V., Lee, H. B., & Lyketsos, C. (2008). Examining a bidirectional association between depressive symptoms and diabetes. *JAMA, 299*, 2751–2759.

Goldstein, B. I., Fagiolini, A., Houck, P., & Kupfer, D. J. (2009). Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. *Bipolar Disorders, 11*, 657–662.

Goldston, K., & Baillie, A. J. (2008). Depression and coronary heart disease: A review of the epidemiological evidence, explanatory mechanisms and management approaches. *Clinical Psychology Review, 28*, 288–306.

Grippo, A. J. (2009). Mechanisms underlying altered mood and cardiovascular dysfunction: The value of neurobiological and behavioral research with animal models. *Neuroscience & Biobehavioral Reviews, 33*, 171–180.

Grippo, A. J., & Johnson, A. K. (2002). Biological mechanisms in the relationship between depression and heart disease. *Neuroscience & Biobehavioral Reviews, 26*, 941–962.

Grippo, A., Beltz, T., & Johnson, A. (2003). Behavioral and cardiovascular changes in the chronic mild stress model of depression. *Physiology & Behavior, 78*, 703–710.

Grippo, A. J., Francis, J., Beltz, T. G., Felder, R. B., & Johnson, A. K. (2005a). Neuroendocrine and cytokine profile of chronic mild stress-induced anhedonia. *Physiology & Behavior, 84*, 697–706.

Grippo, A. J., Sullivan, N. R., Damjanoska, K. J., Crane, J. W., Carrasco, G. A., Shi, J., Chen, Z., Garcia, F., Muma, N. A., & Van de Kar, L. D. (2005b). Chronic mild stress induces behavioral and physiological changes, and may alter serotonin 1A receptor function, in male and cycling female rats. *Psychopharmacology, 179*, 769–780.

Gutierrez, E. G., Banks, W. A., & Kastin, A. J. (1993). Murine tumor necrosis factor alpha is transported from blood to brain in the mouse. *Journal of Neuroimmunology, 47*, 169–176.

Hansson, G. K., & Hermansson, A. (2011). The immune system in atherosclerosis. *Nature Immunology, 12*, 204–212.

Herbst, S., Pietrazak, R., Wagner, J., White, W., & Petry, N. (2007). Lifetime major depression is associated with coronary heart disease in older adults: Results from the national epidemiologic survey on alcohol and related conditions. *Psychosomatic Medicine, 69*, 729–734.

Hidalgo, J., Florit, S., Giralt, M., Ferrer, B., Keller, C., & Pilegaard, H. (2010). Transgenic mice with astrocyte-targeted production of interleukin-6 are resistant to high-fat diet-induced increases in body weight and body fat. *Brain, Behavior, and Immunity, 24*, 119–126.

Hijona, E., Hijona, L., Arenas, J. I., & Bujanda, L. (2010). Inflammatory mediators of hepatic steatosis. *Mediators of Inflammation, 2010*, 837419.

Hotamisligil, G. S. (2010). Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell, 140*, 900–917.

Janssen, D. G., Caniato, R. N., Verster, J. C., & Baune, B. T. (2010). A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. *Human Psychopharmacology, 25*, 201–215.

Janszky, I., Ahnve, S., Lundberg, I., & Hemmingsson, T. (2010). Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. *Journal of the American College of Cardiology, 56*, 31–37.

Jones, D. J., Bromberger, J. T., Sutton-Tyrrell, K., & Matthews, K. A. (2003). Lifetime history of depression and carotid atherosclerosis in middle-aged women. *Archives of General Psychiatry, 60*, 153–160.

Joynt, K. E., Whellan, D. J., & O'Connor, C. M. (2003). Depression and cardiovascular disease: Mechanisms of interaction. *Biological Psychiatry, 54*, 248–261.

Katon, W., Russo, J., Lin, E., Heckbert, S., Ciechanowski, P., Ludman, E., & Korff, M. (2009). Depression and diabetes: Factors associated with major depression at five-year follow-up. *Psychosomatics, 50*, 570.

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., & Gatt, J. M. (2010). Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. *Biological Psychiatry, 67*, 1067–1074.

Kendler, K., Gardner, C., Riske, A., & Gatz, M. (2009). Major depression and coronary artery disease in the swedish twin registry. *Archives of General Psychiatry, 66*, 857–863.

Kiecolt-Glaser, J. K., Preacher, K. J., MacCallum, R. C., Atkinson, C., Malarkey, W. B., & Glaser, R. (2003). Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National academy of Sciences of the United States of America, 100*, 9090–9095.

Koopmans, B., Pouwer, F., de Bie, R., Leusink, G., Denollet, J., & Pop, V. (2009). Associations between vascular co-morbidities and depression in insulin-naive diabetes patients: The DIAZOB Primary Care Diabetes study. *Diabetologia, 52*, 2056–2063.

Kooy, K. V. D., Hout, H. V., Marwijk, H., Marten, H., Stehouwer, G., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases: A systematic review and meta analysis. *International Journal of Geriatric Psychiatry, 22*, 613–626.

Kop, W. J., & Gottdiener, J. S. (2005). The role of immune system parameters in the relationship between depression and coronary artery disease. *Psychosomatic Medicine, 67*, S37–S41.

Kronfol, Z. (2002). Immune dysregulation in major depression: A critical review of existing evidence. *The International Journal of Neuropsychopharmacology, 5*, 333–343.

Larson, S., Owens, P., Ford, D., & Eaton, W. (2001). Depressive disorder, dysthymia, and risk of stroke: Thirteen-year follow-up from the Baltimore epidemiologic catchment area study. *Stroke, 32*, 1979–1983.

Lauzon, C., Beck, C. A., Huynh, T., Dion, D., Racine, N., Carignan, S., Diodati, J. G., Charbonneau, F., Dupuis, R., & Pilote, L. (2003). Depression and prognosis following hospital admission because of acute myocardial infarction. *Canadian Medical Association Journal, 168*, 547–552.

Le, T. K., Able, S. L., & Lage, M. J. (2006). Resource use among patients with diabetes, diabetic neuropathy, or diabetes with depression. *Cost Effectiveness and Resource Allocation, 4*, 18.

LeMay, L. G., Vander, A. J., & Kluger, M. J. (1990). The effects of psychological stress on plasma interleukin-6 activity in rats. *Physiology and Behavior, 47*, 957–961.

Leonard, B. E., & Myint, A. (2009). The psychoneuroimmunology of depression. *Human Psychopharmacology, 24*, 165–175.

Lespérance, F., Frasure-Smith, N., Talajic, M., & Bourassa, M. G. (2002). 5-year risk of cardiac mortality in relation to initial severity and 1-year changes in depression symptoms after myocardial infarction. *ACC Current Journal Review, 11*, 17–17.

Lett, H. S., Blumenthal, J. A., Babyak, M. A., Sherwood, A., Strauman, T., Robins, C., & Newman, M. F. (2004). Depression as a risk factor for coronary artery disease: Evidence, mechanisms, and treatment. *Psychosomatic Medicine, 66*, 305–315.

Lin, E., Rutter, C., Katon, W., Heckbert, S., Ciechanowski, P., Oliver, M., Ludman, E., Young, B., Williams, L., & McCulloch, D. (2010). Depression and advanced complications of diabetes. *Diabetes Care, 33*, 264.

Lippi, G., Montagnana, M., Facaloro, E., & Franchini, M. (2009). Mental depression and cardiovascular disease: A multifaceted, bidirectional association. *Seminars in Thrombosis and Hemostasis, 35*, 325–336.

Lumeng, C. N., DelProposto, J. B., Westcott, D. J., & Saltiel, A. R. (2008). Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes. *Diabetes, 57*, 3239–3246.

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W., & Zitman, F. G. (2010). Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry, 67*, 220–229.

Maes, M. (2011). Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 35*, 664–675.

Maes, M., Bosmans, E., Meltzer, H. Y., Scharpe, S., & Suy, E. (1993a). Interleukin-1β: A putative mediator of HPA axis hyperactivity in major depression? *The American Journal of Psychiatry, 150*, 1189–1193.

Maes, M., Scharpe, S., Meltzer, H., Bosmans, E., Suy, E., Calabrese, J., & Cosyns, P. (1993b). Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. *Psychiatry Research, 49*, 11–27.

Maletic, V., Robinson, M., Oakes, T., Iyengar, Ball, S., & Russell, J. (2007). Neurobiology of depression: An integrated view of key findings. *International Journal of Clinical Practice, 61*, 2030–2040.

Malpas, S. C. (2010). Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. *Physiological Reviews, 90*, 513–557.

Malzberg, B. (1937). Mortality among patients with evolutionary melancholia. *The American Journal of Psychiatry, 93*, 1231–1238.

Maraldi, C., Volpato, S., Penninx, B. W., Yaffe, K., Simonsick, E. M., Strotmeyer, E. S., Cesari, M., Kritchevsky, S. B., Perry, S., Ayonayon, H. N., & Pahor, M. (2007). Diabetes mellitus, glycemic control, and incident depressive symptoms among 70- to 79- year-old persons: The health, aging, and body composition study. *Archives of Internal Medicine, 167*, 1137–1144.

Matthews, K. A., Chang, Y. F., Sutton-Tyrrell, K., Edmundowicz, D., & Bromberger, J. T. (2010). Recurrent major depression predicts progression of coronary calcification in healthy women: Study of Women's Health Across the Nation. *Psychosomatic Medicine, 72*, 742–747.

Maury, E., & Brichard, S. M. (2010). Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Molecular and Cellular Endocrinology, 314*, 1–16.

Maury, E., Noel, L., Detry, R., & Brichard, S. M. (2009). In vitro hyperresponsiveness to tumor necrosis factor-alpha contributes to adipokine dysregulation in omental adipocytes of obese subjects. *Journal of Clinical Endocrinology and Metabolism, 94*, 1393–1400.

McIntyre, R. S., Kenna, H. A., Nguyen, H. T., Law, C. W., Sultan, F., Woldeyohannes, H. O., Adams, A. K., Cheng, J. S., Lourenco, M., Kennedy, S. H., & Rasgon, N. L. (2010a). Brain volume abnormalities and neurocognitive deficits in diabetes mellitus: Points of pathophysiological commonality with mood disorders? *Advances in Therapy, 27*, 63–80.

McIntyre, R. S., Park, K. Y., Law, C. W., Sultan, F., Adams, A., Lourenco, M. T., Lo, A. K., Soczynska, J. K., Woldeyohannes, H., Alsuwaidan, M., Yoon, J., & Kennedy, S. H. (2010b). The association between conventional antidepressants and the metabolic syndrome: A review of the evidence and clinical implications. *CNS Drugs, 24*, 741–753.

Meijer, A., Conradi, H. J., Bos, E. H., Thombs, B. D., VAN Melle, J. P., & DE Jonge, P. (2011). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. *General Hospital Psychiatry, 33*, 203–216.

Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychology, 21*, 531–541.

Molife, C. (2010). Is depression a modifiable risk factor for diabetes burden? *Journal of Primary Care and Community Health, 1*, 55.

Musselman, D. L., Betan, E., Larsen, H., & Phillips, L. S. (2003). Relationship of depression to diabetes types 1 and 2: Epidemiology, biology, and treatment. *Biological Psychiatry, 54*, 317–329.

Nicholson, A., Kuper, H., & Hemingway, H. (2006). Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *European Heart Journal, 27*, 2763–2774.

O'Connor, J. C., Satpathy, A., Hartman, M. E., Horvath, E. M., Kelley, K. W., Dantzer, R., Johnson, R. W., & Freund, G. G. (2005). IL-1beta-mediated innate immunity is amplified in the db/db mouse model of type 2 diabetes. *Journal of Immunology, 174*, 4991–4997.

Osby, U., Brandt, L., Correia, N., Ekbom, A., & Sparen, P. (2001). Excess mortality in bipolar and unipolar disorder in Sweden. *Archives of General Psychiatry, 58*, 844–850.

Pace, T. W., Hu, F., & Miller, A. H. (2007). Cytokine-effects on glucocorticoid receptor function: Relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain, Behavior, and Immunity, 21*, 9–19.

Pan, W., & Kastin, A. J. (2007). Adipokines and the blood–brain barrier. *Peptides, 28*, 1317–1330.

Penninx, B., Beekman, A., Honig, A., Deeg, D., Schoevers, R., Eijk, J. V., & Tilburg, W. V. (2001). Depression and cardiac mortality: Results from a community-based longitudinal Study. *Archives of General Psychiatry, 58*, 221–227.

Petaja, J. (2011). Inflammation and coagulation. An overview. *Thrombosis Research, 127*(Suppl 2), S34–S37.

Pyykkonen, A. J., Raikkonen, K., Tuomi, T., Eriksson, J. G., Groop, L., & Isomaa, B. (2011). Association between depressive symptoms and metabolic syndrome is not explained by antidepressant medication: Results from the PPP-Botnia Study. Annals of Medicine.

Rabe, K., Lehrke, M., Parhofer, K. G., & Broedl, U. C. (2008). Adipokines and insulin resistance. *Molecular Medicine, 14*, 741–751.

Raison, C. L., & Miller, A. H. (2003). When not enough is too much: The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *The American Journal of Psychiatry, 160*, 1554–1565.

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology, 27*, 24–31.

Rajagopalan, S., Brook, R., Rubenfire, M., Pitt, E., Young, E., & Pitt, B. (2001). Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. *The American Journal of Cardiology, 88*, 196–198.

Rothermundt, M., Arolt, V., Fenker, J., Gutbrodt, H., Peters, M., & Kirchner, H. (2001). Different immune patterns in melancholic and non-melancholic major depression. *European Archives of Psychiatry and Clinical Neuroscience, 251*, 90–97.

Rudisch, B., & Nemeroff, C. B. (2003). Epidemiology of comorbid coronary artery disease and depression. *Biological Psychiatry, 54*, 227–240.

Rybakowski, J., Wykretowicz, A., Heymann-Szlachcinska, A., & Wysocki, H. (2006). Impairment of endothelial function in unipolar and bipolar depression. *Biological Psychiatry, 60*, 889–891.

Scherrer, J., Xian, H., Bucholz, K., Eisen, S., Lyons, M., Goldberg, J., Tsuang, M., & True, W. (2003). A twin study of depression symptoms, hypertension, and heart disease in middle-aged men. *Psychosomatic Medicine, 65*, 548–557.

Schlatter, J., Ortuño, F., & Cervera-Enguix, S. (2001). Differences in interleukins' patterns between dysthymia and major depression. *European Psychiatry, 16*, 317–319.

Schlatter, J., Ortuño, F., & Cervera-Enguix, S. (2004). Monocytic parameters in patients with dysthymia versus major depression. *Journal of Affective Disorders, 78*, 243–247.

Serretti, A., & Mandelli, L. (2010). Antidepressants and body weight: A comprehensive review and meta-analysis. *Journal of Clinical Psychiatry, 71*, 1259–1272.

Seldenrijk, A., Van Hout, H. P., Van Marwijk, H. W., De Groot, E., Gort, J., Rustemeijer, C., Diamant, M., & Penninx, B. W. (2011). Carotid atherosclerosis in depression and anxiety: Associations for age of depression onset. *World Journal of Biological Psychiatry, 12*, 549–558.

Sharma, A. N., Elased, K. M., Garrett, T. L., & Lucot, J. B. (2010). Neurobehavioral deficits in db/db diabetic mice. *Physiology and Behavior, 101*(3), 381–388.

Sherwood, A., Hinderliter, A. L., Watkins, L. L., Waugh, R. A., & Blumenthal, J. A. (2005). Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *Journal of the American College of Cardiology, 46*, 656–659.

Shimokawa, H. (1999). Primary endothelial dysfunction: Atherosclerosis. *Journal of Molecular and Cellular Cardiology, 31*, 23–37.

Shiotani, I., Sato, H., Kinjo, K., Nakatani, D., Mizuno, H., Ohnishi, Y., Hishida, E., Kijima, Y., & Hori, M. (2002). Depressive symptoms predict 12-month prognosis in elderly patients with acute myocardial infarction. *Journal of Cardiovascular Risk, 9*, 153–160.

Skurk, T., Alberti-Huber, C., Herder, C., & Hauner, H. (2007). Relationship between adipocyte size and adipokine expression and secretion. *Journal of Clinical Endocrinology and Metabolism, 92*, 1023–1033.

Smith, P. J., Blumenthal, J. A., Babyak, M. A., Doraiswamy, P. M., Hinderliter, A., Hoffman, B. M., Waugh, R., & Sherwood, A. (2009). Intima-media thickness and age of first depressive episode. *Biological Psychology, 80*, 361–364.

Smolderen, K. G., Spertus, J. A., Reid, K. J., Buchanan, D. M., Krumholz, H. M., Denollet, J., Vaccarino, V., & Chan, P. S. (2009). The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circulation Cardiovascular Quality and Outcomes, 2*, 328–337.

Snaphaan, L., van der Werf, S., Kanselaar, K., & de Leeuw, F. E. (2009). Post-stroke depressive symptoms are associated with post-stroke characteristics. *Cerebrovascular Diseases, 28*, 551–557.

Sorensen, C., Brandes, A., Hendricks, O., Thrane, J., Friis-Hasche, E., Haghfelt, T., & Bech, P. (2006). Depression assessed over 1-year survival in patients with myocardial infarction. *Acta Psychiatrica Scandinavica, 113*, 290–297.

Soszynski, D., Kozak, W., Rudolph, K., Conn, C. A., & Kluger, M. J. (1997). Open field-induced rise in body temperature and plasma IL-6 is mediated by beta-adrenoceptors in the brain. Ann. N.Y. *Academy of Sciences, 813*, 413–419.

Sotnikov, S. V., Stepaniuk, V. L., & Umriukhin, A. E. (2009). Influence of exposure to immobilisation stress on blood concentration of TNF alpha and IL-4 in rats active and passive in the open field test. *Zhurnal Vysshei Nervnoi Deiatelnosti Imeni I. P. Pavlova, 59*, 736–742.

Stuart, M., & Baune, B. T. (2012). Depression and type 2 diabetes: Inflammatory mechanisms of a psycho-neuroendocrine co-morbidity. *Neuroscience and Biobehavioral Reviews, 36*, 658–676.

Suarez, E., Krishnan, R., & Lewis, J. (2003). The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. *Psychosomatic Medicine, 65*, 362–368.

Surtees, P. G., Wainwright, N. W. J., Luben, R. N., Wareham, N. J., Bingham, S. A., & Khaw, K.-T. (2008). Depression and ischemic heart disease mortality: Evidence from the EPIC-Norfolk United Kingdom Prospective Cohort Study. *The American Journal of Psychiatry, 165*, 515–523.

Thaneerat, T., Tangwongchai, S., & Worakul, P. (2010). Prevalence of depression, hemoglobin A1C level, and associated factors in outpatients with type-2 diabetes. *Asian Biomedicine (Research Reviews and News), 3*, 383.

Thomas, A. J., Davis, S., Morris, C., Jackson, E., Harrison, R., & O'Brien, J. T. (2005). Increase in interleukin-1{beta} in late-life depression. *The American Journal of Psychiatry, 162*, 175–177.

Thombs, B. D., Bass, E. B., Ford, D. E., Stewart, K. J., Tsilidis, K. K., Patel, U., Fauerbach, J. A., Bush, D. E., & Ziegelstein, R. C. (2006). Prevalence of depression in survivors of acute myocardial infarction. *Journal of General Internal Medicine, 21*, 30–38.

van der Feltz-Cornelis, C. M., Nuyen, J., Stoop, C., Chan, J., Jacobson, A. M., Katon, W., Snoek, F., & Sartorius, N. (2010). Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: A systematic review and meta-analysis. *General Hospital Psychiatry, 32*, 380–395.

Varma, V., Yao-Borengasser, A., Rasouli, N., Nolen, G. T., Phanavanh, B., Starks, T., Gurley, C., Simpson, P., McGehee, R. E., Jr., Kern, P. A., & Peterson, C. A. (2009). Muscle inflammatory response and insulin resistance: Synergistic interaction between macrophages and fatty acids leads to impaired insulin action. *American Journal of Physiology, Endocrinology and Metabolism, 296*, E1300–E1310.

von Kanel, R., Kudielka, B. M., Hanebuth, D., Preckel, D., & Fischer, J. E. (2005). Different contribution of interleukin-6 and cortisol activity to total plasma fibrin concentration and to acute mental stress-induced fibrin formation. *Clinical Science (London), 109*, 61–67.

von Kanel, R., Kudielka, B. M., Preckel, D., Hanebuth, D., & Fischer, J. E. (2006). Delayed response and lack of habituation in plasma interleukin-6 to acute mental stress in men. *Brain, Behavior, and Immunity, 20*, 40–48.

Willner, P. (2005). Chronic Mild Stress (CMS) revisited: Consistency and behavioral-neurobiological concordance in the effects of CMS. *Neuropsychobiology, 52*, 90–110.

Winkley, K. (2008). The epidemiology of depression in diabetes. *European Diabetes Nursing, 5*, 91–96.

Wolf, J. M., Rohleder, N., Bierhaus, A., Nawroth, P. P., & Kirschbaum, C. (2009). Determinants of the NF-kappaB response to acute psychosocial stress in humans. *Brain, Behavior, and Immunity, 23*, 742–749.

Yang, J., Li, S., & Zheng, Y. (2009). Predictors of depression in Chinese communitydwelling people with type 2 diabetes. *Journal of Clinical Nursing, 18*, 1295–1304.

Genetics and Epigenetics in Cardiac Psychology

Richard Bayles and Assam El-Osta

Contents

Abstract

Precisely how regulated patterns of gene expression under the control of diverse signaling pathways underlie the homeostatic control of neuroanatomical aspects of cardiac function remains unclear. The autonomic nervous system is

R. Bayles (✉)
Laboratory for Vascular Translational Science, Inserm UMR-S1148, Paris, France
e-mail: richard.bayles@inserm.fr

A. El-Osta
Epigenetics in Human Health and Disease Laboratory, Epigenomics Profiling Facility, The Alfred Medical Research and Education Precinct, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Department of Pathology, The University of Melbourne, Parkville, VIC, Australia

Central Clinical School, Department of Medicine, Monash University, Melbourne, VIC, Australia
e-mail: assam.el-osta@bakeridi.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_40

distinguished by the sympathetic and parasympathetic nervous systems that are under the direct control of transcription factors that function as either activators or repressors of gene expression. While several regulatory determinants are known to coordinate the actions of activators and repressors, how these factors serve to maintain genes implicated in the neurocardiac axis is the subject of review. The discovery of regulatory complexes that serve as a functional linkage between DNA-bound transcription factors and altered chromatin structures indicates that posttranslational modifications of core histones connect aspects of neurocardiac gene function. The complexity of these regulators to alter noradrenaline transporter (NET) gene function is explored here. Recent evidence of chromatin-modifying enzymes regulating NET expression might apply to genes implicated in neurocardiology.

Keywords
Sympathetic nervous system • Noradrenaline transporter • Epigenetics • Chromatin modification

Introduction

To begin addressing the relationship between psychology and cardiovascular disease at the genetic level, the basic physiology at the interface between the brain and the heart must be considered. Arguably this places the sympathetic nervous system (SNS) at center stage. The initial focus of this chapter on the SNS and its primary synaptic regulator, the noradrenaline transporter (NET), will therefore serve as an example of a promising candidate gene important in both psychology and cardiovascular medicine. Later in the chapter, epigenetics will be introduced, and a number of other genes of relevance will be discussed, highlighting how the dynamic environment of gene regulation will be an important field in the future of psychocardiology.

Activation of the SNS in humans has been investigated in a variety of diseases, and there are a range of physiological indices of varying precision that are used by different groups to characterize sympathetic nerve function and function of the NET which is critical to the termination of the sympathetic neuronal signal. These methods used to interrogate the SNS in human subjects are discussed in more detail in other chapters. It is important to note, however, that in the context of genetic association studies, consideration of which phenotypic measurements may be feasible is of prime importance. On one hand, association of genotype with behavioral, emotional, or basic physiological symptoms of a disease can be of value. On the other hand, with the use of more precise indices of NET function, for example, association studies can not only be more informative but more powerful (ultimately measuring something more likely to be functionally related to the NET gene *SLC6a2*). Indices used in the past range from relatively unsophisticated measures of noradrenaline and its metabolites in blood and urine to radioisotope methods to determine uptake of noradrenaline across individual organs (Lambert and Grassi

2010). Using noradrenaline isotope dilution methodology during a steady-state infusion of tritiated NA, it is possible to assess the rate of spillover of noradrenaline to plasma (Esler et al. 1980). This technique, coupled with the simultaneous sampling of arterial and coronary sinus blood, provides the most precise analysis of cardiac sympathetic activity and also provides a reliable estimate of the efficiency of noradrenaline reuptake (Esler 1993). Physiological responses to pharmacological interventions and/or postural alterations can also be used to estimate NET function in patients (Gerson et al. 2002; Yoh et al. 2009; Yano et al. 1999). Of course a reduction in NET function could be due not only to a defect in the gene encoding NET but disruption of any molecule in the pathway that regulates the correct posttranscriptional processing and the spatial and temporal positioning of NET in the cell.

Evidence of Dysfunctional Sympathetic Nerve Activity and Noradrenaline Reuptake

Approximately one third of unmedicated patients with depression have elevated whole body and cardiac noradrenaline spillover to plasma (Barton et al. 2007). While such an increase in noradrenaline spillover to plasma may be due to an elevated rate of nerve firing, alternatively, a decrease in the efficiency of noradrenaline reuptake could also augment noradrenaline spillover to plasma. Reduced extraction of tritiated noradrenaline across the heart and diminished cardiac DHPG production in patients with MDD has been reported (Barton et al. 2007). Given the specificity of noradrenaline uptake by NET, the reduced uptake observed suggests a defect in NET function. Reduced cardiac uptake of tritium-labeled noradrenaline has also been demonstrated in response to healthy aging (Esler et al. 1995, 2002a), treatment with the selective NET inhibitor desipramine (Esler et al. 1991), in patients with panic disorder (Wilkinson et al. 1998; Alvarenga et al. 2006), pure autonomic failure (Meredith et al. 1991), congestive heart failure (Eisenhofer et al. 1996; Kaye et al. 1994), essential hypertension (Schlaich et al. 2004), and renal artery stenosis (Petersson et al. 2002). Comorbidities of those diseases described above are common and may involve a combination of shared and unique features of the disorders (Keller et al. 2000). Diagnostic precision is therefore critical in any association study given the specific nerve dysfunction that may be present in each disorder.

The NET Gene and Its Analysis

As a single gene product of central importance to a range of diseases, the NET gene has been the subject of many investigations searching for variation that may explain the phenotypic differences observed. Over 1,000 naturally occurring single nucleotide polymorphisms (SNPs) had been identified in the NET gene according to the SNP database of the National Center for Biotechnology Information

(NCBI; www.ncbi.nlm.nih.gov/snp), USA). Many of the coding SNPs were initially identified by Halushka et al. (1999) in a screen of candidate genes involved in blood pressure homeostasis (Halushka et al. 1999). As reviewed by Bonisch and Bruss (2006), 23 amino acid coding SNPs have been described. Of these, one is associated with orthostatic intolerance. Of the rest, none have been associated with disease, yet eight have been associated with a functional change in NET expression or activity (Bonisch and Bruss 2006). While the functional impairments associated with some amino acid coding variations have been established, the distribution and consequences of a large number of noncoding SNPs in the NET gene remain unclear.

SNPs located in the noncoding regulatory regions of genes are called regulatory SNPs. Any functional regulatory SNP in a gene can ultimately only either increase or decrease effective expression levels of functional protein; however, the precise regulatory mechanisms by which each SNP acts may only be relevant under specific physiological conditions. Regulatory SNPs may affect the regulation of gene transcription by the creation or removal of a transcription-factor binding site or a miRNA consensus sequence, a change in mRNA stability, or altered splicing (Prokunina and Alarcn-Riquelme 2004). Regulatory SNPs may also exert tissue-specific effects by changing consensus sequences for tissue-specific regulatory factors (Prokunina and Alarcn-Riquelme 2004). SNPs within a single gene such as the NET gene may therefore be associated with specific symptoms of NET dysfunction which may be disease specific or common to a range of diseases. This may explain why SNPs within the NET gene can be associated with some diseases and not others and highlights the importance of having detailed knowledge of the specific NET dysfunction present in each disorder. This detail is difficult to achieve with large cohorts.

A number of noncoding polymorphisms in the *SLC6a2* gene have been studied in a variety of association studies with results often conflicting or not reproducible in other cohorts (Ksiazek et al. 2006; Zill et al. 2002; Chang et al. 2007; Inoue et al. 2004, 2007; Ryu et al. 2004; Ono et al. 2003; Zolk et al. 2012). The inconsistent findings in many of these studies reflect the difficulty in genetic association studies in complex diseases. Differences in SNP distribution exist between different ethnicities, often making the confirmation of associations in different populations difficult. Another limitation is that patients often require extensive professional clinical characterization, which can limit the number of subjects participating in a study. A compromise is often required between having a high-powered study with large numbers and having clinically well-defined patient groups with large amounts of data per subject.

The most basic clinical data is critical in any association study of the *SLC6a2* gene. The incorporation of covariates to account for differences in age and gender, for example, is standard in genetic association studies but is of particular relevance in a study of the *SLC6a2* gene. There are differences and indeed functional relationships between these covariates and sympathetic nerve activity and in NET function (Schroeder et al. 2004). Changes in sympathetic activity and phenotypic reduction in NET function with aging have been demonstrated (Esler et al. 2002a, b).

Additionally, sympathetic activity is influenced by gender and BMI (Lambert et al. 2007a). Controlling for BMI in hypertension research is also complex given the links between hypertension and obesity (Eikelis and Esler 2005). Controlling for anxiety/personality type is also difficult in a background of comorbid conditions. An individual's emotions and state of arousal can have a significant impact on the sympathetic nervous system and associated laboratory measures (Lambert et al. 2007b). This represents another important consideration particularly relevant during patient recruitment, phenotyping, and sampling. Genes are not a static landscape. While the focus here is on the *SLC6a2* gene, many of these difficulties apply to other traditional candidate gene studies in psychiatric and cardiovascular research.

The complex interactions of the many phenotypic measures described above add to the difficulty in determining and achieving sufficient subject numbers for an association analysis. Even selecting a specific disease group based on standard diagnostic criteria often does not account for the complexity within a disease group. MDD, for example, is characterized by multiple subcategories of symptoms including affective, cognitive, and somatic symptoms, all of which may vary greatly between populations (Casper et al. 1985). In future association studies in MDD, it would be ideal to have greater subject numbers with detailed depression inventory scores *and* physiological data relating to gene function for all subjects. Sufficient numbers would allow for the analysis of MDD as a set of quantitative traits relating to severity of specific somatic and affective symptoms, allowing for more precise phenotyping and more informative genotype associations (Duncan et al. 2009; Hejjas et al. 2009). Although the simple measurement of blood pressure may facilitate diagnosis of hypertension, blood pressure is under highly complex control by multiple biological systems, making association with any one factor (even an important factor such as NET) difficult. It is clear therefore, for a number of reasons outlined above, that in-depth characterization of phenotype is critical before statistics are of any use. Unfortunately statistical power can ultimately be compromised in studies attempting to consider too many endophenotypes in small cohorts.

Statistical Analysis

A common limitation, and one which besets most previous NET SNP association studies, is the number of SNPs analyzed. In a recent study which attempted to replicate candidate gene associations in MDD in the large-scale genome-wide association data from the GAIN study (Boomsma et al. 2008), the *SLC6a2* gene was one of only four genes out of 57 to be supported as a statistically significant candidate gene (Bosker et al. 2011). The SNP coverage in this analysis was enriched by using HapMap data to address SNPs that were not present on the arrays used. Individual SNPs could not reach statistical significance for association with MDD when correcting for multiple comparisons. However, a significantly higher number of SNPs in the *SLC6a2* gene were associated with MDD than could be expected by chance, taking into account linkage disequilibrium (Bosker et al. 2011). No common

genetic association with MDD was found to be significant in a subsequent meta-analysis, however, leading to the conclusion that "common variants of intermediate or large effect do not have main effects in the genetic architecture of MDD" (Wray et al. 2012).

Through analysis of the common difficulties of association studies in complex diseases, it is clear why very few disease associations have been published to date with genetic factors such as SNPs in the *SLC6a2* gene and many other candidate genes. A common conclusion of many genotyping studies is that there was simply insufficient power to detect associations, and future studies should be performed with greater numbers or more clearly defined populations. This is often true. However, an alternative conclusion may be to question whether if an association were so hard to find and what value would it have with regard to diagnosis or treatment. This may be an important question to consider before embarking on such studies.

Epigenetics

The inherited biological component of complex diseases may involve much more than simple sequence variation (Mill and Petronis 2007), when it comes to transcriptional regulation. Epigenetic analyses may provide alternative mechanisms by which heritable gene expression can be explained. Epigenetics is the study of heritable changes in gene expression without a change in the sequence of DNA. Investigation of how the genomic expression profile can be modified by the environment in a long-term, intergenerational manner is an exciting prospect in the study of complex diseases.

Two main mechanisms are involved in alterations in gene expression, a change in DNA sequence or a change in local chromatin (Turner and Morris 2010). Chromatin is the complex of DNA, noncoding RNAs (ncRNAs), histones, and other proteins in the cell nucleus. The sum of the DNA methylation state, histone modifications, and chromatin structure together determine the efficiency with which a gene can be transcribed. There are four main mechanisms involved in heritable epigenetic regulation: DNA methylation, ncRNAs, chromatin remodeling, and histone modifications. All of these regulatory mechanisms, unlike DNA mutation, are reversible and dynamic processes (Henikoff and Matzke 1997); however it is important to note that even a transient environmental stimulus can have long-lasting intergenerational effects on chromatin state (Anway et al. 2005). In the transcriptionally inactive state, chromatin is tightly compacted (heterochromatin), restricting access of transcriptional machinery to genes. In the transcriptionally active state, chromatin opens up and allows transcriptional machinery to freely transcribe genes (euchromatin) (Tsankova et al. 2007).

There has been a lot of talk of gene-environment (GxE) interactions recently, in psychiatry in particular. Essentially it is epigenetics and dynamic chromatin regulation that are at the interface of GxE interactions. Perhaps the greatest difficulty in studying epigenetic regulation in psychocardiology lies in the inability to access the

tissues of interest in live human research subjects. An individual's genotype is the same in any given tissue, and any easily accessible tissue can be used to determine their entire genomic sequence. In the study of epigenetics, however, it is important to remember that DNA is not inherited; chromosomes are! Chromosomes consist of much more than DNA, and an individual's chromatin state is highly dynamic. The chromatin state of a gene can be cell or tissue specific, developmentally regulated, and influenced by a range of environmental factors (Mill and Petronis 2007; Grunau et al. 2000). It is therefore necessary to know both where and when a gene expression difference may be occurring and then whether the tissue of interest is accessible. The use of various peripheral tissues, cultured cell lines, and animal models has been both necessary and useful in identifying potentially important factors where human tissue has been unavailable (Akbarian and Nestler 2013).

There has been significant progress in the understanding of epigenetic processes involved in both psychiatric and cardiovascular diseases; however, there is still a serious lack of communication between these traditionally separate fields. Here some areas will be highlighted where epigenetics may begin to shed light on some of the associations and/or physiologically shared features of psychiatric and cardiovascular diseases.

NET

As discussed previously, functional variation of the NET gene sequence is rare, and evidence of NET dysfunction in the clinic is variable in terms of the specific location in the body and age of onset. Epigenetics may provide a mechanism by which long-term changes in NET gene expression can be controlled. Promoter hypermethylation was originally hypothesized to be a potential mechanism of transcriptional silencing of the *SLC6a2* gene in diseases with evidence of NET dysfunction (Esler et al. 2006, 2008). Analyses of the *SLC6a2* gene promoter in both human blood and mouse neurons did not associate DNA methylation with NET expression however (Bayles et al. 2013). Expression of NET was in fact correlated with histone modifications and binding of the transcriptional regulatory complex methyl-CpG binding protein 2 (MECP2) (Harikrishnan et al. 2010; Bayles et al. 2010, 2012) (see Fig. 1). In particular, depolarization of neurons in vitro was shown to induce an increase in NET expression (Harikrishnan et al. 2010; Habecker et al. 2006). This may be of particular relevance to diseases with evidence of NET dysfunction, since many of these diseases are also characterized by altered nerve firing patterns (Lambert et al. 2006, 2007a, 2008a, b, 2010). The potential clinical relevance of understanding the transcriptional mechanisms of the *SLC6a2* gene is high. Functional expression of NET in response to histone deacetylase (HDAC) inhibition is currently being exploited in the treatment of cancer, with preclinical evidence of enhanced drug delivery to tumors via increased NET expression (More et al. 2011; Jia et al. 2011). Characterizing the interplay between genetic variation, transcription factors, and chromatin regulation at the *SLC6a2* locus in the context of disease is an important area of future research.

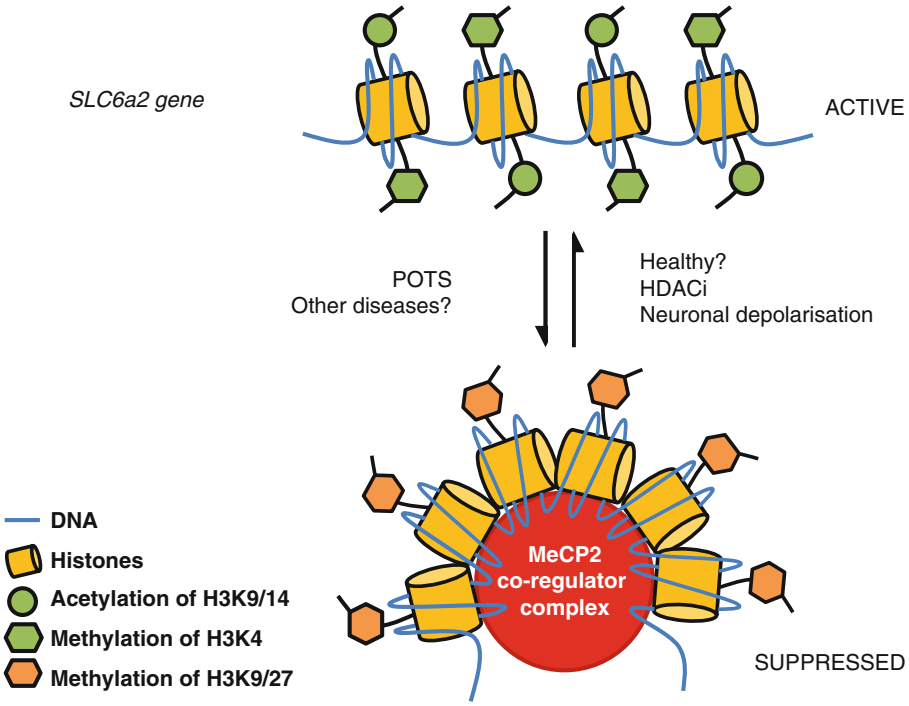


Fig. 1 Chromatin-based regulation of the *SLC6a2* promoter. Representation of the *SLC6a2* gene promoter associated with histone proteins in active and suppressed state. Activation of *SLC6a2* transcription in response to treatment with a histone deacetylase inhibitor (HDACi) or depolarization has been shown to involve the release of the transcription factor MECP2 and the modification of lysine residues of histone H3

BDNF

Brain-derived neurotrophic factor (BDNF) is one of the most well-studied genes in relation to psychiatric disease and is at the heart of the neurotrophic hypothesis of depression, which suggests that depression involves a loss of neuronal neurotrophic support (Duman and Li 2012). The action of BDNF is complex, depending on a balance between a precursor form (proBDNF) and the mature BDNF form, and the response depends on the location and levels of the appropriate receptors. However, a common finding in both human studies and in animal models of depression and anxiety is reduced levels of circulating mature BDNF (Montag et al. 2010). The critical role of BDNF has been established in vulnerability to stress, the development of depression, and antidepressant action in both humans and animal models (Tsankova et al. 2004, 2006; Fuchikami et al. 2009; Covington et al. 2011; Walker et al. 2013). For example, in humans, reduced BDNF overflow specifically from the brain has been associated with suicide risk in MDD (Dawood et al. 2007). In

agreement with this finding, reduced BDNF levels have been associated with increased BDNF gene promoter methylation in the postmortem brains of suicide completers (Keller et al. 2010).

The integrity of the BDNF gene appears to be clinically relevant at both the genetic and epigenetic level. Multiple studies have associated reduced levels of BDNF with altered DNA methylation, and many believe that BDNF gene methylation may be useful as a biomarker of depression (Song et al. 2014). The BDNF Val66Met polymorphism is a common coding variant in the BDNF gene, which has also been associated with many psychophysiological traits, including trait anxiety and sympathovagal balance (Montag et al. 2010; Yang et al. 2010). BDNF has been shown to be expressed in the nodose ganglion and released in the nucleus tractus solitarius through vagal afferents, directly enhancing autonomic regulation of cardiovascular function and especially the baroreflex response (Clark et al. 2011). The functional expression levels of BDNF in the nucleus tractus solitarius may be important, especially in relation to the changes in heart rate variability and cardiac baroreflex associated with anxiety (Sevoz-Couche et al. 2013). Centrally derived BDNF has been shown to be cardioprotective, preventing cardiac remodeling following myocardial infarction in mice (Okada et al. 2012). How this may relate to the poorer cardiovascular outcomes associated with depression post MI remains to be investigated.

DISC1

The disrupted-in-schizophrenia gene, *DISC1*, was originally associated with psychiatric illness in a family cohort in Scotland (St Clair et al. 1990). In addition to schizophrenia, *DISC1* has been associated with autism spectrum disorders and affective disorders (Kilpinen et al. 2008; Thomson et al. 2005). Like affective disorders, schizophrenia is associated with diabetes and ultimately with cardiovascular disease (Chien et al. 2009; Bresee et al. 2010). In fact the main cause of excess premature mortality in patients with schizophrenia has been determined to be cardiovascular disease (Hennekens et al. 2005). While much of the cardiovascular risk associated with schizophrenia and affective disorders is undoubtedly related to lifestyle, *DISC1* is a candidate gene well placed to begin to explain many of these associations and comorbidities in a biological context.

At the genetic level, *DISC1* exists on the q arm of chromosome 1 in a locus also associated with type 2 diabetes (Lin and Shuldiner 2010). At the expression level, the protein product of the *DISC1* gene is important for normal neural development (Niwa et al. 2010). In fact when expression of *DISC1* was disrupted in mice, a depression-like behavior and reduced cognitive function were observed (Niwa et al. 2010). In a study of primary vascular endothelial cells under high or low glucose conditions, histone acetylation typically associated with transcriptional activation was found to be reduced at the *DISC1* gene under hyperglycemic conditions (Pirola et al. 2011). This study provides the intriguing possibility of how an environmental stimulus (hyperglycemia) associated with metabolic disease

may directly lead to the disruption of *DISC1* in the brain, for example, leading to predicted/associated chronic psychological phenotypes (Pirola et al. 2010). While much work would be required to validate such a hypothesis, this is an example of how it is hoped that an understanding of epigenetic regulation of transcription may begin to explain associations determined at the epidemiological level.

TH

Tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine synthesis, is known to have a tissue-specific expression profile strongly associated with the methylation status of its gene promoter (Aranyi et al. 2005). Promoter methylation of the TH gene has also been shown to be directly modifiable in specific brain regions in response to different levels of dietary lipid intake (Vucetic et al. 2012). Interestingly, disruption of *DISC1*, in combination with stress, leads to long-term changes in TH expression, related to changes in DNA methylation of the TH gene, which are reversible with a glucocorticoid receptor antagonist (Niwa et al. 2013). The clinical relevance of such animal study findings remains to be established.

GR

The glucocorticoid receptor (GR) has long been studied in relation to its role in the hypothalamic-pituitary-adrenal stress axis. Glucocorticoid involvement in the regulation of sympathetic nerves has also long been established, including modulation of TH expression (Stachowiak et al. 1988; Brown and Fisher 1986). The gene encoding the GR was one of the first examples of a gene being epigenetically modified in response to stress, with those modifications and associated behavioral alterations being inherited by subsequent generations (Weaver et al. 2004). These findings in rats were ultimately translated to humans, where in postmortem brain samples, altered GR gene methylation and expression was correlated with childhood abuse (McGowan et al. 2009). Other studies attempting to correlate MDD or PTSD with altered GR gene methylation in a peripheral tissue source have also met with some success (Carvalho et al. 2014; Labonte et al. 2014). The lasting influence of stress on glucocorticoid signaling could potentially play an important and sustained role in the regulation of the autonomic nervous system.

5-HTT

The serotonin (5-HT) transporter (5-HTT) remains the primary target of first-line treatments in affective disorders, and both the genetic and epigenetic regulation of the 5-HTT gene *SLC6a4* are important. There are a number of common variations in the sequence of the 5-HTT gene promoter, including long and short forms, with and/or without other single nucleotide polymorphisms. There is little agreement

however on the significance of the many associations between the serotonin transporter gene-linked polymorphic region (5HTTLPR) and stress or affective disorders however (Karg et al. 2011). Serotonergic neurotransmission is highly complex, and dissecting the precise functional role of 5HTTLPR variants in humans is difficult. Analysis of serotonin turnover specifically in the brain revealed higher turnover in patients with MDD compared to healthy controls, and higher serotonin turnover was also associated with the short allele of the 5HTTLPR (Barton et al. 2008). Further studies are required to resolve the relevant mechanisms involved at the brain region specific, neuronal, and synaptic level.

Recent studies have been successful in identifying differences in 5-HTT mRNA expression in peripheral blood samples of healthy and diseased populations. In separate analyses of patients with depression or bipolar disorder, differences in 5-HTT mRNA expression have been associated with differences in *SLC6a4* promoter methylation (Sugawara et al. 2011; Wankerl et al. 2014). Importantly, the study of twins discordant for bipolar disorder provided strong evidence for differences in *SLC6a2* methylation being related to the environmental factors rather than genetic background (Sugawara et al. 2011). It is hoped that findings of such changes at the level of chromatin regulation in peripheral tissues will correlate with systemic differences in serotonergic neurotransmission, providing biomarkers for affective disorders. Little is known about the importance of 5-HTT genotype and expression in relation to cardiovascular homeostasis; however, serotonergic signaling has been shown to be an important mediator of anxiety-induced changes in heart rate variability and the sensitivity of the cardiac baroreflex response (Sevoz-Couche et al. 2013).

Conclusions

Mapping a new route to understand the regulatory pathways that underlie the neurocardiovascular axis is a challenge because of the complexity of transcription factors and proteins that alter chromatin structure and gene function. While the *SLC6a2* gene is implicated in disease with evidence of NET dysfunction specified by histone tail modification, deconvoluting how the epigenome regulates patterns of gene expression remains complicated. With more than 100 histone modifications implicated in transcription, repair, replication, and genome stability, the challenge is now to understand their specific combinatorial functions. Whereas determining specific biological function given the expansive size of the human genome remains a formidable task, genome-wide mapping approaches provide new opportunities to unravel the importance of regulatory networks. In one attempt to characterize functional elements in the human genome, the National Human Genome Research Institute (NHGRI) launched a public research consortium named ENCODE (Encyclopedia of DNA Elements) to identify functional elements in the human genome sequence (Anonymous 2004). Since its launch in September 2003, the ENCODE consortium has discovered many new transcription-factor binding site motifs (Yip et al. 2012; Neph et al. 2012), integrating chromatin patterns (Thurman et al. 2012;

Wang et al. 2012a), as well as the importance of intergenic regions and gene definitions (Djebali et al. 2012; Harrow et al. 2012). In short time, these and many other studies have shown that patterns of gene expression are mapped by histone modifications, transcription factor binding, and DNA methylation, including noncoding RNA characterization (Banfai et al. 2012; Wang et al. 2012b). While big studies such as these have contributed some unexpected findings in genome biology, they have also stimulated new areas of research (Rafehi et al. 2014). Open data from large-scale epigenome sequencing projects remain a critical resource, and early access allows researchers to interconnect clinical and preclinical observations with informative genomics to unravel the complexity of the epigenetic-psychocardiovascular axis.

References

Akbarian, S., & Nestler, E. J. (2013). Epigenetic mechanisms in psychiatry. *Neuropsychopharmacology, 38*(1), 1–2.

Alvarenga, M. E., Richards, J. C., Lambert, G., & Esler, M. D. (2006). Psychophysiological mechanisms in panic disorder: A correlative analysis of noradrenaline spillover, neuronal noradrenaline reuptake, power spectral analysis of heart rate variability, and psychological variables. *Psychosomatic Medicine, 68*(1), 8–16.

Anonymous. (2004). The ENCODE (ENCyclopedia Of DNA Elements) project. *Science, 306* (5696):636–640.

Anway, M. D., Cupp, A. S., Uzumcu, M., & Skinner, M. K. (2005). Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science, 308*(5727), 1466–1469.

Aranyi, T., et al. (2005). The tissue-specific methylation of the human tyrosine hydroxylase gene reveals new regulatory elements in the first exon. *Journal of Neurochemistry, 94*(1), 129–139.

Banfai, B., et al. (2012). Long noncoding RNAs are rarely translated in two human cell lines. *Genome Research, 22*(9), 1646–1657.

Barton, D. A., et al. (2007). Sympathetic activity in major depressive disorder: Identifying those at increased cardiac risk?. *Journal of Hypertension, 25*(10), 2117–2124.

Barton, D. A., et al. (2008). Elevated brain serotonin turnover in patients with depression: Effect of genotype and therapy. *Archives of General Psychiatry, 65*(1), 38–46.

Bayles, R., Baker, E., Eikelis, N., El-Osta, A., & Lambert, G. (2010). Histone modifications regulate the norepinephrine transporter gene. *Cell Cycle, 9*(22), 4600–4601.

Bayles, R., et al. (2012). Epigenetic modification of the norepinephrine transporter gene in postural tachycardia syndrome. *Arteriosclerosis, Thrombosis, and Vascular Biology, 32*(8), 1910–1916.

Bayles, R., et al. (2013). Methylation of the SLC6a2 gene promoter in major depression and panic disorder. *PLoS One, 8*(12), e83223.

Bonisch, H., & Bruss, M. (2006). The norepinephrine transporter in physiology and disease. *Handbook of Experimental Pharmacology, 175*, 485–524.

Boomsma, D. I., et al. (2008). Genome-wide association of major depression: Description of samples for the GAIN Major Depressive Disorder Study: NTR and NESDA biobank projects. *European Journal of Human Genetics: EJHG, 16*(3), 335–342.

Bosker, F. J., et al. (2011). Poor replication of candidate genes for major depressive disorder using genome-wide association data. *Molecular Psychiatry, 16*(5), 516–532.

Bresee, L. C., Majumdar, S. R., Patten, S. B., & Johnson, J. A. (2010). Prevalence of cardiovascular risk factors and disease in people with schizophrenia: A population-based study. *Schizophrenia Research, 117*(1), 75–82.

Brown, M. R., & Fisher, L. A. (1986). Glucocorticoid suppression of the sympathetic nervous system and adrenal medulla. *Life Sciences, 39*(11), 1003–1012.

Carvalho, L. A., et al. (2014). Inflammatory activation is associated with a reduced glucocorticoid receptor alpha/beta expression ratio in monocytes of inpatients with melancholic major depressive disorder. *Translational Psychiatry, 4*, e344.

Casper, R. C., et al. (1985). Somatic symptoms in primary affective disorder. Presence and relationship to the classification of depression. *Archives of General Psychiatry, 42*(11), 1098–1104.

Chang, C. C., et al. (2007). Lack of association between the norepinephrine transporter gene and major depression in a Han Chinese population. *Journal of Psychiatry and Neuroscience, 32*(2), 121–128.

Chien, I. C., et al. (2009). Prevalence of diabetes in patients with schizophrenia in Taiwan: A population-based National Health Insurance study. *Schizophrenia Research, 111*(1-3), 17–22.

Clark, C. G., Hasser, E. M., Kunze, D. L., Katz, D. M., & Kline, D. D. (2011). Endogenous brain-derived neurotrophic factor in the nucleus tractus solitarius tonically regulates synaptic and autonomic function.. *The Journal of Neuroscience, 31*(34), 12318–12329.

Covington, H. E., 3rd, et al. (2011). A role for repressive histone methylation in cocaine-induced vulnerability to stress. *Neuron, 71*(4), 656–670.

Dawood, T., et al. (2007). Reduced overflow of BDNF from the brain is linked with suicide risk in depressive illness. *Molecular Psychiatry, 12*(11), 981–983.

Djebali, S., et al. (2012). Landscape of transcription in human cells. *Nature, 489*(7414), 101–108.

Duman, R. S., & Li, N. (2012). A neurotrophic hypothesis of depression: Role of synaptogenesis in the actions of NMDA receptor antagonists. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 367*(1601), 2475–2484.

Duncan, L. E., Hutchison, K. E., Carey, G., & Craighead, W. E. (2009). Variation in brain-derived neurotrophic factor (BDNF) gene is associated with symptoms of depression. *Journal of Affective Disorders, 115*(1–2), 215–219.

Eikelis, N., & Esler, M. (2005). The neurobiology of human obesity. *Experimental Physiology, 90*(5), 673–682.

Eisenhofer, G., et al. (1996). Cardiac sympathetic nerve function in congestive heart failure. *Circulation, 93*(9), 1667–1676.

Esler, M. (1993). Clinical application of noradrenaline spillover methodology: Delineation of regional human sympathetic nervous responses. *Pharmacology & Toxicology, 73*(5), 243–253.

Esler, M., et al. (1980). Determination of noradrenaline uptake, spillover to plasma and plasma concentration in patients with essential hypertension. *Clinical Science (London), 59*(Suppl 6), 311s–313s. in eng.

Esler, M. D., et al. (1991). Effects of desipramine on sympathetic nerve firing and norepinephrine spillover to plasma in humans. *The American Journal of Physiology, 260*(4 Pt 2), R817–R823.

Esler, M. D., et al. (1995). Aging effects on human sympathetic neuronal function. *The American Journal of Physiology, 268*(1 Pt 2), R278–R285.

Esler, M., et al. (2002a). Influence of ageing on the sympathetic nervous system and adrenal medulla at rest and during stress. *Biogerontology, 3*(1–2), 45–49.

Esler, M., et al. (2002b). The influence of aging on the human sympathetic nervous system and brain norepinephrine turnover. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology, 282*(3), R909–R916.

Esler, M., et al. (2006). The neuronal noradrenaline transporter, anxiety and cardiovascular disease. *Journal of Psychopharmacology, 20*(4 Suppl), 60–66.

Esler, M., et al. (2008). Human sympathetic nerve biology: Parallel influences of stress and epigenetics in essential hypertension and panic disorder. *Annals of the New York Academy of Sciences, 1148*, 338–348.

Fuchikami, M., Morinobu, S., Kurata, A., Yamamoto, S., & Yamawaki, S. (2009). Single immobilization stress differentially alters the expression profile of transcripts of the brain-

derived neurotrophic factor (BDNF) gene and histone acetylation at its promoters in the rat hippocampus. *International Journal of Neuropsychopharmacology, 12*(1), 73–82.

Gerson, M. C., et al. (2002). Carvedilol improves left ventricular function in heart failure patients with idiopathic dilated cardiomyopathy and a wide range of sympathetic nervous system function as measured by iodine 123 metaiodobenzylguanidine. *Journal of Nuclear Cardiology, 9*(6), 608–615.

Grunau, C., Hindermann, W., & Rosenthal, A. (2000). Large-scale methylation analysis of human genomic DNA reveals tissue-specific differences between the methylation profiles of genes and pseudogenes. *Human Molecular Genetics, 9*(18), 2651–2663.

Habecker, B. A., Willison, B. D., Shi, X., & Woodward, W. R. (2006). Chronic depolarization stimulates norepinephrine transporter expression via catecholamines. *Journal of Neurochemistry, 97*(4), 1044–1051.

Halushka, M. K., et al. (1999). Patterns of single-nucleotide polymorphisms in candidate genes for blood-pressure homeostasis. *Nature Genetics, 22*(3), 239–247.

Harikrishnan, K. N., et al. (2010). Alleviating transcriptional inhibition of the norepinephrine slc6a2 transporter gene in depolarized neurons. *The Journal of Neuroscience, 30*(4), 1494–1501.

Harrow, J., et al. (2012). GENCODE: The reference human genome annotation for the ENCODE project. *Genome Research, 22*(9), 1760–1774.

Hejjas, K., et al. (2009). Association between depression and the Gln460Arg polymorphism of P2RX7 gene: A dimensional approach. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 150B*(2), 295–299.

Henikoff, S., & Matzke, M. A. (1997). Exploring and explaining epigenetic effects. *Trends in Genetics, 13*(8), 293–295.

Hennekens, C. H., Hennekens, A. R., Hollar, D., & Casey, D. E. (2005). Schizophrenia and increased risks of cardiovascular disease. *American Heart Journal, 150*(6), 1115–1121.

Inoue, K., Itoh, K., Yoshida, K., Shimizu, T., & Suzuki, T. (2004). Positive association between T-182C polymorphism in the norepinephrine transporter gene and susceptibility to major depressive disorder in a japanese population. *Neuropsychobiology, 50*(4), 301–304.

Inoue, K., et al. (2007). No association of the G1287A polymorphism in the norepinephrine transporter gene and susceptibility to major depressive disorder in a japanese population. *Biological and Pharmaceutical Bulletin, 30*(10), 1996–1998.

Jia, Z. Y., et al. (2011). In vitro and in vivo studies of adenovirus-mediated human norepinephrine transporter gene transduction to hepatocellular carcinoma. *Cancer Gene Therapy, 18*(3), 196–205.

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry, 68*(5), 444–454.

Kaye, D. M., et al. (1994). Neurochemical evidence of cardiac sympathetic activation and increased central nervous system norepinephrine turnover in severe congestive heart failure. *Journal of the American College of Cardiology, 23*(3), 570–578.

Keller, J., et al. (2000). Neuropsychological differentiation of depression and anxiety. *Journal of Abnormal Psychology, 109*(1), 3–10.

Keller, S., et al. (2010). Increased BDNF promoter methylation in the Wernicke area of suicide subjects. *Archives of General Psychiatry, 67*(3), 258–267.

Kilpinen, H., et al. (2008). Association of DISC1 with autism and Asperger syndrome. *Molecular Psychiatry, 13*(2), 187–196.

Ksiazek, P., Buraczynska, K., & Buraczynska, M. (2006). Norepinephrine transporter gene (NET) polymorphism in patients with type 2 diabetes. *Kidney and Blood Pressure Research, 29*(6), 338–343.

Labonte, B., Azoulay, N., Yerko, V., Turecki, G., & Brunet, A. (2014). Epigenetic modulation of glucocorticoid receptors in posttraumatic stress disorder. *Translational Psychiatry, 4*, e368.

Lambert, G., & Grassi, G. (2010). Indices of sympathetic activity and the paradox of chromogranin A. *Journal of Hypertension, 28*(4), 676–678.

Lambert, E., et al. (2006). Single-unit analysis of sympathetic nervous discharges in patients with panic disorder. *The Journal of Physiology, 570*(Pt 3), 637–643.
Lambert, E., et al. (2007a). Gender differences in sympathetic nervous activity: Influence of body mass and blood pressure. *Journal of Hypertension, 25*(7), 1411–1419.
Lambert, E., et al. (2007b). Psychological stress and the development of heart disease. *Current Psychiatry Reviews, 3*(4), 252–258.
Lambert, E., et al. (2008a). Single-unit sympathetic discharge pattern in pathological conditions associated with elevated cardiovascular risk. *Clinical and Experimental Pharmacology and Physiology, 35*(4), 503–507.
Lambert, E., et al. (2008b). Altered sympathetic nervous reactivity and norepinephrine transporter expression in patients with postural tachycardia syndrome. *Circulation. Arrhythmia and Electrophysiology, 1*(2), 103–109.
Lambert, E., et al. (2010). Association between the sympathetic firing pattern and anxiety level in patients with the metabolic syndrome and elevated blood pressure. *Journal of Hypertension, 28*(3), 543–550.
Lin, P. I., & Shuldiner, A. R. (2010). Rethinking the genetic basis for comorbidity of schizophrenia and type 2 diabetes. *Schizophrenia Research, 123*(2–3), 234–243.
McGowan, P. O., et al. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience, 12*(3), 342–348.
Meredith, I. T., et al. (1991). Biochemical evidence of sympathetic denervation of the heart in pure autonomic failure. *Clinical Autonomic Research, 1*(3), 187–194.
Mill, J., & Petronis, A. (2007). Molecular studies of major depressive disorder: The epigenetic perspective. *Molecular Psychiatry, 12*(9), 799–814.
Montag, C., Basten, U., Stelzel, C., Fiebach, C. J., & Reuter, M. (2010). The BDNF Val66Met polymorphism and anxiety: Support for animal knock-in studies from a genetic association study in humans. *Psychiatry Research, 179*(1), 86–90.
More, S. S., et al. (2011). Vorinostat increases expression of functional norepinephrine transporter in neuroblastoma in vitro and in vivo model systems. *Clinical Cancer Research, 17*(8), 2339–2349.
Neph, S., et al. (2012). An expansive human regulatory lexicon encoded in transcription factor footprints. *Nature, 489*(7414), 83–90.
Niwa, M., et al. (2010). Knockdown of DISC1 by in utero gene transfer disturbs postnatal dopaminergic maturation in the frontal cortex and leads to adult behavioral deficits. *Neuron, 65*(4), 480–489.
Niwa, M., et al. (2013). Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids. *Science, 339*(6117), 335–339.
Okada, S., et al. (2012). Brain-derived neurotrophic factor protects against cardiac dysfunction after myocardial infarction via a central nervous system-mediated pathway. *Arteriosclerosis, Thrombosis, and Vascular Biology, 32*(8), 1902–1909.
Ono, K., et al. (2003). Epidemiological evidence of an association between SLC6A2 gene polymorphism and hypertension. *Hypertension Research, 26*(9), 685–689.
Petersson, M. J., et al. (2002). Increased cardiac sympathetic drive in renovascular hypertension. *Journal of Hypertension, 20*(6), 1181–1187.
Pirola, L., Balcerczyk, A., Okabe, J., & El-Osta, A. (2010). Epigenetic phenomena linked to diabetic complications. *Nature Reviews Endrocrinology, 6*(12), 665–675.
Pirola, L., et al. (2011). Genome-wide analysis distinguishes hyperglycemia regulated epigenetic signatures of primary vascular cells. *Genome Research, 21*(10), 1601–1615.
Prokunina, L., & Alarcn-Riquelme, M. E. (2004). Regulatory SNPs in complex diseases: Their identification and functional validation. *Expert Reviews in Molecular Medicine, 2004*, 1–15.
Rafehi, H., et al. (2014). Vascular histone deacetylation by pharmacological HDAC inhibition. *Genome Research, 24*(8), 1271–1284.
Ryu, S. H., et al. (2004). Association between norepinephrine transporter gene polymorphism and major depression. *Neuropsychobiology, 49*(4), 174–177.

Schlaich, M. P., et al. (2004). Sympathetic augmentation in hypertension: Role of nerve firing, norepinephrine reuptake, and angiotensin neuromodulation. *Hypertension, 43*(2), 169–175.

Schroeder, C., et al. (2004). Phenotypical evidence for a gender difference in cardiac norepinephrine transporter function. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology, 286*(5), R851–R856.

Sevoz-Couche, C., et al. (2013). Involvement of the dorsomedial hypothalamus and the nucleus tractus solitarii in chronic cardiovascular changes associated with anxiety in rats. *Journal of Physiology, 591*(Pt 7), 1871–1887.

Song, Y., et al. (2014). Altered DNA methylation status of human brain derived neurotrophic factor gene could be useful as biomarker of depression. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 165*(4), 357–364.

St Clair, D., et al. (1990). Association within a family of a balanced autosomal translocation with major mental illness. *Lancet, 336*(8706), 13–16.

Stachowiak, M. K., Rigual, R. J., Lee, P. H., Viveros, O. H., & Hong, J. S. (1988). Regulation of tyrosine hydroxylase and phenylethanolamine N-methyltransferase mRNA levels in the sympathoadrenal system by the pituitary-adrenocortical axis. *Brain Research, 427*(3), 275–286.

Sugawara, H., et al. (2011). Hypermethylation of serotonin transporter gene in bipolar disorder detected by epigenome analysis of discordant monozygotic twins. *Translational Psychiatry, 1*, e24.

Thomson, P. A., et al. (2005). Association between the TRAX/DISC locus and both bipolar disorder and schizophrenia in the Scottish population. *Molecular Psychiatry, 10*(7), 657–668, 616.

Thurman, R. E., et al. (2012). The accessible chromatin landscape of the human genome. *Nature, 489*(7414), 75–82.

Tsankova, N. M., Kumar, A., & Nestler, E. J. (2004). Histone modifications at gene promoter regions in rat hippocampus after acute and chronic electroconvulsive seizures. *The Journal of Neuroscience, 24*(24), 5603–5610.

Tsankova, N. M., et al. (2006). Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nature Neuroscience, 9*(4), 519–525.

Tsankova, N., Renthal, W., Kumar, A., & Nestler, E. J. (2007). Epigenetic regulation in psychiatric disorders. *Nature Review Neuroscience, 8*(5), 355–367.

Turner, A. M., & Morris, K. V. (2010). Controlling transcription with noncoding RNAs in mammalian cells. *Biotechniques, 48*(6), ix–xvi.

Vucetic, Z., Carlin, J. L., Totoki, K., & Reyes, T. M. (2012). Epigenetic dysregulation of the dopamine system in diet-induced obesity. *Journal of Neurochemistry, 120*(6), 891–898.

Walker, M. P., LaFerla, F. M., Oddo, S. S., & Brewer, G. J. (2013). Reversible epigenetic histone modifications and Bdnf expression in neurons with aging and from a mouse model of Alzheimer's disease. *Age (Dordrecht, Netherlands), 35*(3), 519–531.

Wang, J., et al. (2012a). Sequence features and chromatin structure around the genomic regions bound by 119 human transcription factors. *Genome Research, 22*(9), 1798–1812.

Wang, H., et al. (2012b). Widespread plasticity in CTCF occupancy linked to DNA methylation. *Genome Research, 22*(9), 1680–1688.

Wankerl, M., et al. (2014). Effects of genetic and early environmental risk factors for depression on serotonin transporter expression and methylation profiles. *Translational Psychiatry, 4*, e402.

Weaver, I. C., et al. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7*(8), 847–854.

Wilkinson, D. J., et al. (1998). Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. *Archives of General Psychiatry, 55*(6), 511–520.

Wray, N. R., et al. (2012). Genome-wide association study of major depressive disorder: New results, meta-analysis, and lessons learned. *Molecular Psychiatry, 17*(1), 36–48.

Yang, A. C., et al. (2010). BDNF Val66Met polymorphism alters sympathovagal balance in healthy subjects. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 153B*(5), 1024–1030.

Yano, T., Yamabe, H., & Yokoyama, M. (1999). Washout rate of 123I-metaiodobenzylguanidine increased by posture change or exercise in normal volunteers. *Annals of Nuclear Medicine, 13* (2), 89–93.

Yip, K. Y., et al. (2012). Classification of human genomic regions based on experimentally determined binding sites of more than 100 transcription-related factors. *Genome Biology, 13* (9), R48.

Yoh, M., et al. (2009). Resting muscle sympathetic nerve activity, cardiac metaiodobenzylguanidine uptake, and exercise tolerance in patients with left ventricular dysfunction. *Journal of Nuclear Cardiology, 16*(2), 244–250.

Zill, P., et al. (2002). Identification of a naturally occurring polymorphism in the promoter region of the norepinephrine transporter and analysis in major depression. *Neuropsychopharmacology, 26*(4), 489–493.

Zolk, O., Ott, C., Fromm, M. F., & Schmieder, R. E. (2012). Effect of the rs168924 single-nucleotide polymorphism in the SLC6A2 catecholamine transporter gene on blood pressure in caucasians. *Journal of Clinical Hypertension (Greenwich, Conn.), 14*(5), 293–298.

Gene-Environment Interactions, Stress, and Depression

Sarah Cohen-Woods and Kaitlin Nicole Harkess

Contents

Abstract

Depression is one of the most prevalent disorders worldwide, with high comorbidity with cardiovascular disease (CVD). Despite significant heritability, robust genetic associations are yet to be identified in depression. Multiple factors are accountable for this, including that genetic studies have not widely considered environmental factors, despite their established association with depression. One such factor is stress, a robust risk factor for depression; many genetic studies have failed to include nurture in their research into depression. The first gene-environment interaction (GxE) study in depression was published in 2003, reporting a significant interaction between a functional polymorphism in the serotonin transporter gene (5-HTTLPR) and recent

S. Cohen-Woods (✉)
Matthew Flinders Fellow, School of Psychology, Flinders University, Adelaide, SA, Australia
e-mail: sarah.cohenwoods@flinders.edu.au

K.N. Harkess
School of Psychology, University of Adelaide, Adelaide, SA, Australia
e-mail: Kaitlin.harkess@adelaide.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_41

stressors to predict depression. Many studies aimed to replicate this finding, as well as investigate other candidate genes (i.e., *CRHR1*, *GR*, *FKBP5*, *BDNF*). Initially, findings appeared not to reach a clear consensus; however, a closer analysis of the literature has shown that there are consistencies when specific methodological aspects are considered (i.e., timing of stressors). While there are some exciting and strongly evidenced findings, GxE research continues to face some significant challenges. This includes recognition of the importance of subtle method differences and also sample size. Samples are relatively small due to the time required to ascertain high-quality environmental data relative to standard genetic association studies, compromising power. Ascertaining large samples must therefore be made a priority in GxE research to enable further discoveries. GxE studies in depression have the potential to inform disease mechanisms that may be relevant to CVD, informing future CVD-depression research.

Keywords

Gene-environment interaction • Depression • Stress • Childhood maltreatment • Psychiatric genetics • Serotonin transporter • HPA axis • Brain-derived neurotrophic factor (BDNF)

Introduction

Depression is one of the most prevalent disorders worldwide, with estimates of between 10 % and 17 % of the general population suffering during the course of their lifetime (Kessler et al. 1994). The World Health Organization (WHO) predicts prevalence to increase, becoming the leading cause of disability in developed nations by 2030 (World Health Organization 2008). Depression impairs both cognitive and social functioning, negatively impacting the quality of life of sufferers (Lepine and Briley 2011). Associated with elevated rates of morbidity and mortality, it is an established risk factor for cardiac mortality (Barth et al. 2004) functioning in a dose-response manner (Lesperance et al. 2002). To better understand how depression may be related to cardiac mortality, the pathways to depression must be better understood. While heritability has been established to have a significant role in influencing susceptibility to depression, the environment, such as exposure to stressors, has also been implicated. In the 1990s and early 2000s, much attention was focused on investigating genetic risk factors in depression; however, more recently, gene-environment interaction (GxE) studies have gained traction. These aim to investigate how genetic profiles predict vulnerability to negative effects of an environmental factor, such as stress, on the risk of developing depression. In this chapter, the current research in this emerging field is discussed.

Heritability

Depression is moderately to highly heritable, with twin studies estimating heritability between 30 % and 80 % (e.g., McGuffin et al. 1996; Sullivan et al. 2000). A meta-analysis of five twin studies (four population based) indicates genetic factors account for 37 % of variance, with unique environment explaining 63 % (Sullivan et al. 2000). Higher heritability estimates are reported when diagnostic unreliability is taken into account, as measurement error inflates unique environment estimates, and more severe depression also yields heritability estimates in the upper range (McGuffin et al., 1996). Given the heritability, substantial time and resources have been dedicated to investigating genetic risk factors in depression. However, non-shared environmental effects remain substantial and important. Indeed, in the last decade, there have been multiple genome-wide association studies investigating depression, with little success in identifying robust and replicable risk genes for depression (Cohen-Woods et al. 2013). With this rise in availability of broad molecular genetic data using genome-wide analyses, it has become possible to assess genetic contribution of the genetic variation measured in non-related individuals. This has led to a concept named the "heritability gap": heritability estimates from twin data exceed estimates derived from the molecular data by about 16 % in depression (Uher 2014). This could be attributed to many reasons including the type of genetic variation being studied (common vs. rare), allelic heterogeneity (same gene but different alleles within the gene having the same functional impact), epigenetic variation (not detected in genome-wide studies), and the potential of significant influence of the environment on genetic risk factors, i.e., gene-environment interactions (Cohen-Woods et al. 2013; Uher 2014).

Environment

Unique environmental factors, as well as genetic factors, are important in variance observed in depression. Stressful events have been implicated as risk factors in the etiology of depression (Kendler et al. 1999), including childhood maltreatment (e.g., Widom et al. 2007), family discord (e.g., Gilman et al. 2003), poverty (e.g., Yoshikawa et al. 2012), and stressful life events (e.g., Kendler et al. 1999). The dynamic nature of lives and environments offer researchers little control, and so more "controlled" stress models are often investigated in animals. This includes many models, some with artificial stressors imposed (e.g., maternal separation, chronic mild stress) and others capitalizing on "natural" variation such as differing maternal affection between rats (see Ladd et al. 2000; Meaney and Szyf 2005; Weaver et al. 2004). Differences in licking and grooming rates of pups have been associated with less fearful and stress-based HPA responses and reversible variation in DNA methylation patterns, both persisting into adulthood (Meaney and Szyf 2005). In humans, altered C-reactive protein levels in the peripheral blood have

been reported in individuals that have experienced stressful events and/or suffered depression (Danese et al. 2008). This is particularly exacerbated in individuals experiencing a current depressive episode with a history of stressors in childhood (Danese et al. 2008). Such findings emphasize the influential role of early-life environment and potential impact across the life-span.

Gene-Environment Interactions and Depression

While significant, environmental effects do not impact all individuals in the same way. Stress-diathesis and vulnerability-stress models suggest some individuals are more susceptible to negative effects of stress than others: psychiatric symptoms develop as a result of personal vulnerability (e.g., genetics) and environmental stressors (e.g., childhood abuse) (Myin-Germeys et al. 2003). Gene-environment interactions fall within this, hypothesizing a causal mechanism where an individual's genetic profile mediates the effects of (or their sensitivity to) environmental exposures, impacting on the development of behavior or illness such as depression (Rutter et al. 2006). Gene-environment correlations differ to interactions, describing the probability of an environmental exposure and not the effects or sensitivity to exposure (see Fig. 1).

Variability in behavioral responses to stress dependent on genotype have been reported in both primates and humans (Bennett et al. 2002; Caspi et al. 2002). In 2002, Caspi and colleagues conducted a seminal GxE study demonstrating a genetic variant in the monoamine oxidase gene (*MAOA*) that moderates the effect of childhood maltreatment and subsequent development of antisocial behaviors

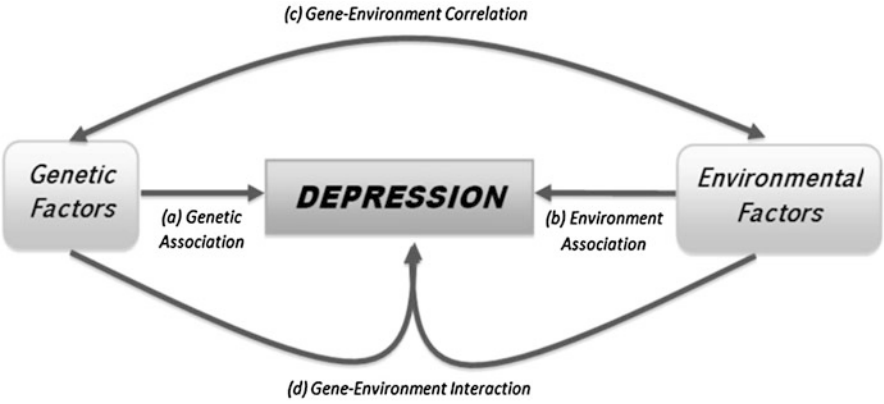


Fig. 1 Basic methods used to understand genetic and environmental etiology of depression. (**a**–**c**) *Do not* use interaction terms, testing for an association between the hypothesized predictor and depression; (**d**) applies an interaction term (this is typically gene [coded 0,1,2]* environment [coded categorical or continuous]) – multiplicative and additive (using risk differences) interactions can be analyzed

(Caspi et al. 2002). This was followed up by a study investigating genetic risk in the serotonin transporter gene (*5-HTT* or *SLC6A4*) interacting with recent life stress to moderate risk of developing depression (Caspi et al. 2003). This emerging field has gained pace dramatically in the last 10 years, eliciting much scientific discourse; these studies have been cited over 3,400 and 5,800 times, respectively. As interest in gene-environment models of depression grows, more genetic polymorphisms and systems have been investigated. While monoaminergic genes interacting with stressful life events were a natural starting point for gene-environment investigations in depression, these will be discussed later in the chapter due to the many lessons this literature now presents. Instead, two other commonly implicated systems will be the first to be addressed: the HPA axis and neurotrophic system.

The Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis regulates stress hormones and has a role in the etiology and treatment of depression and anxiety (e.g., Binder et al. 2004; de Kloet et al. 2005). The neuroendocrine system regulates the physiological experience of stress, through activation of the sympathetic nervous system. This leads to endocrine glands releasing a number of hormones, including corticotropin-releasing hormone (CRH), which starts a waterfall effect via stimulating production of adrenocorticotropic hormone (ACTH) (de Kloet et al. 2005). After periods of stress, cortisol levels are normalized quickly when glucocorticoid sensitivity is functioning well; however, a lack of sensitivity slows this process (de Kloet et al. 2005). Individuals suffering a depressive episode have been found to exhibit abnormal HPA functioning (Kunugi et al. 2006), and so genetic polymorphisms of the HPA system are potential mediators of the effects of stress in risk of developing depression.

To date, three main HPA-axis candidates have been investigated in the context of gene-environment studies in depression (see Table 1). The first is the corticotrophin-releasing hormone 1 (*CRHR1*) gene. This is a logical target within the corticosteroid receptor hypothesis, which proposes that a set point of the HPA system changes in depression resulting in reduced corticosteroid receptor (CR) signaling and an increase in corticotropin-releasing hormone (Holsboer 2000). In 2008, a protective haplotype in the *CRHR1* gene was first identified to interact with childhood maltreatment to decrease risk of developing depression (Bradley et al. 2008). Functionally, it is striking that an interaction between childhood maltreatment and the *CRHR1* genotype also evokes HPA system changes as measured by cortisol (Cicchetti et al. 2011; Tyrka et al. 2009), and in young children aged 3–5, an interaction with stressors and a genetic profile score (including genetic variation from *CRHR1* and *FKBP5*) predicted cortisol and amygdala volume (Pagliaccio et al. 2014). Bradley's initial finding has been replicated in two further studies: in a cohort of English women (Polanczyk et al. 2009) and African-American women (Kranzler et al. 2011). However, both of these studies also presented evidence that this haplotype was *not* protective in other samples: in a

Table 1 Summary of studies examining interaction effects between stressful life or childhood events and HPA-axis candidate genes on depression risk

First author (year)	Sample size	Population	Outcome (instrument)	Stress measure	Gene	SNP	Effect/primary study findings (*p*-value)
Liu (2013)	528 (256 MDD)	Chinese	Depression (HAMD-21, CGI)	Life stress (The Holmes and Rahe stress scale)	*CRHR1*	rs1876828 rs242939 rs242941	Significant interaction increasing risk of persistent MDD between negative life events and the G-allele (rs242939) (p=.023), and/or GGT-haplotype (p=.037)
Cicchetti (2011)	439 children (51 early abuse, 187 maltreated not early abuse)	African-American, Latino, and Caucasian; 7–13 years	Depressive/ internalising symptoms (CDI, TRF), salivary cortisol	Childhood maltreatment (DHS records assessed with Maltreatment Classification System and Maternal Maltreatment Classification Interview)	*CRHR1*	rs7209436 rs110402 rs242924	*Depression*: No significant interaction between childhood maltreatment and the TAT-haplotype (p =.276) on depressive/ internalising symptoms Significant G-G-E interaction of risk between childhood maltreatment, TAT-haplotype, 5-HTTLPR genotype on depressive/ internalising symptoms (p=.04) *Cortisol phenotypes*: Significant interaction between early abuse and high depression/ internalising symptoms on cortisol slope

							(p =.008), with a flatter slope. Significant interaction of risk between abuse and two copies of TAT-haplotype on cortisol levels (p=.003), marked by an attenuated slope of change
Kranzler (2011)	3,080	1,211 European-Americans & 1,869 African-Americans	Major depressive episode (SSADDA)	Adverse childhood experience (SSADDA)	*CRHR1*	rs7209436 rs110402 rs242924	*Depression*: Significant interaction increasing risk of depression between adverse childhood experiences and the TAT-haplotype (p=.005) in African-American women; no significant interaction in European-American women or men, or African-American men *Depressive Episode*: Significant interaction increasing risk of MDE between adverse childhood experiences and the TAT-haplotype (p=0.035) in African-American women; no significant interaction in the other groups

(*continued*)

Table 1 (continued)

First author (year)	Sample size	Population	Outcome (instrument)	Stress measure	Gene	SNP	Effect/primary study findings (*p*-value)
Grabe (2010)	1,683	Caucasian (German)	Depression (BDI-2)	Childhood maltreatment (CTQ)	*CRHR1*	28 SNPs (3 haplotype-block analyses, and TAT-haplotype)	Significant interaction increasing risk of depression between physical neglect and 23 of the 28 SNPs (polymorphism), reaching gene-wide significance. The largest effect stemmed from rs17689882 (p=0.0013) Significant interaction increasing risk of depression between physical neglect and TAT-haplotype (p =.0156; 1.4 increase in BDI score per haplotype). Other haplotypes also presented evidence for interaction with physical neglect, yielding a protective or risk effect dependent on the haplotype measured, with most significant p-value of 0.0061 relating to 1.6 point increase on

							the BDI scale (ACC risk haplotype comprising rs171440, rs8072451, rs81189). Please refer to original paper for details on other haplotypes
Polanczyk (2009)	Discovery 1116	English women (>90 % Caucasian)	Depression (Diagnostic Interview Schedule for DSM-IV)	Childhood maltreatment (CTQ)	*CRHR1*	rs7209436* rs110402* rs242924* rs4792887	Significant protective interaction between childhood maltreatment and TAT-haplotype(*) on development of past-year (p=.04), and recurrent MDD (p=.03)
	Replication 1037	New Zealanders (>90 %+ Caucasian)	Depression (Diagnostic Interview Schedule/DSM-IV)	Compilation of 5 measures Prospective: 1) behavioural observations of mother-child interactions 2) parental reports of discipline, 3) changes in role of primary caregiver; Retrospective: 4) physical abuse 5) sexual abuse	*CRHR1*	rs7209436 rs110402 rs242924	No significant interaction
Bradley (2008)	560	African-Americans	Depression (BDI and SCID-I)	Childhood maltreatment (CTQ)	*CRHR1*	15 SNPs (including TAT haplotype)	Significant interaction protective of depression between childhood abuse and the TCA-haplotype comprising of

(*continued*)

Table 1 (continued)

First author (year)	Sample size	Population	Outcome (instrument)	Stress measure	Gene	SNP	Effect/primary study findings (*p*-value)
							rs7209436, rs4792887, and rs110402 ($p < .001$), and/or TAT=haplotype ($p < .005$)
Bet (2009)	901 (244 with childhood adversity)	Caucasian Dutch, 65+ years	Depression (CES-D)	Childhood Adversity (No formal scale - asked if person had experienced personal life events during youth)	*GR/ NR3C1*	22/23EK N363S 9beta BclI	Significant interaction increasing risk of depressive symptoms between childhood adversity and 22/23EK allele ($p = .02$) and 9beta allele ($p = .04$) Significant protective interaction on recurrent depressive symptoms between childhood adversity and one BClI allele ($p = .01$) Trend for interaction between childhood adversity and the 22/23EK allele with reduced cortisol levels, and elevated cortisol binding globulin (CBG)

							(p=.10), as opposed to without childhood adversity (p=.21) Trend for protective interaction between childhood adversity and carrying one BclI allele with lower CBG levels (p=.07). This is also observed in those without childhood adversity (p=.03), indicating that genetic basis is important alone

Literature investigating *FKBP5*, *BDNF*, and *5HTT* have not been detailed in this table as they have been previously tabulated due to thorough review articles and/or meta-analyses (Zannas and Binder 2014; Hosang et al. 2014; Karg et al. 2011)
MDD major depressive disorder, *MDE* major depressive episode, G-G-E gene by environment interaction, *CES-D* Center for Epidemiological Studies Depression scale, *CASI* comprehensive addiction severity index for adolescents, *HAMD-21* Hamilton depression rating scale 21-item, *CGI* clinical global impression scale, *CDI* children's depression inventory, *TRF* teacher's report form, *DHS* department of human services, *SSADDA* semi-structured assessment for drug dependence and alcoholism, *BDI* beck depression inventory, *BDI-2* beck depression inventory 2nd edition, *CTQ* childhood trauma questionnaire, *DSM-IV* diagnostic and statistical manual of mental disorders, 4th edition, *DEX* dexamethasone, *CRH* corticotropin-releasing hormone, *SCID-I* structured clinical interview for DSM disorders – research version. *single nucleotide polymorphisms constituting the TAT-haplotype

mixed-gender New Zealand replication sample (Polanczyk et al. 2009) and in a female Caucasian-American sample (Kranzler et al. 2011). Polanczyk and colleagues (2009) propose that these conflicting results reflect that the TAT haplotype is protective against emotional *memories* being made; the replication study utilized prospective measures of childhood maltreatment rather than the retrospective Childhood Trauma Questionnaire (CTQ) aimed at assessing traumatic experiences in an individual's childhood (Pennebaker and Susman 1988). However, it is worth noting one study that also used the CTQ and investigated a Caucasian population identified the TAT haplotype to be a risk (not protective) factor in the case of childhood trauma, specifically physical neglect (Grabe et al. 2010). Grabe and colleagues investigated a total of 28 SNPs, demonstrating interactions with physical neglect with 23 SNPs and with TAT as a *risk* haplotype (see Table 1). This study used a "state" measure (Beck's Depression Inventory, BDI) (Grabe et al. 2010) rather than a clinical diagnostic measure such as the Structured Clinical Interview for DSM Disorders (SCID), which was used by other studies (Polanczyk et al. 2009). Another study also reported increased risk predicting depressive and internalizing symptoms (Cichetti et al. 2011); however, this was in a young childhood sample. Reasons for variability will be discussed later in this chapter, but note that types of measures and outcomes measured varied greatly between studies. While the TAT haplotype is the most commonly analyzed in *CRHR1* in the context of GxE studies in depression, other haplotypes have also been investigated (see Table 1). As a whole, these findings are supportive of *CRHR1* modulating the development of adulthood depression stemming from adversity in both childhood and adulthood.

The glucocorticoid receptor gene has also been investigated in the context of life stress and depression. Glucocorticoid hormones are steroid hormones involved in the stress response, immunosuppression, inflammation, and behavior (McEwen 2007). These hormones are mediated by the GR protein which modulates cortisol transcription and the negative feedback loop to the HPA axis when terminating the stress response. Abnormal *GR* expression may contribute to depression through stress-induced hyperactivity of the HPA axis (Carvalho et al. 2013). Despite strong candidacy, only one study is published investigating this variant: a longitudinal study of 922 elderly Caucasians (Bet et al. 2009). Here an increased risk of depressive symptoms was demonstrated with an interaction between childhood adversity and the *GR* polymorphisms 22/23EK and 9beta. This study demonstrated a multiplicative interaction, with individuals that experienced childhood adversity at increased risk of depressive symptoms, while those that experienced no childhood adversity exhibited decreased risk. Similar to findings in *CRHR1* (Cicchetti et al. 2011; Tyrka et al. 2009), Bet and colleagues also explored functional effects. A trend for interaction with 22/23EK and childhood adversity was reported with reduced cortisol levels and elevated cortisol-binding globulin (CBG) ($p = 0.10$) (Bet et al. 2009). Some unusual findings were also reported. In the face of childhood adversity, carrying one BclI variant was found to be protective for the development of recurrent depressive symptoms ($p = 0.01$), as opposed to carrying none or two variants (Bet et al. 2009). If replicated, this depicts a complex relationship between

GR variants and depression, as heterozygous effects are unusual. It may seem counterintuitive for one gene to have variants that are protective (i.e., BcII) and variants that are risk factors (i.e., 22/23EK); however, different genetic variants can have different functional effects within the same gene. It is possible that the BcII variant elicits the opposite functional effect to the 22/23EK variant, although this was not reported by Bet and colleagues (2009).

HPA-axis regulation, elicited by adaptive *GR* changes, has been found to influence the effectiveness of antidepressants, and the reoccurrence of depression has been associated with FK506-binding protein 51 (FKBP5) expression (Binder et al. 2004). FKBP5 is closely related to the stress system, regulating GR sensitivity. *FKBP5*'s expression is upregulated by GR activation and individual differences in GR sensitivity and stress hormones, leading to reduced efficacy in terminating the HPA-axis stress response (Binder 2009). This dysregulation in the stress response may be a risk factor in the development of stress-related disorders. In particular, the *FKBP5* SNPrs1360780 T-allele interacts with childhood abuse to increase risk of mental illness (Appel et al. 2011; Binder et al. 2008; Dackis et al. 2012; Xie et al. 2010). Initially, this variant was analyzed in context of post-traumatic stress disorder (PTSD), with severity predicted by the interaction of four *FKBP5* SNPs and child abuse severity in African-American adults (Binder et al. 2008; Xie et al. 2010). This functional haplotype has since also been reported to interact with childhood maltreatment or childhood trauma to directly increase risk of depression (Appel et al. 2011; Zimmermann et al. 2011). Traumas experienced in later life however have not shown evidence to interact with the *FKBP5* haplotype, suggesting that it is a developmentally sensitive interaction that is observed (Zannas and Binder 2014). Further, less explored *FKBP5* haplotype variants and SNPs have also been found to interact with childhood maltreatment to predict increased suicide attempts in African-Americans (Roy et al. 2010) and increased amygdala reactivity in Caucasian youth (White et al. 2012), both of which correlate significantly with depression (Dannlowski et al. 2007; Isometsa 2014).

The Neurotrophic System

Brain-derived neurotrophic factor (BDNF) is important in neuronal growth and survival and facilitates neurotransmission and synaptic plasticity (Kunugi et al. 2010). A functional SNP (rs6265) in *BDNF* has been associated with stress reactivity (Alexander et al. 2010), which may act via a pathway integrated with the HPA axis. HPA-axis hyperactivity activates and elevates glucocorticoid levels, leading to decreased *BDNF* expression, which has been observed in depressed patients (Bet et al. 2009; Kunugi et al. 2010). Antidepressants increase BDNF synthesis and signaling (Castren et al. 2007; Kunugi et al. 2010), while administration of BDNF has similar effects to antidepressants (Schmidt and Duman 2010). Not surprisingly, *BDNF* has been hypothesized to modulate brain neuroplasticity, such as mood change (Castren et al. 2007) and depression (e.g., Hosang et al. 2014). An interactive relationship between life stress and *BDNF* in increasing depression risk has been

substantiated by a number of studies, although these findings have not been consistent (see Hosang et al. 2014). Due to the inconsistent findings, a recent meta-analysis combined these studies to determine if an interaction of *BDNF's* rs6265 (Val66Met) and life stress does mediate depression (Hosang et al. 2014). A higher number of Met-alleles were associated with a greater susceptibility to depression in the event of life stress, with the strongest interaction observed in response to daily stressors; Met carriers experienced a greater risk of depressive outcome compared to Val/Val individuals (Kalueff et al. 2006; Wichers et al. 2008). The effect of the Met-alleles was strongest in the case of stressful life events in adulthood, rather than childhood adversity (Hosang et al. 2014). For instance, a study examining both childhood adversity and recent life stress in women found that only recent life stress interacted with *BDNF* to predict onset of a depressive episode (Brown et al. 2014). In fact, it has been suggested that this outcome may be independent in females, while the *BDNF* rs6265 (Val66Met) interaction with childhood adversity remains significant in males (van Oostrom et al. 2012). Such results demonstrate gender may moderate gene-environment interaction pathways.

Another neurotrophic gene investigated is 8-sialyltransferase (ST8SIA). *ST8SIA* is involved in neuronal plasticity through assisting the folding of related proteins; restriction of this plasticity has been linked to other disorders such as schizophrenia, autism, and bipolar disorder (McAuley et al. 2012). McAuley et al. (2012) suggest that vulnerability to later environmental insults may then stem from a lack of plasticity. A small study investigating stressful life events (SLEs) and short-term antidepressant response supports that *BDNF* and *ST8SIA* polymorphisms affect the carriers' response to treatment (Mandelli et al. 2014). One hundred and fourteen patients with mood disorders were evaluated retrospectively and prospectively for 4 weeks. Their individual short-term response to antidepressant treatment was not associated with genetic variation when they had experienced an SLE at the onset of their mood disorder (Mandelli et al. 2014). However, not being exposed to an SLE at the onset of mood disorder predicted a slower response to antidepressants in carriers of both a *BDNF* haplotype (rs11030101 A-allele and rs11030104 G-allele) and a *ST8SIA* haplotype (rs11853992 A-allele and rs17522085 G-allele) (Mandelli et al. 2014). These results were unexpected as neuroplastic factors were hypothesized to act as pro-survival variants and thereby enhance antidepressant responses (Mandelli et al. 2014). As SLEs are generally considered risk factors for mood disorder onset, it is particularly interesting that their precedence predicted a swifter antidepressant response. To explain seemingly contradictory results in this area, more complex networks are starting to be investigated in the form of gene-gene-environment interactions; however, these studies face significant challenges with respect to power.

The Monoamine System

The monoamine hypothesis in depression is one of the oldest molecular hypotheses in the literature. Monoamines, namely, serotonin and norepinephrine, are used to

alleviate the symptoms of depression. Thus, it has been hypothesized that polymorphisms in the monoamine system are implicated in the etiology of depression (Lerer et al. 2001). The serotonin system has been the most widely studied in depression due to the target of modern antidepressants (selective serotonin reuptake inhibitors). Serotonin is a protein that is critical for central nervous system function and has been heavily implicated in mood regulation (Lesch et al. 1996).

The first psychological/psychiatric study to investigate serotonin at the molecular genetic level was in 1996 and analyzed 5-HTTLPR and neuroticism (Lesch et al. 1996). The serotonin transporter (*5-HTT*or *SLC6A4*) gene has an upstream region called the serotonin-transporter-linked polymorphic region (5-HTTLPR), which is responsible for the production of the 5HTT and reuptake of serotonin (Cohen-Woods et al. 2013; Lesch et al. 1996). The repeats are reduced to two alleles: long (L) and short (S); the S-allele results in reduced 5-HTTLPR expression (Lesch et al. 1996). This initial study reported an association accounting for 7–9 % of genetic variance contributing to anxiety-related personality traits; however, this has not been robustly replicated, and this estimate of genetic variance is extremely large. It is now accepted that where individual genetic risk factors are identified, contribution will be much smaller (<1 %) (Wray et al. 2011).

The 5-HTTLPR has been widely investigated in depression; however, results with straight genetic association analyses have been inconsistent (e.g., Collier et al. 1996; Furlong et al. 1998; Hauser et al. 2003). Due to this gene's strong candidacy in depression and that findings in gene-depression association studies had not been consistent, this was the first gene (and 5-HTTLPR, the first variant) to be investigated in context with stressful life events (SLEs) and depression (Caspi et al. 2003). This was the first GxE study in depression and as mentioned previously has created a large amount of academic discourse. Caspi and colleagues reported a significant GxE interaction, with the S-allele predicting vulnerability to depression in individuals that experienced stressful life events in the 5 years preceding and also in those that experienced childhood maltreatment (Caspi et al. 2003). Individuals with the L-allele were at reduced risk, as were S-allele carriers that had not experienced stressful events. This resulted in a proliferation of studies attempting to replicate this finding: some successful, some not (see Karg et al. 2011). While it might be unexpected that the 5-HTTLPR studies have not been described first in this chapter, as the most widely studied gene, it has also taught researchers in the field the most lessons in GxE analyses to date.

With many studies published (>55), lacking consistency in their conclusions, two meta-analyses were published in close succession stating there is no evidence for a significant interaction between 5-HTTLPR and stressful life events in predicting depression (Munafo et al. 2008; Risch et al. 2009). This had a significant impact on the field. A striking point is that these studies included a very small subset of available studies investigating the 5HTTLPR and stressful events (not restricting to SLEs), just 5 (Munafo et al. 2008) and 14 (Risch et al. 2009) out of 56 publications. This was for many reasons, including a lack of primary raw data being available and analyses being restricted to SLEs and no other kind of stressors (childhood maltreatment or medical conditions) (Karg et al. 2011). Karg and

colleagues addressed this issue by running meta-analyses that included all studies, combining them at the level of significance tests with no requirement for equivalent raw data (method by Hedges and Olkin 1985). They also investigated if the *type* of stressor analyzed was important, separating SLEs, childhood maltreatment, and specific medical conditions. Through meta-analysis of 54 studies, many more than those included in the first two meta-analyses, a highly significant interaction was reported between the 5HTTLPR (S-allele as risk) and stress in predicting risk for depression, restricted to childhood maltreatment and specific medical conditions with SLEs providing less robust evidence (Karg et al. 2011). This could be due to less consistent reporting of SLEs relative to childhood maltreatment or clear medical conditions and/or an indication that timing of stressors could be important in the understanding of GxE interactions and mechanisms. One potential mechanism by which GxE interactions may act is through epigenetic changes such as DNA methylation. Epigenetic changes may occur in response to a stressful exposure but only at critical time points in the life-span.

Other factors have also been suggested to have a significant impact in understanding the interaction between 5-HTTLPR and stress in depression, such as persistent (recurrent) depression rather than single-episode depression being a more robust outcome (Brown et al. 2013; Uher et al. 2011). Subjectivity of the stress measures themselves also influences how replicable findings are in the context of this gene, with less subjective measures eliciting greater evidence for interaction, particularly longitudinal measures that do not rely on recall (Uher and McGuffin 2010). Of course, different variants are likely to be sensitive in different ways, for example, it has been suggested that the haplotype in *CRHR1* might possess a more robust interaction *with* retrospective measures such as the Childhood Trauma Questionnaire, which was attributed to emotional memories rather than the stressor being the interactive factor (Polanczyk et al. 2009).

In addition to the serotonin transporter gene, other serotonergic and monoaminergic genes have also been examined in depression in adolescents and adults exposed to a variety of stressors including composite measure of "family-based environmental risk," SLEs, and childhood maltreatment: *HTR2A*, *HTR2C*, *MAOA*, *TPH*, *DRD2*, *DRD4*, *DAT1*, and *AP-2b* (e.g., Dunn et al. 2013; Eley et al. 2004; Kim-Cohen et al. 2006). Some studies indicate timing of stressors is important (i.e., *DRD4* variation and sexual abuse; (Dunn et al. 2013) or gender (i.e., *MAOA* variation and childhood maltreatment or SLEs; (Kim-Cohen et al. 2006; Ma et al. 2013)); however, these genes have been less widely studied with variable conclusions. It is currently difficult to assess how much the reported interactions are robustly sensitive to factors such as timing of the stressors, type of stressors measured, types of measures (objective, subjective, retrospective, or prospective), outcomes measured (i.e., recurrent depression, single episode, or current mood state), or gender, but as more studies are published, this will become clearer.

Clinical Significance

The scale and impact of depression on global health directly (World Health Organization 2008) and indirectly through increased incidence of comorbid illness including cardiovascular disease (Bondy 2007) mean that understanding the biological etiology of depression has the potential to have a huge clinical impact. It is significant not only that CVD and depression are highly comorbid (Bondy 2007) but that they share significant risk factors, such as stress (Rosengren et al. 2004; Yusuf et al. 2004). GxE studies in depression have potential to inform future investigations in CVD through candidate systems in association with stress and also through methodological issues such as those described in this chapter. Further, through understanding *how* gene-environment interactions can have their impact (e.g., epigenetic changes such as DNA methylation), it will also inform studies investigating the overlap between CVD and depression. In the long term, this will help inform mechanisms by which significant stressors have the potential to impact so negatively on some people but not all. Environmental "programming" effects of early experience (such as low "maternal affection") can be reversed through pharmacological and environmental (cross-fostering) interventions (Weaver et al. 2004). Histone deacetylase inhibitors (used to reverse methylation) are highly toxic and not appealing in the clinical setting where onset of illness (or risk through stress exposure) occurs early in life; however, less toxic compounds with antitumor efficacy in the context of cancer are being identified and trialed (Vigushin and Coombes 2004). It is therefore not implausible that less toxic agents may be identified in the future in the context of other illness. Through the establishment of robust GxE interactions, further pharmacological and/or sociological or psychological interventions could be identified, which have real potential to impact policy, health, and the future of many individuals globally.

Conclusions and Future Directions

The study of gene-environment interactions in depression is an emerging and exciting avenue that may lead to a better understanding of biological systems involved in depression and other comorbid illnesses such as cardiovascular disease (McCaffery et al. 2006). While findings are promising, with evidence for interactions between stress and candidate genes in the HPA axis, neurotrophic and monoaminergic systems, few are robust. Due to the sheer volume of studies investigating the serotonin transporter gene, the specific aspects that are critical in seeing a robust gene-environment interaction between 5-HTTLPR and stress exposure are beginning to be well understood (i.e., childhood stressors, not stressful life events in adulthood, and the use of objective measures). The literature thus highlights that gene-environment studies need to be carefully considered and face some significant challenges.

One such challenge that needs to be addressed is that biological and statistical interactions are different, and this is not widely recognized in the literature (Rothman and Greenland 2005). A vast majority of studies apply multiplicative (statistical) interactions, with no consideration for additive (the more biologically plausible) interaction terms; to clarify the role of GxE interactions in depression risk, it will be important to pursue multiple different methods with greater transparency of researchers in reporting their findings (Caspi and Moffitt 2006; Uher 2014). GxE studies have faced some other significant criticisms, such as robust replications being needed that anticipate methodological issues such as those described in this chapter, and also a problem with studies being underpowered to detect effects (Duncan and Keller 2011). Unfortunately, in contrast to straight genetic studies where just some basic demographic information and phenotype categorical data are typically required, GxE studies require more in-depth assessment. This impacts the sizes of samples available, which can be striking particularly in the context of large genetic association studies. Another common criticism is that the field is "susceptible to the publication bias" (Duncan and Keller 2011). However, researchers are addressing this through meta-analyses where possible. Two meta-analyses published (analyzing 5-HTTLPR and *BDNF* rs6265) have demonstrated that publication bias is unlikely to have a significant impact on their (positive) findings as multiple studies of a moderate size ($\sim$700) would be required to change significant findings (Hosang et al. 2014; Karg et al. 2011). Challenges faced by meta-analyses include the use of multiple methods applied to published data, with a lack of raw data being available. As mentioned earlier in the chapter, there are statistical methods around this, but also there is openness in the field to collaborate to address these concerns head on. Culverhouse and colleagues have brought together as many researchers as possible to analyze the raw 5-HTTLPR and stress (adult- and childhood) data from each group using standardized analytic script to enable "pure" meta-analyses to be run (Culverhouse et al. 2013). All published study authors were requested to participate, and many individuals with unpublished data are also participating; inevitably, some authors declined the invitation (Moffitt and Caspi 2014); however, secondary meta-analyses including these studies will also be run. This demonstrates a willingness to address issues where possible that have been raised by critics (Duncan and Keller 2011).

A priority now must be ascertaining large samples with reliable phenotypic and good quality temporal environmental measures, with careful consideration given to environmental factors measured and hypotheses tested. Systematic genome-wide GxE studies will not be possible without this due to restricted power with samples currently available. This will require collaboration between researchers to obtain sufficient numbers and strong consideration given to optimal approaches to achieve this (i.e., starting from scratch or, perhaps more financially feasible, obtaining genotype data for cohorts where strong environmental data is already available but no genetic data). This is an exciting time for the psychiatric genetic and epidemiological communities, with nature and nurture merging together to yield interesting and promising research.

References

Alexander, N., Osinsky, R., Schmitz, A., Mueller, E., Kuepper, Y., & Hennig, J. (2010). The BDNF Val66Met polymorphism affects HPA-axis reactivity to acute stress. *Psychoneuroendocrinology, 35*(6), 949–953.

Appel, K., Schwahn, C., Mahler, J., Schulz, A., Spitzer, C., Fenske, K., ... Grabe, H. J. (2011). Moderation of adult depression by a polymorphism in the FKBP5 gene and childhood physical abuse in the general population. *Neuropsychopharmacology, 36*(10), 1982–1991. doi:10.1038/npp.2011.81.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine, 66*(6), 802–813. doi:10.1097/01.psy.0000146332.53619.b2.

Bennett, A. J., Lesch, K. P., Heils, A., Long, J. C., Lorenz, J. G., Shoaf, S. E., ... Higley, J. D. (2002). Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Molecular Psychiatry, 7*(1), 118–122. doi:10.1038/sj/mp/4000949.

Bet, P. M., Penninx, B. W., Bochdanovits, Z., Uitterlinden, A. G., Beekman, A. T., van Schoor, N. M., ... Hoogendijk, W. J. (2009). Glucocorticoid receptor gene polymorphisms and childhood adversity are associated with depression: New evidence for a gene-environment interaction. *American Journal of Medical Genetics Part B Neuropsychiatric Genetics, 150B*(5), 660–669. doi:10.1002/ajmg.b.30886.

Binder, E. B. (2009). The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology, 34*(Suppl 1), S186–S195. doi:10.1016/j.psyneuen.2009.05.021.

Binder, E. B., Salyakina, D., Lichtner, P., Wochnik, G. M., Ising, M., Putz, B., ... Muller-Myhsok, B. (2004). Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nature Genetics, 36*(12), 1319–1325. doi:10.1038/ng1479.

Binder, E. B., Bradley, R. G., Liu, W., Epstein, M. P., Deveau, T. C., Mercer, K. B., ... Ressler, K. J. (2008). Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA, 299*(11), 1291–1305. doi:10.1001/jama.299.11.1291.

Bondy, B. (2007). Common genetic factors for depression and cardiovascular disease. *Dialogues in Clinical Neuroscience, 9*(1), 19–28.

Bradley, R. G., Binder, E. B., Epstein, M. P., Tang, Y., Nair, H. P., Liu, W., ... Ressler, K. J. (2008). Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene. *Archives of General Psychiatry, 65*(2), 190–200. doi:10.1001/archgenpsychiatry.2007.26.

Brown, G. W., Ban, M., Craig, T. K., Harris, T. O., Herbert, J., & Uher, R. (2013). Serotonin transporter length polymorphism, childhood maltreatment, and chronic depression: A specific gene-environment interaction. *Depression and Anxiety, 30*(1), 5–13. doi:10.1002/da.21982.

Brown, G. W., Craig, T. K., Harris, T. O., Herbert, J., Hodgson, K., Tansey, K. E., & Uher, R. (2014). Functional polymorphism in the brain-derived neurotrophic factor gene interacts with stressful life events but not childhood maltreatment in the etiology of depression. *Depression and Anxiety, 31*(4), 326–334. doi:10.1002/da.22221.

Carvalho, L. A., Nikkheslat, N., & Pariante, C. M. (2013). Inflame-beat: Insufficient glucocorticoid signalling and inflammatory activation in coronary heart disease patients with depression. *European Neuropsychopharmacology, 23*((Carvalho L.A.) University College London, Epidemiology and Public Health, London, United Kingdom), S342–S343.

Caspi, A., & Moffitt, T. E. (2006). Gene-environment interactions in psychiatry: Joining forces with neuroscience. *Nature Review Neuroscience, 7*(7), 583–590. doi:10.1038/nrn1925.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., ... Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*(5582), 851–854. doi:10.1126/science.1072290.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., ... Poulton, R. (2003). Influence of life-stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386–389. doi:10.1126/science.1083968.

Castren, E., Voikar, V., & Rantamaki, T. (2007). Role of neurotrophic factors in depression. *Current Opinion in Pharmacology, 7*(1), 18–21. doi:10.1016/j.coph.2006.08.009.

Cicchetti, D., Rogosch, F. A., & Oshri, A. (2011). Interactive effects of corticotropin releasing hormone receptor 1, serotonin transporter linked polymorphic region, and child maltreatment on diurnal cortisol regulation and internalizing symptomatology. *Development and Psychopathology, 23*(Special Issue 04), 1125–1138. doi:10.1017/S0954579411000599.

Cohen-Woods, S., Craig, I. W., & McGuffin, P. (2013). The current state of play on the molecular genetics of depression. *Psychological Medicine, 43*(4), 673–687. doi:10.1017/s0033291712001286.

Collier, D. A., Stober, G., Li, T., Heils, A., Catalano, M., Di Bella, D., ... Lesch, K. P. (1996). A novel functional polymorphism within the promoter of the serotonin transporter gene: Possible role in susceptibility to affective disorders. *Molecular Psychiatry , 1*(6), 453–460.

Culverhouse, R. C., Bowes, L., Breslau, N., Nurnberger, J. I., Jr., Burmeister, M., Fergusson, D. M., ... Bierut, L. J. (2013). Protocol for a collaborative meta-analysis of 5-HTTLPR, stress, and depression. *BMC Psychiatry, 13*, 304. doi:10.1186/1471-244x-13-304.

Dackis, M. N., Rogosch, F. A., Oshri, A., & Cicchetti, D. (2012). The role of limbic system irritability in linking history of childhood maltreatment and psychiatric outcomes in low-income, high-risk women: Moderation by FK506 binding protein 5 haplotype. *Development and Psychopathology, 24*(4), 1237–1252. doi:10.1017/s0954579412000673.

Danese, A., Moffitt, T. E., Pariante, C. M., Ambler, A., Poulton, R., & Caspi, A. (2008). Elevated inflammation levels in depressed adults with a history of childhood maltreatment. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Archives of General Psychiatry, 65*(4), 409–415. doi:10.1001/archpsyc.65.4.409.

Dannlowski, U., Ohrmann, P., Bauer, J., Kugel, H., Arolt, V., Heindel, W., ... Suslow, T. (2007). Amygdala reactivity to masked negative faces is associated with automatic judgmental bias in major depression: A 3 T fMRI study. *Journal of Psychiatry & Neuroscience, 32*(6), 423–429.

de Kloet, E. R., Joels, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Review Neuroscience, 6*(6), 463–475. doi:10.1038/nrn1683.

Duncan, L. E., & Keller, M. C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *The American Journal of Psychiatry, 168*(10), 1041–1049. doi:10.1176/appi.ajp.2011.11020191.

Dunn, E. C., McLaughlin, K. A., Slopen, N., Rosand, J., & Smoller, J. W. (2013). Genetic variants modify the association between developmental timing of exposure to physical and sexual abuse and depressive symptoms in young adulthood: Evidence of a sensitive period?. *Depression and Anxiety, 54*, e20–e20.

Eley, T. C., Sugden, K., Corsico, A., Gregory, A. M., Sham, P., McGuffin, P., ... Craig, I. W. (2004). Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry, 9*(10), 908–915. doi:10.1038/sj.mp.4001546.

Furlong, R. A., Ho, L., Walsh, C., Rubinsztein, J. S., Jain, S., Paykel, E. S., ... Rubinsztein, D. C. (1998). Analysis and meta-analysis of two serotonin transporter gene polymorphisms in bipolar and unipolar affective disorders. [Meta-Analysis Research Support, Non-U.S. Gov't]. *American Journal of Medical Genetics, 81*(1), 58–63. [Research Support, Non-U.S. Gov't]. *Molecular Psychiatry, 14*(7), 681–695. doi:10.1038/mp.2008.143.

Gilman, S. E., Kawachi, I., Fitzmaurice, G. M., & Buka, L. (2003). Socio-economic status, family disruption and residential stability in childhood: Relation to onset, recurrence and remission of major depression. *Psychological Medicine, 33*(8), 1341–1355.

Grabe, H. J., Schwahn, C., Appel, K., Mahler, J., Schulz, A., Spitzer, C., ... Volzke, H. (2010). Childhood maltreatment, the corticotropin-releasing hormone receptor gene and adult depression in the general population. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 153B*(8), 1483–1493. doi:10.1002/ajmg.b.31131.

Hauser, J., Leszczyńska, A., Samochowiec, J., Czerski, P. M., Ostapowicz, A., Chlopocka, M., & Rybakowski, J. K. (2003). Association analysis of the insertion/deletion polymorphism in serotonin transporter gene in patients with affective disorder. *European Psychiatry, 18*(3), 129–132. doi:10.1016/s0924-9338(03)00026-9.

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. Orlando: Academic.

Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology, 23*(5), 477–501. doi:10.1016/s0893-133x(00)00159-7.

Hosang, G. M., Shiles, C., Tansey, K. E., McGuffin, P., & Uher, R. (2014). Interaction between stress and the BDNF Val66Met polymorphism in depression: A systematic review and meta-analysis. *BMC Medicine, 12*, 7. doi:10.1186/1741-7015-12-7.

Isometsa, E. (2014). Suicidal behaviour in mood disorders – Who, when, and why? *Canadian Journal of Psychiatry, 59*(3), 120–130. [Research Support, N.I.H., Extramural]. *Journal of Psychiatric Research*, *47*(2), 233–239. doi:10.1016/j.jpsychires.2012.10.009.

Kalueff, A. V., Avgustinovich, D. F., Kudryavtseva, N. N., & Murphy, D. L. (2006). BDNF in anxiety and depression. *Science, 312*(5780), 1598–1599. doi:10.1126/science.312.5780.1598; author reply 1598–1599.

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry, 68*(5), 444–454. doi:10.1001/archgenpsychiatry.2010.189.

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *The American Journal of Psychiatry, 156*(6), 837–841.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., … Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Co-morbidity Survey. *Archives of General Psychiatry, 51*(1), 8–19.

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., & Moffitt, T. E. (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry, 11*(10), 903–913. doi:10.1038/sj.mp.4001851.

Kranzler, H. R., Feinn, R., Nelson, E. C., Covault, J., Anton, R. F., Farrer, L., & Gelernter, J. (2011). A CRHR1 haplotype moderates the effect of adverse childhood experiences on lifetime risk of major depressive episode in African-American women. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 156*(8), 960–968. doi:10.1002/ajmg.b.31243.

Kunugi, H., Ida, I., Owashi, T., Kimura, M., Inoue, Y., Nakagawa, S., … Mikuni, M. (2006). Assessment of the dexamethasone/CRH test as a state-dependent marker for hypothalamic-pituitary-adrenal (HPA) axis abnormalities in major depressive episode: A multicenter study. *Neuropsychopharmacology, 31*(1), 212–220. doi:10.1038/sj.npp.1300868.

Kunugi, H., Hori, H., Adachi, N., & Numakawa, T. (2010). Interface between hypothalamic-pituitary-adrenal axis and brain-derived neurotrophic factor in depression. *Psychiatry and Clinical Neurosciences, 64*(5), 447–459. doi:10.1111/j.1440-1819.2010.02135.x.

Ladd, C. O., Huot, R. L., Thrivikraman, K. V., Nemeroff, C. B., Meaney, M. J., & Plotsky, P. M. (2000). Long-term behavioral and neuroedocrine adaptations to adverse early experience. *Progress in Brain Research, 122*, 81–103.

Lepine, J. P., & Briley, M. (2011). The increasing burden of depression. *Neuropsychiatric Disease and Treatment, 7*(Suppl 1), 3–7. doi:10.2147/ndt.s19617.

Lerer, B., Macciardi, F., Segman, R. H., Adolfsson, R., Blackwood, D., Blairy, S., … Mendlewicz, J. (2001). Variability of 5-HT2C receptor cys23ser polymorphism among European populations and vulnerability to affective disorder. *Molecular Psychiatry, 6*(5), 579–585. doi:10.1038/sj.mp.4000883.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., … Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*(5292), 1527–1531.

Lesperance, F., Frasure-Smith, N., Talajic, M., & Bourassa, M. G. (2002). Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation, 105*(9), 1049–1053.

Liu, Z., Liu, W., Yao, L., Yang, C., Xiao, L., Wan, Q., . . . Xiao, Z. (2013). Negative life events and corticotropin-releasing-hormone receptor1 gene in recurrent major depressive disorder. *Scientific Reports, 3*. doi:10.1038/srep01548.

Ma, J., Yu, S. Y., Liang, S., Ding, J., Feng, Z., Yang, F., . . . Su, L. Y. (2013). [Association between MAOA-u VNTR polymorphism and its interaction with stressful life events and major depressive disorder in adolescents]. *Zhongguo Dang Dai Er Ke Za Zhi, 15*(7), 563–568.

Mandelli, L., Emiliani, R., Porcelli, S., Fabbri, C., Albani, D., & Serretti, A. (2014). Genes involved in neuroplasticity and stressful life events act on the short-term response to antidepressant treatment: A complex interplay between genetics and environment. *Human Psychopharmacology, 29*(4), 388–391. doi:10.1002/hup.2411.

McAuley, E. Z., Scimone, A., Tiwari, Y., Agahi, G., Mowry, B. J., Holliday, E. G., . . . Fullerton, J. M. (2012). Identification of sialyltransferase 8B as a generalized susceptibility gene for psychotic and mood disorders on chromosome 15q25-26. *PLoS One, 7*(5), e38172. doi:10.1371/journal.pone.0038172.

McCaffery, J. M., Frasure-Smith, N., Dubé, M.-P., Théroux, P., Rouleau, G. A., Duan, Q., & Lespérance, F. (2006). Common genetic vulnerability to depressive symptoms and coronary artery disease: A review and development of candidate genes related to inflammation and serotonin. *Psychosomatic Medicine, 68*(2), 187–200. 110.1097/1001.psy.0000208630.0000279271.a0000208630.

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews, 87*(3), 873–904. doi:10.1152/physrev.00041.2006.

McGuffin, P., Katz, R., Watkins, S., & Rutherford, J. (1996). A hospital-based twin register of the heritability of DSM-IV unipolar depression. *Archives of General Psychiatry, 53*(2), 129–136.

Meaney, M. J., & Szyf, M. (2005). Environmental programming of stress responses through DNA methylation: Life at the interface between a dynamic environment and a fixed genome. *Dialogues in Clinical Neuroscience, 7*(2), 103–123.

Moffitt, T. E., & Caspi, A. (2014). Bias in a protocol for a meta-analysis of 5-HTTLPR, stress, and depression. *BMC Psychiatry, 14*, 179. doi:10.1186/1471-244x-14-179.

Munafo, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: A meta-analysis. *Biological Psychiatry, 63*(9), 852–857. doi:10.1016/j.biopsych.2007.08.016.

Myin-Germeys, I., Peeters, F., Havermans, R., Nicolson, N. A., DeVries, M. W., Delespaul, P., & Van Os, J. (2003). Emotional reactivity to daily life-stress in psychosis and affective disorder: An experience sampling study. *Acta Psychiatrica Scandinavica, 107*(2), 124–131.

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., . . . Barch, D. M. (2014). Stress-system genes and life-stress predict cortisol levels and amygdala and hippocampal volumes in children. *Neuropsychopharmacology, 39*(5), 1245–1253. doi:10.1038/npp.2013.327.

Pennebaker, J. W., & Susman, J. R. (1988). Disclosure of traumas and psychosomatic processes. *Social Science and Medicine, 26*(3), 327–332.

Polanczyk, G., Caspi, A., Williams, B., Price, T. S., Danese, A., Sugden, K., . . . Moffitt, T. E. (2009). Protective effect of CRHR1 gene variants on the development of adult depression following childhood maltreatment: Replication and extension. *Archives of General Psychiatry, 66*(9), 978–985. doi:10.1001/archgenpsychiatry.2009.114.

Risch, N., Herrell, R., Lehner, T., Liang, K. Y., Eaves, L., Hoh, J., . . . Merikangas, K. R. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. *JAMA, 301*(23), 2462–2471. doi:10.1001/jama.2009.878.

Rosengren, A., Hawken, S., Ounpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A., . . . Yusuf, S. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in

11119 cases and 13648 controls from 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*(9438), 953–962. doi:10.1016/s0140-6736(04)17019-0.

Rothman, K. J., & Greenland, S. (2005). Causation and causal inference in epidemiology. *American Journal of Public Health, 95*(Suppl 1), S144–S150. doi:10.2105/ajph.2004.059204.

Roy, A., Gorodetsky, E., Yuan, Q., Goldman, D., & Enoch, M. A. (2010). Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide. *Neuropsychopharmacology, 35*(8), 1674–1683. doi:10.1038/npp.2009.236.

Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene-environment interplay and psychopathology: Multiple varieties but real effects. *The Journal of Child Psychology and Psychiatry, 47*(3-4), 226–261. doi:10.1111/j.1469-7610.2005.01557.x.

Schmidt, H. D., & Duman, R. S. (2010). Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. *Neuropsychopharmacology, 35*(12), 2378–2391. doi:10.1038/npp.2010.114.

Sullivan, P. F., Neale, M. C., & Kendler, K.S. (2000). Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry, 157*(10), 1552–62.

Tyrka, A. R., Price, L. H., Gelernter, J., Schepker, C., Anderson, G. M., & Carpenter, L. L. (2009). Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor gene: Effects on hypothalamic-pituitary-adrenal axis reactivity. *Biological Psychiatry, 66*(7), 681–685. doi:10.1016/j.biopsych.2009.05.012.

Uher, R. (2014). Gene-environment interactions in severe mental illness. *Front Psychiatry, 5*, 48. doi:10.3389/fpsyt.2014.00048.

Uher, R., & McGuffin, P. (2010). The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. *Molecular Psychiatry, 15*(1), 18–22. doi:10.1038/mp.2009.123.

Uher, R., Caspi, A., Houts, R., Sugden, K., Williams, B., Poulton, R., & Moffitt, T. E. (2011). Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: Replications and implications for resolving inconsistent results. *Journal of Affective Disorders, 135*(1-3), 56–65. doi:10.1016/j.jad.2011.03.010.

van Oostrom, I., Franke, B., Rijpkema, M., Gerritsen, L., Arias-Vasquez, A., Fernandez, G., & Tendolkar, I. (2012). Interaction between BDNF Val66Met and childhood stressful life events is associated to affective memory bias in men but not women. *Biological Psychology, 89*(1), 214–219. doi:10.1016/j.biopsycho.2011.10.012.

Vigushin, D. M., & Coombes, R. C. (2004). Targeted histone deacetylase inhibition for cancer therapy. *Current Cancer Drug Targets, 4*(2), 205–218.

Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., … Meaney, M. J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7*(8), 847–854. doi:10.1038/nn1276. http://www.nature.com/neuro/journal/v7/n8/suppinfo/nn1276_S1.html

White, M. G., Bogdan, R., Fisher, P. M., Muñoz, K. E., Williamson, D. E., & Hariri, A. R. (2012). FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. *Genes, Brain, and Behavior, 11*(7), 869–878. doi:10.1111/j.1601-183X.2012.00837.x.

Wichers, M., Kenis, G., Jacobs, N., Myin-Germeys, I., Schruers, K., Mengelers, R., … van Os, J. (2008). The psychology of psychiatric genetics: Evidence that positive emotions in females moderate genetic sensitivity to social stress associated with the BDNF Val66Met polymorphism. *Journal of Abnormal Psychology, 117*(3), 699–704. doi:10.1037/a0012909.

Widom, C. S., DuMont, K., & Czaja, S. J. (2007). A prospective investigation of major depressive disorder and co-morbidity in abused and neglected children grown up. *Archives of General Psychiatry, 64*(1), 49–56. doi:10.1001/archpsyc.64.1.49.

World Health Organization, W. (2008). The global burden of disease 2004. Retrieved 14 Sept 2014.

Wray, N. R., Purcell, S. M., & Visscher, P. M. (2011). Synthetic associations created by rare variants do not explain most GWAS results. *PLoS Biology, 9*(1), e1000579. doi:10.1371/journal.pbio.1000579.

Xie, P., Kranzler, H. R., Poling, J., Stein, M. B., Anton, R. F., Farrer, L. A., & Gelernter, J. (2010). Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. *Neuropsychopharmacology, 35*(8), 1684–1692. doi:10.1038/npp.2010.37.

Yoshikawa, H., Aber, J. L., & Beardslee, W. R. (2012). The effects of poverty on the mental, emotional, and behavioral health of children and youth: Implications for prevention. *The American Psychologist, 67*(4), 272–284. doi:10.1037/a0028015.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., . . . Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*(9438), 937–952. doi:10.1016/s0140-6736(04)17018-9.

Zannas, A. S., Binder, E. B. (2014). Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. *Genes Brain and Behaviour, 13*(1), 25–37.

Zimmermann, P., Bruckl, T., Nocon, A., Pfister, H., Binder, E. B., Uhr, M., . . . Ising, M. (2011). Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: Results from a 10-year prospective community study. *The American Journal of Psychiatry, 168*(10), 1107–1116. doi:10.1176/appi.ajp.2011.10111577.

Diabetes, Depression, and Cardiovascular Risk

Marcel Adriaanse and Frans Pouwer

Contents

Abstract

Diabetes and depression are major public issues that often co-occur. Both diseases affect a growing number of people worldwide and are projected to be among the five leading causes of disease burden in 2030. Approximately 10–30 % of the people with type 1 (5–10 % of all diabetes cases) or type 2 diabetes is affected by depression. There is ample evidence that the association between type 2 diabetes and depression is bidirectional. Depression is

M. Adriaanse (✉)
Department of Health Sciences and the EMGO+ Institute for Health and Care Research, VU University Amsterdam, Amsterdam, The Netherlands
e-mail: marcel.adriaanse@vu.nl

F. Pouwer
Center of Research on Psychology in Somatic diseases (CoRPS) FSW, Tilburg University, Tilburg, The Netherlands
e-mail: f.pouwer@uvt.nl

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_43

likely to increase the risk of cardiovascular complications and mortality in people with diabetes. Several behavioral mechanisms (e.g., treatment nonadherence, physical inactivity, and poor diet) and biological mechanisms (e.g., deregulation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, vascular pathology, and central obesity) explain the link between depression and cardiovascular risk in diabetes patients. It has been postulated that treatment of depression could improve cardiovascular outcomes. Due to limited number of studies, there is currently no convincing evidence that pharmacological or psychological treatment of depression improves cardiovascular outcomes. Various organizations suggest screening for depression in their guidelines or recommendations for diabetes care. At present, there is no substantial evidence of the effectiveness of screening for depression among diabetes patients and is therefore not recommended. Future trials should focus on (a) the development of innovative interventions that can help to prevent depression, type 2 diabetes, and cardiovascular diseases in a cost-effective way and (b) long-term prospective studies that disentangle the mechanisms that link depression with unfavorable cardiovascular risks in diabetes patients.

Keywords
Diabetes • Depression • Cardiovascular risk • Mechanisms • Treatment • Screening

Introduction

Diabetes and depression are major public health issues. Worldwide, more than 382 million people are estimated to have diabetes (International Diabetes Federation 2013) and approximately 300 million people have major depression (Vos et al. 2012). These figures are expected to increase, and both disorders are projected to be among the five leading causes of disease burden by 2030 (Mathers and Loncar 2006). Diabetes and depression often co-occur and have attracted much research attention in the last two decades. It has been estimated that people with diabetes are twice as likely as the general population to suffer from depression (Roy and Lloyd 2012). Patients with depression and diabetes, compared with patients with diabetes alone, generally have lower quality of life (Ali et al. 2010), less optimal self-care and decreased adherence to medical treatment recommendations (Gonzalez et al. 2008), poor glycemic (HbA_{1c}) control (Lustman and Clouse 2005), lower levels of physical activity (Koopmans et al. 2009), and less healthy eating behaviors. Moreover, comorbid depression among diabetes patients has a profound negative impact on poor cardiovascular outcomes including mortality (van Dooren et al. 2013). In addition, diabetes patients with depression use healthcare services more often than their nondepressed counterparts, which is associated with a substantial increase in healthcare-related costs (Bosmans and Adriaanse 2012).

The aim of this chapter is to provide an overview of relationships between diabetes, depression, and cardiovascular risk. Whenever possible, mainly systematic reviews and meta-analyses were selected. Firstly, studies about the epidemiology and etiology of diabetes, depression, and the co-occurrence of both diseases are presented. Next, longitudinal studies that focus on depression as a risk factor for the development and progression of cardiovascular diseases and for mortality in persons with diabetes will be demonstrated. The different potential biological and behavioral mechanisms that underlie the associations between depression and cardiovascular diseases and mortality, the impact of treatments, screening options, and directions for future research will be discussed.

Diabetes

Diabetes mellitus is a chronic and serious metabolic disease, characterized by a high blood glucose level (hyperglycemia). Diabetes is affecting a growing number of people worldwide. The number of people with diabetes has increased from 153 million in 1980 to an estimated 347 million in 2008 (Danaei et al. 2011). Today there are approximately 382 million people living with diabetes, the majority aged between 40 and 59, with 80 % of them living in low- and middle-income countries. This alarming number is expected to reach 471 million by 2035 (International Diabetes Federation 2013). Roughly half of all deaths due to diabetes in adults were in people under the age of 60 in 2013 and in less-developed regions like sub-Saharan Africa, in which proportion climbs to 75 %. In terms of human suffering as well as in financial terms, the burden of diabetes is enormous, provoking 5.1 million deaths and taking up some an estimated USD 548 billion dollars in healthcare spending (11 % of the total spent worldwide) in 2013 (International Diabetes Federation 2013).

There are two main types of diabetes: type 1 and type 2 diabetes. These two types differ in etiology and clinical presentation. Type 1 diabetes (5–10 % of all diabetes cases) is due to autoimmune destruction of the insulin producing beta-cells of the pancreas. As a result, insulin secretion is minimized or even absent, leading to hyperglycemia (Bluestone et al. 2010). Onset most often occurs in childhood, but the disease can also develop in adults. It often presents with acute diabetes symptoms (i.e., frequent thirst, increased thirst, and excessive hunger) and markedly elevated blood glucose levels. Most people are diagnosed soon after the onset of hyperglycemia. Treatment of type 1 diabetes involves lifelong use of exogenous insulin, by means of multiple daily injections or by using insulin pump therapy. Type 2 diabetes (about 90 % of all diabetes cases) results from a diminished sensitivity to insulin (insulin resistance) by peripheral target tissues and an abnormal insulin secretion by beta-cells (beta-cell dysfunction). The risk of developing type 2 diabetes is most likely an interaction between genetic predisposition, a sedentary lifestyle, and obesity. Type 2 diabetes may go undiagnosed for several years due to the gradual increase of hyperglycemia and symptoms. Most people

develop type 2 diabetes after the age of 40, although the age of onset for type 2 diabetes decreases. Treatment of type 2 diabetes consists of healthy lifestyle advices, glucose lowering drugs, and/or insulin therapy.

Depression

Depressive disorders are among the most common psychiatric disorders, with the overall prevalence of current depressive symptoms being 8.7 %; the lifetime prevalence rate of a diagnosis by a health professional is 15.7 % (Strine et al. 2008). Major depressive disorder (MDD), the most serious form of the unipolar depressive disorders, is the most prevalent disease among adults that is described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, American Psychiatric Association 2000), with a lifetime prevalence of 16.6 % (Kessler et al. 2005). The key symptoms of depression are anhedonia (loss of interest or pleasure) and dysphoria (low mood). Other symptoms include fatigue; change in appetite (with weight loss or weight gain as a result); sleep disturbances; loss of self-esteem; inappropriate feelings of guilt, agitation, or psychomotor retardation noticed by others; inability to concentrate; and suicidal ideation (American Psychiatric Association 2000). Less optimal self-care behaviors, such as decreased medication adherence, poor nutrition, and lack of exercise, are common in persons with depression and diabetes (Lin et al. 2004).

Depression in Type 1 Diabetes

Barnard et al. conducted a systematic review including 14 studies and found that the prevalence of clinical depression in controlled studies was 12 % for adult people with type 1 diabetes compared with 3.2 % for control subjects. In studies with no control group, the prevalence was 13.4 %. However, of these 14 studies, only 4 examined prevalence in control groups, and only three used a psychiatric, diagnostic interview; the other studies relied on self-report measures of depression (Barnard et al. 2006). In 2009, Gendelman et al. reported that depression was more common in persons with type 1 diabetes compared to nondiabetic subjects, using the Beck Depression Inventory II (BDI-II) cut score (17.5 vs. 5.7 %) or by using either BDI-II cut score or antidepressant use (32.1 vs. 16.0 %; men 25.5 vs. 11.6; women 37.9 vs. 20.5 %) (Gendelman et al. 2009). These conclusions were based on 458 patients with type 1 diabetes and 546 without diabetes within the coronary artery calcification in type 1 diabetes study. More recently, using cross-sectional data from outpatients with type 1 diabetes in the Netherlands, Pouwer et al. observed that 33–36 % reported elevated depression scores when using the WHO-5 questionnaire, 25–33 % when using the Centre for Epidemiological Studies Depression Scale (CES-D), and 8–10 % when using the WHO Composite International Diagnostic Interview (CIDI). Johnson et al. (2013) reviewed the prevalence of depression among young people (up to 25 years old) with type 1 diabetes.

Twenty-three articles were included; three out of the five studies that had used a comparison group found no differences between young persons with type 1 diabetes and controls (Johnson et al. 2013). However, three other studies showed higher rates of depression compared to population norms. Based on these eight studies, the authors concluded that current evidence is inconclusive about whether there is an increased prevalence of depression among young adults with type 1 diabetes (Johnson et al. 2013).

In sum, there is as yet no clear evidence to support that individuals with type 1 diabetes have increased rates of depression. This is mainly due to the restricted number of studies, the quality of the studies (lack of a control group), the research design (majority of studies is cross-sectional), and the measurement of depression (not using a diagnostic interview) (Barnard et al. 2006; Johnson et al. 2013).

Depression in Type 2 Diabetes

In 2006 Ali et al. published a systematic review and meta-analysis in order to estimate the prevalence and odds of depression in adults with type 2 diabetes, compared with those without (Ali et al. 2006). Ten controlled studies were included with a total of 51,331 people. The prevalence of depression appeared to be significantly higher in patients with type 2 diabetes compared with those without [17.6 vs. 9.8 %, OR = 1.6, 95 % CI 1.5–1.7] and higher in females (23.8 %) compared with males (12.8 %). Additional analyses showed that the odds compared to nondiabetic controls for depression were particularly high in male patients with type 2 diabetes (OR = 1.9, 95 % CI 1.7–2.1 in male subsamples, OR = 1.3, 95 % CI 1.2–1.4 in female subsamples). Additional support for the global increased prevalence of depression in diabetes comes from two studies conducted in 60 and 47 countries respectively (Moussavi et al. 2007; Mommersteeg et al. 2013). In the study of Moussavi et al., the self-reported 1-year prevalence of depressive symptoms in diabetes was 9.3 % compared with 3.2 % in people without chronic diseases. Likewise, Mommersteeg et al. showed that, globally, individuals with diabetes had increased odds of an episode of depressive symptoms compared with those without diabetes (adjusted OR = 2.36, 95 % CI 1.91–2.92).

Finally, results from another meta-analysis found that although previously diagnosed diabetes was associated with increased risk of depressive symptoms, the risk of depression in subjects with undiagnosed diabetes or impaired glucose metabolism (prediabetes) was similar to that of nondiabetic controls (Nouwen et al. 2011). These outcomes suggest that the burden of having a chronic disease and not the pathophysiological changes associated with diabetes development, in particular the impaired or disturbed glucose metabolism, does contribute to the development of depression in type 2 diabetes. However, though it is clear that having type 2 diabetes doubles the odds of depression, the exact pathophysiological mechanisms remain largely unclear.

Bidirectional Relationship of Diabetes and Depression

There is now abundant evidence from longitudinal studies that the association between type 2 diabetes and depression is bidirectional with depression increasing the risk of type 2 diabetes and type 2 diabetes increasing the risk of depression (Mezuk et al. 2008; Golden et al. 2008). Depression is a stronger predictor of type 2 diabetes than vice versa. People with type 2 diabetes have a 15 % increased risk of depression compared to people without diabetes, whereas depression is associated with a 60 % increased risk of developing type 2 diabetes (Mezuk et al. 2008). Golden et al. reported a modest association of baseline depressive symptoms with incident type 2 diabetes that was partially explained by lifestyle factors, i.e., daily caloric intake, smoking status, alcohol use, and physical activity. In the same study, impaired fasting glucose and untreated type 2 diabetes were inversely associated with incident depressive symptoms, whereas treated type 2 diabetes showed a positive association with depressive symptoms (Golden et al. 2008). Further support for the bidirectional relationship between diabetes and depression has been provided by several other recent studies (Pan et al. 2010; Renn et al. 2011; Chen et al. 2013; (Nouwen et al. 2010; Rotella and Mannucci 2013).

Depression as a Risk Factor for Cardiovascular Diseases and Mortality

The triad of diabetes, depression, and cardiovascular diseases is closely interrelated. Cardiovascular disease is the most common type of morbidity and mortality in people with diabetes (Marshall and Flyvbjerg 2006). There is accumulating evidence that depression amplifies cardiovascular diseases and mortality in people with diabetes.

Cardiovascular diseases. In their meta-analysis, De Groot et al. (2001) systematically searched for articles published between 1995 and 1999, examining the relationship between depression and diabetes complications in type 1 and type 2 diabetes patients (de Groot et al. 2001). A total of 27 studies were retrieved, and a significant relationship between depression and a variety of diabetes complications (diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction) was confirmed. Yet, all the 27 studies were cross sectional by nature and the authors called for prospective studies.

Since 2001, multiple prospective studies have reported about the impact of depression on cardiovascular complications in diabetes patients. Lin et al. concluded that depression was associated with an increased risk of microvascular (hazard ratio 1.36 [95 % CI 1.05–1.75]) including blindness, end-stage renal disease, amputations, and renal failure deaths) and macrovascular (myocardial infarction, stroke, and cardiovascular procedures) diseases (1.24 [1.0–1.54]), among type 2 diabetes patients who participated in the longitudinal pathways epidemiological study (Lin et al. 2010). Patients with type diabetes alone (n = 40.953) and patients with major depressive disorder alone (n = 77.568) were at

~30 % increase for myocardial infarction, and patients with type 2 diabetes alone were at 82 % increased risk for myocardial infarction, compared with patients without either condition ($n = 214.749$) (Scherrer et al. 2011). The results of the ACCORD study (Action to control Cardiovascular Risk in Diabetes), examining a total of 2053 type 2 diabetes participants, however, showed that depression was not significantly related to the primary composite outcome (cardiovascular death, nonfatal heart attack, or stroke) (HR 1.53 [95 % CI 0.85–2.73]) or to the microvascular composite outcome (0.93 [0.53–1.62]), but all-cause mortality was significantly increased both in those with PHQ-assessed probable major depression (2.24 [1.24–4.06]) and PHQ score of ≥10 (1.84 [1.17–2.89]). The effect of depression on all-cause mortality was not related to previous cardiovascular events or to assignment to intensive or standard glycemic control (Sullivan et al. 2012). Finally, in a 7-year follow-up study of 7835 Chinese type 2 diabetes patients, depression was associated with a two- to threefold increase in the risk of incident cardiovascular disease, especially stroke (Ting et al. 2013). Interestingly, Katon and colleagues studied whether macrovascular or microvascular or coronary, cerebrovascular, or peripheral vascular procedures were associated with depression within the pathways epidemiological study. The results of this prospective study show that baseline severity of depressive symptoms, coronary procedures (i.e., coronary artery bypass surgery, angioplasty, and coronary stent placement) during follow-up, and baseline severity of diabetes symptoms were each independently associated with risk of major depression at 5-year follow-up (Katon et al. 2009).

Depression and cardiovascular mortality. A recent meta-analysis was carried out which examined the relationship between depression, cardiovascular, and all-cause mortality of prospective studies in people with diabetes (van Dooren et al. 2013). A total of 16 studies were included. Depression was associated with an increased mortality risk of all-cause mortality (HR = 1.46, 95 % CI = 1.29–1.66). Although based on only five studies, the results showed a 39 % increased risk for cardiovascular mortality (HR = 1.39, 95 % CI = 1.11–1.73) associated with the presence of depression in diabetes (van Dooren et al. 2013). Based on the evidence of these prospective epidemiological studies, the conclusion can be drawn that depression is likely to increase the risk of cardiovascular diseases and cardiovascular mortality in diabetes. Adjustment for clinical characteristics and health behaviors seemed to attenuate these relationships and thus vital in future studies. Future meta-analysis should confirm the direction and magnitude of these relationships.

Mechanisms Explaining the Link Between Depression and Cardiovascular Risk

There are several potential behavioral and biological mechanisms by which depression may interact with diabetes to worsen the prognosis of cardiovascular risk.

Behavioral mechanisms. A meta-analysis showed that in diabetes patients, depression was associated with reduced treatment nonadherence ($z = 9.97$, $P < 0.0001$) to a wide range of self-care activities (e.g., diet, exercise, medication use)

in both patients with type 1 or type 2 diabetes (Gonzalez et al. 2008). The weighted effect size was near the medium range ($r = 0.21$, 95 % CI 0.17–0.25).

As a consequence of impaired self-care activities, depression may lead to poor glycemic control (Lustman et al. 2000) and diabetes complications (de Groot et al. 2001).

The associations between depression, physical activity, and cardiac outcomes are complex. Depression generally has a strong negative impact on physical activity levels, and this may contribute to the increased cardiovascular risk. Physical inactivity is a common risk for the development of both type 2 diabetes and depression (Buijsse et al. 2011; Dugan et al. 2014; Mammen and Faulkner 2013). In addition, results from a Cochrane review suggest that exercise is moderately more effective than no therapy for reducing symptoms of depression (Cooney et al. 2013). The pooled standardized mean difference (SMD), for the 35 trials, was −0.62 (95 % CI −0.81 to −0.42), indicating a moderate clinical effect in favor of exercise. The methodologically robust trials showed a smaller effect in favor of exercise (Cooney et al. 2013). The SMD from the 8 trials (out of 35) that provided long-term follow-up data found only a small effect in favor of exercise −0.33 (95 % CI −0.63 to −0.03). Depressive symptoms were associated with physical inactivity in primary care type 2 diabetes patients (Koopmans et al. 2009). In the Heart and Soul Study, a prospective cohort study of 1017 outpatients with stable coronary heart disease, it was concluded that the association between depressive symptoms and new cardiovascular events was largely explained by behavioral factors, particularly physical inactivity (Whooley et al. 2008).

Dietary factors may also play a role in linking depression and cardiovascular outcomes in persons with diabetes. For example, change in appetite with subsequent weight gain or weight loss is one of the DSM-IV-TR (American Psychiatric Association 2000) criteria for depression. A poor diet increases the risk of overweight and obesity which are driving factors of the type 2 diabetes epidemic. The Look AHEAD (Action for Health in Diabetes) trial showed that intensive lifestyle intervention can produce sustained weight loss, mean change of −6.15 % of participants initial weight across 4 years, and improvements in fitness, glycemic control, and CVD risk factors (hemoglobin A(1c) levels, systolic blood pressure, and high-density lipoprotein cholesterol levels) in individuals with type 2 diabetes (Look Ahead Research Group and Wing 2010). Alternative behavioral mechanisms that could act as an intermediary between diabetes, depression, and cardiovascular risk are smoking (Ye et al. 2013) and poor sleep (Knutson et al. 2006; Barone and Menna-Barreto 2011).

Biological mechanisms. Depression increases activity of the hypothalamus–pituitary–adrenal (HPA) axis and the sympathetic nervous system (Knol et al. 2006; Krishnan and Nestler 2008), resulting in increased release of cortisol and other glucocorticoids. It is postulated that chronically high cortisol concentrations (as reported in about 50 % of patients with depression) might result in obesity, insulin resistance, and diabetes (Golden 2007). HPA dysregulation has also been associated with CHD risk factors (e.g., abdominal obesity, hypercholesterolemia, hypertension) and is implicated in the pathogenesis of diabetes and CHD (de Jonge et al. 2010; Rosmond and Bjorntorp 2000).

The vascular depression hypothesis suggests a link between vascular pathology and depression in later life. It postulates that cerebrovascular disease can predispose, precipitate, or perpetuate a depressive syndrome in older adults (Alexopoulos 2006; Valkanova and Ebmeier 2013). It implies that micro-damage to small vessels compromises the integrity of the frontal–subcortical circuits involved in mood regulation (Wager-Smith and Markou 2011). There is convincing evidence for a strong relationship between key diseases (cardiovascular disease, diabetes, and stroke) and depression (Valkanova and Ebmeier 2013).

Inflammatory responses accompanying depression also play a role in the progression of vascular complications among diabetes patients. The inflammatory hypothesis of depression proposes a bidirectional association between activation of various aspects of the immune system and depression (Dowlati et al. 2010). The role of inflammatory markers, including C-reactive protein, interleukin-6, and tumor necrosis factor-alpha, is also well known in the pathophysiology of type 2 diabetes (Donath and Shoelson 2011; Hood et al. 2012).

Symptoms of depression are associated with central obesity and cardiovascular disease in people with type 2 diabetes (Labad et al. 2010). Obesity is associated with an increased risk of depression, while depression in turn is associated with an increased risk of obesity (Luppino et al. 2010). To date, findings from a meta-analysis that included 31 randomized trials showed that obese individuals who participated in the intervention group of a weight loss trial experienced reductions in symptoms of depression (Fabricatore et al. 2011). Furthermore, obesity is also one of the most important modifiable risk factors for the development of type 2 diabetes, the cornerstone of lifestyle interventions (i.e., weight reduction and increased physical activity) that prevent or delay the development of type 2 diabetes and its complications (Tuomilehto et al. 2001).

Other biological mechanisms that could link diabetes, depression, and cardiovascular risks are, for example, increased platelet aggregation (von Kanel 2004), lower heart rate variability (Frasure-Smith et al. 2009), and lower omega-3 fatty acid levels (Sontrop and Campbell 2006). The complex interplay between diabetes, depression, and subsequent cardiovascular risk is reflected by the numerous mechanisms described in the literature. Moreover, some of the mechanisms (e.g., poor diet, chronic inflammation, obesity, physical inactivity, and high blood glucose) could be common denominators that contribute to an increased risk of both diabetes and depression (Tabak et al. 2014). Their independent or synergetic effects are to be established in prospective studies.

Does Successful Treatment of Depression Improve CVD Outcomes?

Depression is associated with an increased risk for cardiovascular diseases and higher mortality rates in patients with diabetes. Based on this, one could assume that successful treatment of depression could then improve cardiovascular outcomes. However, currently there is no strong, convincing evidence that

pharmacological or psychological treatment of depression can indeed improve CVD outcomes in patients with diabetes. For example, Bogner et al. used the data from the multisite, practice-randomized, controlled Prevention of Suicide in Primary Care Elderly (PROSPECT). They studied a depression treatment program among 584 participants aged 60–74 of ≥75 years. The authors found that depressed patients with diabetes in the depression treatment program were less likely to have died during the 5-year follow-up interval than depressed diabetic patients in usual care after accounting for baseline differences among patients (adjusted hazard ratio 0.49 [95 % CI 0.24–0.98]). Yet, these outcomes were criticized with regard to flaws in design and methods used (Baumeister et al. 2012). Main critique was that the PROSPECT care intervention was not specifically designed to improve survival. Another important issue was that Bogner et al. used automated variable selection methods in their regression models that often generate substantially inflated type I error rates and artifactually small P values and usually don't produce replicable findings (Thombs and Ziegelstein 2008).

Baumeister et al. systematically reviewed all trials determining the effects of psychological and pharmacological interventions for depression in patients with diabetes and depression (Baumeister et al. 2012). A total of 19 randomized clinical trials with 1592 patients were included. The authors concluded that psychological and pharmacological interventions have moderate and clinically significant effect on depression in diabetes patients. Glycemic control improved moderately in pharmacological trials, while the evidence is inconclusive for psychological interventions. Adherence to diabetic treatment regimens, diabetes complications, death from any cause, health economics, and quality of life has not been investigated sufficiently. Overall, the evidence is sparse and inconclusive due to several low-quality trials with substantial risk of bias and the heterogeneity of examined populations and interventions (Baumeister et al. 2012).

The results of the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHED) trial also showed that depression treatment did not improve cardiac outcomes. ENRICHED was a randomized clinical trial conducted in 2.481 myocardial infarction (MI) patients, comparing cognitive behavioral therapy (CBT), plus sertraline in case of insufficient response, with usual care. Overall this study found modestly improved depression and unable to demonstrate the composite endpoint of all-cause mortality and nonfatal-MI over 2 years (Berkman et al. 2003). A systematic review evaluated the effect of depression treatment on depressive symptoms and cardiac outcome. The authors concluded that depression treatment with medication or cognitive behavioral therapy resulted in modest reductions in depressive symptoms (effect size, 0.20–0.38; r^2, 1–4 %) but no improvement in cardiac outcomes (Thombs et al. 2008).

These studies focus primarily on the treatment of depression only. Collaborative care that focuses on improving management of both depression and diabetes may be more successful in improving clinical and CVD outcomes of both chronic disorders. There is one paper by Katon et al. who conducted a study to determine whether collaborative care of multiple conditions improves disease control in 14 primary care clinics involving 214 participants with poorly controlled diabetes,

coronary heart disease, or both and coexisting depression (Katon et al. 2010). Patients in the intervention group had greater overall 12-month improvement across glycated hemoglobin levels (difference, 0.58 %), LDL cholesterol levels (difference, 6.9 mg per deciliter [0.2 mmol per liter]), systolic blood pressure (difference, 5.1 mmHg), and SCL-20 depression scores (difference, 0.40 points) ($P < 0.001$). In 2013, Huang et al. conducted a meta-analysis to examine whether collaborative care can improve depression and diabetes outcomes in patients with both diseases (Huang et al. 2013). Eight trials containing 2.238 patients showed a significant improvement in depression treatment response (RR = 1.33, 95 % CI = 1.05–1.68), depression remission (adjusted RR = 1.53, 95 % CI = 1.11–2.12), higher rates of adherence to antidepressant medication (RR = 1.79, 95 % CI = 1.19–2.69), and oral hypoglycemic agent (RR = 2.18, 95 % CI = 1.61–2.96), but indicated a nonsignificant reduction in HbA1c values (MD = −0.13, 95 % CI = −0.46–0.19). Unfortunately, none of the eight included collaborative care studies in the meta-analysis (Huang et al. 2013), except the study of Katon et al. (2010) on cardiovascular risk, cardiovascular disease, or mortality.

Evidence Regarding Screening for Depression

Various organizations such as the Canadian Diabetes Association (CDA) (Canadian Diabetes Association Clinical Practice Guidelines Expert C et al. 2013), the American Diabetes Association (ADA) (American Diabetes Association 2013), the American Association of Clinical Endocrinologists (AACE) (Handelsman et al. 2011), and the International Diabetes Federation (IDF) (IDF Clinical Guidelines Task Force 2012) suggest screening for depression patients with diabetes in their guidelines or recommendations for diabetes care, although suggestions on who to screen and methods for screening differ. For example, the CDA suggest screening for depression for all patients with diabetes with recommended questionnaires or interview techniques (Canadian Diabetes Association Clinical Practice Guidelines Expert C et al. 2013). A similar approach is recommended by the AACE, although without specifying the method (Handelsman et al. 2011). The ADA suggests screening only for patients whose self-management is poor (American Diabetes Association 2013).

These recommendations are largely based on expert consensus or clinical experience. Hardly any trials have tested the effectiveness of depression screening in patients with diabetes. Previous research, in patients without diabetes, showed that screening for depression does not improve the recognition of depression, the management of depression, and depressive symptoms in primary care or hospital settings (Gilbody et al. 2008). In a systematic review, there was evidence that depression screening in patients with cardiovascular disease did not produce better outcomes (Thombs et al. 2008). Furthermore, in a randomized controlled trial in an outpatient setting, depression screening with written feedback to patient and clinician in outpatients with diabetes was not effective in reducing depression and mental healthcare utilization, compared to care as usual (Pouwer et al. 2011).

Screening for depression in people with diabetes does not meet all criteria for screening. Criteria for appraising the viability, effectiveness, and appropriateness of a screening program were first described by Wilson and Jungner for the World Health Organization (WHO) in 1968, but are still applicable today (Wilson and Jungner 1968). The criteria are based on ten original principles and relate to knowledge of the disease (e.g., there must be a recognizable latent or early symptomatic stage), knowledge of the test (e.g., suitable test or examination), treatment for the disease (e.g., facilities for diagnosis and treatment available), and cost considerations. Uncertainties remain about the time interval for screening, optimal frequency, the instrument, effectiveness in specific (ethnic) groups, and the overall cost-effectiveness. There is also uncertainty about the implementation of a depression screening program, with extra burden for clinical practices owing to increased numbers of newly detected patients. Furthermore, screening for depression will result in a substantial number of false-positives and unintended harmful consequences and is resource-intensive (Thombs et al. 2012).

So far, there are no randomized controlled studies that evaluated the effects of depression screening on cardiovascular outcomes in patients with diabetes. Given the limited effects of screening on depressive symptoms, it is highly unlikely that screening of depression will subsequently result in a reduction of cardiovascular diseases and mortality. At present, there is no substantial evidence of the effectiveness of screening for depression among diabetes patients and is therefore not recommended.

Future Trials

In the future, efficacy trials should focus on the key questions, such as how to find more optimal ways to prevent and treat depression in persons with diabetes. Ideally, researchers should develop innovative interventions that can help to prevent depression, type 2 diabetes, and cardiovascular diseases or reduce mortality rates, in a cost-effective way (Baumeister et al. 2012). Also, long-term prospective studies are needed to disentangle the mechanisms that link depression with unfavorable cardiovascular risks in diabetes patients. These studies should focus on type 1 or type 2 diabetes patients only; adjust outcomes for clinical characteristics, health behaviors, and complications; and examine whether the associations are attributable to depressive symptoms scales rather than clinically diagnosed depression (diagnostic interview).

Conclusion

Diabetes and depression are public health issues that often co-occur. Approximately 10–30 % of the people with type 1 or type 2 diabetes is affected by depression. The odds of depression in people with type 2 diabetes were twice that of nondiabetic controls. This is less clear for type 1 diabetes patients. There is ample evidence for a

bidirectional relationship between diabetes and depression. Based on primarily prospective studies, it is concluded that depression is likely to increase the risk of cardiovascular complications and cardiovascular mortality in diabetes patients. Plausible behavioral and biological mechanisms were postulated that explain the link between depression and cardiovascular risk in diabetes patients. It is unclear whether treatment of depression improves cardiovascular outcomes. Although advocated by various organizations, there is currently no substantial evidence of the effectiveness of screening for depression among diabetes patients and is therefore not recommended yet.

References

Alexopoulos, G. S. (2006). The vascular depression hypothesis: 10 years later. *Biological Psychiatry, 60*(12), 1304–1305.

Ali, S., Stone, M. A., Peters, J. L., Davies, M. J., & Khunti, K. (2006). The prevalence of co-morbid depression in adults with type 2 diabetes: A systematic review and meta-analysis. *Diabetic Medicine, 23*(11), 1165–1173.

Ali, S., Stone, M., Skinner, T. C., Robertson, N., Davies, M., & Khunti, K. (2010). The association between depression and health-related quality of life in people with type 2 diabetes: A systematic literature review. *Diabetes/Metabolism Research and Reviews, 26*(2), 75–89.

American Diabetes Association. (2013). Standards of medical care in diabetes – 2013. *Diabetes Care, 36*(Suppl 1), S11–S66.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Publishing. Text revision.

Barnard, K. D., Skinner, T. C., & Peveler, R. (2006). The prevalence of co-morbid depression in adults with type 1 diabetes: Systematic literature review. *Diabetic Medicine, 23*(4), 445–448.

Barone, M. T., & Menna-Barreto, L. (2011). Diabetes and sleep: A complex cause-and-effect relationship. *Diabetes Research and Clinical Practice, 91*(2), 129–137.

Baumeister, H., Hutter, N., & Bengel, J. (2012). Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. *Cochrane Database of Systematic Reviews, 12*, CD008381.

Berkman, L. F., Blumenthal, J., Burg, M., et al. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA, 289*(23), 3106–3116.

Bluestone, J. A., Herold, K., & Eisenbarth, G. (2010). Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature, 464*(7293), 1293–1300.

Bosmans, J. E., & Adriaanse, M. C. (2012). Outpatient costs in pharmaceutically treated diabetes patients with and without a diagnosis of depression in a Dutch primary care setting. *BMC Health Services Research, 12*, 46.

Buijsse, B., Simmons, R. K., Griffin, S. J., & Schulze, M. B. (2011). Risk assessment tools for identifying individuals at risk of developing type 2 diabetes. *Epidemiologic Reviews, 33*(1), 46–62.

Canadian Diabetes Association Clinical Practice Guidelines Expert C, Ekoe, J. M., Punthakee, Z., Ransom, T., Prebtani, A. P., & Goldenberg, R. (2013). Screening for type 1 and type 2 diabetes. *Canadian Journal of Diabetes, 37*(Suppl 1), S12–S15.

Chen, P. C., Chan, Y. T., Chen, H. F., Ko, M. C., & Li, C. Y. (2013). Population-based cohort analyses of the bidirectional relationship between type 2 diabetes and depression. *Diabetes Care, 36*(2), 376–382.

Cooney, G. M., Dwan, K., Greig, C. A., et al. (2013). Exercise for depression. *Cochrane Database of Systematic Reviews, 9*, CD004366.

Danaei, G., Finucane, M. M., Lu, Y., et al. (2011). National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: Systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet, 378*(9785), 31–40.

de Groot, M., Anderson, R., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). Association of depression and diabetes complications: A meta-analysis. *Psychosomatic Medicine, 63*(4), 619–630.

de Jonge, P., Rosmalen, J. G., Kema, I. P., et al. (2010). Psychophysiological biomarkers explaining the association between depression and prognosis in coronary artery patients: A critical review of the literature. *Neuroscience and Biobehavioral Reviews, 35*(1), 84–90.

Donath, M. Y., & Shoelson, S. E. (2011). Type 2 diabetes as an inflammatory disease. *Nature Reviews. Immunology, 11*(2), 98–107.

Dowlati, Y., Herrmann, N., Swardfager, W., et al. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry, 67*(5), 446–457.

Dugan, S. A., Bromberger, J. T., Segawa, E., Avery, E., & Sternfeld, B. (2015). Association between physical activity and depressive symptoms: midlife women in SWAN. *Medicine and science in sports and exercise, 47*(2), 335–342.

Fabricatore, A. N., Wadden, T. A., Higginbotham, A. J., et al. (2011). Intentional weight loss and changes in symptoms of depression: A systematic review and meta-analysis. *International Journal of Obesity, 35*(11), 1363–1376.

Frasure-Smith, N., Lesperance, F., Irwin, M. R., Talajic, M., & Pollock, B. G. (2009). The relationships among heart rate variability, inflammatory markers and depression in coronary heart disease patients. *Brain, Behavior, and Immunity, 23*(8), 1140–1147.

Gendelman, N., Snell-Bergeon, J. K., McFann, K., et al. (2009). Prevalence and correlates of depression in individuals with and without type 1 diabetes. *Diabetes Care, 32*(4), 575–579.

Gilbody, S., Sheldon, T., & House, A. (2008). Screening and case-finding instruments for depression: A meta-analysis. *CMAJ, 178*(8), 997–1003.

Golden, S. H. (2007). A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. *Current Diabetes Reviews, 3*(4), 252–259.

Golden, S. H., Lazo, M., Carnethon, M., et al. (2008). Examining a bidirectional association between depressive symptoms and diabetes. *JAMA, 299*(23), 2751–2759.

Gonzalez, J. S., Peyrot, M., McCarl, L. A., et al. (2008). Depression and diabetes treatment nonadherence: A meta-analysis. *Diabetes Care, 31*(12), 2398–2403.

Handelsman, Y., Mechanick, J. I., Blonde, L., et al. (2011). American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocrine Practice, 17*(Suppl 2), 1–53.

Hood, K. K., Lawrence, J. M., Anderson, A., et al. (2012). Metabolic and inflammatory links to depression in youth with diabetes. *Diabetes Care, 35*(12), 2443–2446.

Huang, Y., Wei, X., Wu, T., Chen, R., & Guo, A. (2013). Collaborative care for patients with depression and diabetes mellitus: A systematic review and meta-analysis. *BMC Psychiatry, 13*, 260.

IDF Clinical Guidelines Task Force. (2012). *Global guideline for type 2 diabetes*. Brussels: International Diabetes Federation.

International Diabetes Federation. (2013). *IDF diabetes atlas* (6th ed.). Brussels: International Diabetes Federation.

Johnson, B., Eiser, C., Young, V., Brierley, S., & Heller, S. (2013). Prevalence of depression among young people with type 1 diabetes: A systematic review. *Diabetic Medicine, 30*(2), 199–208.

Katon, W., Russo, J., Lin, E. H., et al. (2009). Depression and diabetes: Factors associated with major depression at five-year follow-up. *Psychosomatics, 50*(6), 570–579.

Katon, W. J., Lin, E. H., Von Korff, M., et al. (2010). Collaborative care for patients with depression and chronic illnesses. *New England Journal of Medicine, 363*(27), 2611–2620.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593–602.

Knol, M. J., Twisk, J. W., Beekman, A. T., Heine, R. J., Snoek, F. J., & Pouwer, F. (2006). Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia, 49*(5), 837–845.

Knutson, K. L., Ryden, A. M., Mander, B. A., & Van Cauter, E. (2006). Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. *Archives of Internal Medicine, 166* (16), 1768–1774.

Koopmans, B., Pouwer, F., de Bie, R. A., van Rooij, E. S., Leusink, G. L., & Pop, V. J. (2009). Depressive symptoms are associated with physical inactivity in patients with type 2 diabetes. The DIAZOB Primary Care Diabetes study. *Family Practice, 26*(3), 171–173.

Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature, 455* (7215), 894–902.

Labad, J., Price, J. F., Strachan, M. W., et al. (2010). Symptoms of depression but not anxiety are associated with central obesity and cardiovascular disease in people with type 2 diabetes: The Edinburgh type 2 diabetes study. *Diabetologia, 53*(3), 467–471.

Lin, E. H., Katon, W., Von Korff, M., et al. (2004). Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care, 27*(9), 2154–2160.

Lin, E. H., Rutter, C. M., Katon, W., et al. (2010). Depression and advanced complications of diabetes: A prospective cohort study. *Diabetes Care, 33*(2), 264–269.

Look Ahead Research Group, & Wing, R. R. (2010). Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: Four-year results of the look AHEAD trial. *Archives of Internal Medicine, 170*(17), 1566–1575.

Luppino, F. S., de Wit, L. M., Bouvy, P. F., et al. (2010). Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry, 67*(3), 220–229.

Lustman, P. J., & Clouse, R. E. (2005). Depression in diabetic patients: The relationship between mood and glycemic control. *Journal of Diabetes and its Complications, 19*(2), 113–122.

Lustman, P. J., Anderson, R. J., Freedland, K. E., de Groot, M., Carney, R. M., & Clouse, R. E. (2000). Depression and poor glycemic control: A meta-analytic review of the literature. *Diabetes Care, 23*(7), 934–942.

Mammen, G., & Faulkner, G. (2013). Physical activity and the prevention of depression: A systematic review of prospective studies. *American Journal of Preventive Medicine, 45*(5), 649–657.

Marshall, S. M., & Flyvbjerg, A. (2006). Prevention and early detection of vascular complications of diabetes. *BMJ, 333*(7566), 475–480.

Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine, 3*(11), e442.

Mezuk, B., Eaton, W. W., Albrecht, S., & Golden, S. H. (2008). Depression and type 2 diabetes over the lifespan: A meta-analysis. *Diabetes Care, 31*(12), 2383–2390.

Mommersteeg, P. M., Herr, R., Pouwer, F., Holt, R. I., & Loerbroks, A. (2013). The association between diabetes and an episode of depressive symptoms in the 2002 World Health Survey: An analysis of 231,797 individuals from 47 countries. *Diabetic Medicine, 30*(6), e208–e214.

Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., & Ustun, B. (2007). Depression, chronic diseases, and decrements in health: Results from the world health surveys. *Lancet, 370* (9590), 851–858.

Nouwen, A., Winkley, K., Twisk, J., et al. (2010). Type 2 diabetes mellitus as a risk factor for the onset of depression: A systematic review and meta-analysis. *Diabetologia, 53*(12), 2480–2486.

Nouwen, A., Nefs, G., Caramlau, I., et al. (2011). Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: A systematic review and meta-analysis of the European depression in diabetes (EDID) research consortium. *Diabetes Care, 34*(3), 752–762.

Pan, A., Lucas, M., Sun, Q., et al. (2010). Bidirectional association between depression and type 2 diabetes mellitus in women. *Archives of Internal Medicine, 170*(21), 1884–1891.

Pouwer, F., Tack, C. J., Geelhoed-Duijvestijn, P. H., et al. (2011). Limited effect of screening for depression with written feedback in outpatients with diabetes mellitus: A randomised controlled trial. *Diabetologia, 54*(4), 741–748.

Renn, B. N., Feliciano, L., & Segal, D. L. (2011). The bidirectional relationship of depression and diabetes: A systematic review. *Clinical Psychology Review, 31*(8), 1239–1246.

Rosmond, R., & Bjorntorp, P. (2000). The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. *Journal of Internal Medicine, 247*(2), 188–197.

Rotella, F., & Mannucci, E. (2013). Diabetes mellitus as a risk factor for depression. A meta-analysis of longitudinal studies. *Diabetes Research and Clinical Practice, 99*(2), 98–104.

Roy, T., & Lloyd, C. E. (2012). Epidemiology of depression and diabetes: A systematic review. *Journal of Affective Disorders, 142*(Suppl), S8–S21.

Scherrer, J. F., Garfield, L. D., Chrusciel, T., et al. (2011). Increased risk of myocardial infarction in depressed patients with type 2 diabetes. *Diabetes Care, 34*(8), 1729–1734.

Sontrop, J., & Campbell, M. K. (2006). Omega-3 polyunsaturated fatty acids and depression: A review of the evidence and a methodological critique. *Preventive Medicine, 42*(1), 4–13.

Strine, T. W., Mokdad, A. H., Balluz, L. S., et al. (2008). Depression and anxiety in the United States: Findings from the 2006 behavioral risk factor surveillance system. *Psychiatric Services, 59*(12), 1383–1390.

Sullivan, M. D., O'Connor, P., Feeney, P., et al. (2012). Depression predicts all-cause mortality: Epidemiological evaluation from the ACCORD HRQL substudy. *Diabetes Care, 35*(8), 1708–1715.

Tabak, A. G., Akbaraly, T. N., Batty, G. D., & Kivimaki, M. (2014). Depression and type 2 diabetes: A causal association? *The Lancet Diabetes & Endocrinology, 2*(3), 236–245.

Thombs, B. D., & Ziegelstein, R. C. (2008). Diabetes, depression, and death: A randomized controlled trial of a depression treatment program for older adults based in primary care (PROSPECT): Response to Bogner et al. *Diabetes Care, 31*(6), e54; author reply e55.

Thombs, B. D., de Jonge, P., Coyne, J. C., et al. (2008). Depression screening and patient outcomes in cardiovascular care: A systematic review. *JAMA, 300*(18), 2161–2171.

Thombs, B. D., Coyne, J. C., Cuijpers, P., et al. (2012). Rethinking recommendations for screening for depression in primary care. *CMAJ, 184*(4), 413–418.

Ting, R. Z., Lau, E. S., Ozaki, R., et al. (2013). High risk for cardiovascular disease in Chinese type 2 diabetic patients with major depression – A 7-year prospective analysis of the Hong Kong Diabetes Registry. *Journal of Affective Disorders, 149*(1–3), 129–135.

Tuomilehto, J., Lindstrom, J., Eriksson, J. G., et al. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine, 344*(18), 1343–1350.

Valkanova, V., & Ebmeier, K. P. (2013). Vascular risk factors and depression in later life: A systematic review and meta-analysis. *Biological Psychiatry, 73*(5), 406–413.

van Dooren, F. E., Nefs, G., Schram, M. T., Verhey, F. R., Denollet, J., & Pouwer, F. (2013). Depression and risk of mortality in people with diabetes mellitus: A systematic review and meta-analysis. *PloS One, 8*(3), e57058.

von Kanel, R. (2004). Platelet hyperactivity in clinical depression and the beneficial effect of antidepressant drug treatment: How strong is the evidence? *Acta Psychiatrica Scandinavica, 110*(3), 163–177.

Vos, T., Flaxman, A. D., Naghavi, M., et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the global burden of disease study 2010. *Lancet, 380*(9859), 2163–2196.

Wager-Smith, K., & Markou, A. (2011). Depression: A repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition? *Neuroscience and Biobehavioral Reviews, 35*(3), 742–764.

Whooley, M. A., de Jonge, P., Vittinghoff, E., et al. (2008). Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA, 300*(20), 2379–2388.

Wilson, J. M. G., & Jungner, G. (1968). *Principles and practice of screening for disease*. Geneva: World Health Organisation.

Ye, S., Muntner, P., Shimbo, D., et al. (2013). Behavioral mechanisms, elevated depressive symptoms, and the risk for myocardial infarction or death in individuals with coronary heart disease: The REGARDS (reason for geographic and racial differences in stroke) study. *Journal of the American College of Cardiology, 61*(6), 622–630.

Insulin Resistance, Glucose Regulation, Obesity, and Mood

Richard Keegan and Nenad Naumovski

Contents

Abstract

The following chapter details current understanding of interactions between insulin, or insulin resistance, obesity, and mood and affect as key mediators of this association. The functions of insulin in the periphery and central nervous system are reviewed, and insulin resistance is explained. Three different levels of affective states are defined: pure affect, mood, and emotion, although it is noted that more research currently focuses on mood and mood disorders. Insulin crosses the blood-brain barrier using saturable transporters, whereupon

R. Keegan (✉)
Research Institute for Sport and Exercise, Faculty of Health, University of Canberra, Canberra, ACT, Australia
e-mail: Richard.Keegan@Canberra.edu.au

N. Naumovski
School of Public Health and Nutrition, Faculty of Health, University of Canberra, Canberra, ACT, Australia
e-mail: Nenad.Naumovski@Canberra.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_64

it influences a range of functions ranging from memory to the regulation of mood and reward-seeking behaviors including eating. The review notes striking similarities between the neurological consequences of diabetes and depressive illness, including decreases in hippocampal formation volume. Hence, the development of insulin resistance would appear to disrupt these systems, contributing to the development of mood disorders such as major depressive disorder and the overconsumption of calorie-dense foods. The precise mechanisms for these processes remain unclear and are likely to be highly complex and multifaceted. Possible mechanisms for these relationships are outlined, including insulin resistance, HPA-axis dysfunction, autonomic nervous system imbalance, endothelial dysfunction, platelet overactivity, inflammation responses, and chronic psychosocial distress. Any or all of these systems offer plausible explanations, and there is no reason to suppose that there is only one correct option from those listed. In addition to studying the cellular and physiological levels of analysis, research must incorporate consideration of the subjective experiences generated by these systems. In particular, there may be explanatory value in examining the less stable short-term experiences of emotions, as well as more stable mood states.

Keywords
Heart disease • Psychogenic heart disease • Aetiology of heart disease • Psychocardiology • Mental illness • Cardiovascular disease • Insulin Resistance - Mood

Introduction

The following chapter details the current empirical understanding of the role of insulin resistance, glucose regulation, and mood in obesity and related disorders. For many years, the scientific subjects of nutrition, psychology, pharmacology, and physiology have often progressed quite independently. It is possible to work as a scientist in some of these fields with relatively little knowledge of the others and to do so quite comfortably. In recent years, however, and particularly in tackling important and complex problems such as obesity, the need for interdisciplinary research and theories has become increasingly clear. Research drawn from different disciplines typically uses different methodological approaches, different language, and interpretations and produces different types of theories or models. As such, if we are to successfully generate solutions to problems that span disciplinary boundaries, we will need to use interdisciplinary strategies. Obesity, diabetes, and cardiovascular disease are inarguably significant problems, spanning several disciplinary boundaries. Thus the following chapter will explore the interplay between insulin resistance, glucose regulation, and mood in relation to obesity and related illnesses.

Insulin Resistance and Glucose Regulation

Insulin is one of the most potent anabolic agents involved in the synthesis and storage of macronutrients (lipids, proteins, and carbohydrates) as well as being involved in their breakdown and release into circulation (Chang et al. 2004). The secretion of insulin from the pancreatic islets of Langerhans into the circulation is characterized as pulsatile, due to the secretory bursts of millions of islet cells. This is also well characterized; the β-cells are stimulated by glucose leading to the secretion of insulin in two phases (biphasic). An initial rapid burst (within 1 min, peaking at 3–5 min and lasting around 10 min) is closely followed by a less dense but more sustained and prolonged release of the insulin (Bratanova-Tochkova et al. 2002; Wilcox 2005). Once plasma glucose concentration is increased, such as after the consumption of a meal, glucose enters the pancreatic β-cells via the glucose transporter located on the cell plasma membrane. The intracellular glucose is then phosphorylated by glucokinase producing the glucose 6-phosphate and generating adenosine triphosphate (ATP). The ATP itself is a signaling molecule for the insulin secretion in the β-cells as the cell itself is equipped with the ATP-sensitive potassium channels (K_{ATP} channels). The K_{ATP} channels close on increase in cytoplasmic ATP and therefore depolarize the membrane and as a consequence open the voltage-dependent calcium channels. This is followed by the influx of Ca^{2+} ions, and this increase in the Ca^{2+} concentration rapidly increases the rate of insulin excretion via exocytosis (Komatsu et al. 2013). Although glucose is the primary stimulus for insulin secretion, other macronutrients (proteins and fats), hormones, and various inputs from the neuronal stimuli can also modify this response of the β-cells.

Similarly to many other peptide hormones, insulin exhibits its action by binding to specific receptors found throughout the body including fat, liver, and muscle cells (and the central nervous system). The main action of insulin in the periphery is to stimulate reduction in circulating glucose levels by triggering cells to increase the uptake of glucose. Furthermore, insulin also signals the liver to increase and promote glycogenesis, and it simultaneously inhibits the secretion of another hormone, glucagon from pancreatic cells. Glucagon has the opposing effects of insulin and, as such, works in the regulation of circulating glucose (Aronoff et al. 2004; Samuel and Shulman 2012). Hepatic glucose production maintains the basal blood glucose regulation during the fasting stage, and once circulating glucose levels become depleted and fall below the normal range, termed hypoglycemia, secretion of glucagon is increased. This effectively leads to the hepatic glucose stimulation and increase in gluconeogenesis with return of plasma glucose to normal levels. This mechanism is not required during and immediately following the meal, as glucagon secretion is suppressed, and when coupled with the insulin effect on the liver, it results in near total suppression of hepatic glucose output (Aronoff et al. 2004).

Insulin resistance (IR) occurs when cells in the body fail to respond to insulin (Chiu et al. 2007). As such, insulin continues to be produced, but cells do not respond to its presence, leading glucose in the blood to accumulate, termed

hyperglycemia. In response, β-cells in the pancreas produce more insulin than normal, which is termed *hyperinsulinemia*. The resistance extends to injected insulin as well as that produced endogenously. One of insulin's functions is to regulate delivery of glucose into cells to provide them with energy (Morino et al. 2006). Insulin-resistant cells cannot absorb glucose, amino, and fatty acids, and in addition these molecules also "leak" out of the cells via osmosis principle. The intracellular environment of the affected cells exhibits a decrease in the ratio of insulin to glucagon that consequently inhibits glycolysis and therefore decreases energy production. The resulting hyperglycemia can also cause adverse health effects such as damage to heart tissue, even in people without diabetes (Rubin et al. 2012).

IR manifests differently in different cell types. For example, in the muscle and fat cells, IR reduces glucose uptake as well as the intracellular storage of glucose (as glycogen and/or triglycerides). In contrast, IR in liver cells results in reduced glycogen synthesis and storage, leading to a failure to regulate glucose levels in the blood. The resultant hyperglycemia and hyperinsulinemia are a major component of metabolic syndrome: a disorder of energy utilization and storage, involving a combination of symptoms including (i) abdominal (central) obesity, (ii) elevated blood pressure, (iii) elevated fasting plasma glucose, (iv) high serum triglycerides, and (v) low high-density lipoprotein (HDL) cholesterol levels (Edwardson et al. 2012).

IR can be initially indicated by the following signs and symptoms (Muniyappa et al. 2008): (i) "brain fogginess" and inability to focus; (ii) hyperglycemia; (iii) sleepiness, especially after meals; (iv) weight gain, fat storage, and difficulty losing weight – specifically the fat in IR is generally stored in and around abdominal organs (irrespective of gender); (v) hypertension – one of insulin's effects is to control arterial wall tension throughout the body; (vi) increased inflammatory markers (e.g., cytokines); (vii) depression; and (viii) increased appetite. IR can be precipitated by (i) genetic factors (e.g., family history with type 2 diabetes, Donohue syndrome, etc.), (ii) ethnicity, (iii) age (especially over 40–45 years), (iv) obesity (especially abdominal obesity), (v) sedentary lifestyle, (vi) hypertension, (vii) hypertriglyceridemia, (viii) low level of HDL cholesterol, and (ix) any previous history of prediabetes or gestational diabetes (Mayfield 1998). Overall, insulin, IR, and the regulation of glucose appear to be central factors in a complex array of related diseases, including diabetes, obesity, cardiac illnesses, strokes, and some mental illnesses.

Diabetes mellitus (DM) is a metabolic disorder that is characterized by chronic hyperglycemia, resulting in the disturbances of macronutrient metabolism. At present, DM affects more than 150 million people worldwide, and estimates are that by the year 2025 this number will be doubled (Zimmet et al. 2001). Traditionally, DM is divided in two very predominant categories: type 1 diabetes, commonly referred to as insulin-dependent diabetes mellitus (IDDM), and type 2 diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM). In addition to these two most predominant categories of diabetes, gestational diabetes that occurs during the pregnancy (Harrison et al. 2015; Hawkins et al. 2015), latent

autoimmune diabetes of adults (LADA) or type 1.5 diabetes (Hernandez et al. 2015), and relatively newly emerged term of Type 3 diabetes are also common (de la Monte 2014).

Type 1 diabetes is a condition that occurs when the body's own immune system destroys the pancreatic β-cells, and as such, the pancreas is not able to produce insulin resulting in increase in glucagon levels. IDDM has a very strong genetic component, occurring in around 5–10 % of all individuals affected by diabetes, meaning its onset is most predominant in childhood and early adulthood (i.e., younger than 20). Type 2 diabetes mellitus is the most common form of this disease affecting up to 95 % of the individuals diagnosed. This type of diabetes is characterized by IR, impaired insulin secretion, or a combination of these two factors resulting in hyperglycemia. Traditionally, diagnosis of this type of diabetes occurs with individuals that are older than 40, although recent trends have seen this average creep downwards. Although a genetic predisposition for this condition cannot be ignored, factors such as obesity, lack of physical activity, and poor diet play a significant risk in developing NIDDM. It is important to emphasize that there is no cure for this condition; rather, the adoption and maintenance of a healthy lifestyle (including the increase in physical activity and maintenance of healthy body weight) have shown suppression of NIDDM (Chisholm et al. 2010; Daneman 2006).

The neurodegeneration that is manifested in sporadic Alzheimer's disease is associated with a number of molecular and biochemical abnormalities, such as reduced glucose metabolism and impaired insulin signaling pathway (Steen et al. 2005). Type 3 diabetes is a relatively new concept that has been deployed to describe the development of IR in the brain tissue, as separate from peripheral tissues, and therefore acting as a major contributor to cognitive impairment. Over recent years, the research in this area has considerably expanded in light of evidence supporting the importance of brain IR in relation to cognitive impairment (de la Monte 2014).

Insulin Resistance and Obesity

It is well documented that IR and obesity appear to be closely related. While the causal system behind this is arguably very complicated, there are clear links to be made. Excess body weight can lead to increased free fatty acids and triglycerides in the blood (Roden et al. 1996), which in turn appear to increase IR (Koyama et al. 1997; Roden et al. 1996; Schinner et al. 2005). Likewise, once established, insulin resistance results in hyperinsulinemia. Given that insulin stimulates the storage of energy into fat cells – which tend to retain their sensitivity even as hepatic and skeletal muscle cells become resistant – IR stimulates the formation of new fatty tissue and accelerates weight gain (Isganaitis and Lustig 2005). Furthermore, both IR and obesity often have the same underlying cause: systematic overeating. Chronic and repeated hyperglycemia and hyperinsulinemia as well as elevated levels of blood lipids, all caused by a hypercaloric diet, would both

contribute to increased IR and trigger the storage of energy in adipose tissue (Unger and Scherer 2010). In relation to the effects of mood, high levels of cortisol within the bloodstream (a key indicator of stress) can contribute to the development of insulin resistance (Giovannini et al. 1982; Sluijs et al. 2010). Further still, resistance to the appetite-suppressing hormone leptin, which is released to trigger feelings of fullness and discourage further eating, also tends to accompany both obesity and IR (Myers et al. 2008). Hence, while the two are closely related, it is not possible to say which is the primary cause of this relationship, and as such, it can be postulated that IR can display without obesity and vice versa obesity without IR.

Insulin Affecting the Brain

Insulin, almost exclusively produced by the pancreas in mammals (Lacroix et al. 2008), crosses the blood-brain barrier using saturable transporters, whereupon it performs a very different role in the central nervous system (CNS) as compared to the periphery (Banks et al. 2012): saturable meaning that above a certain blood serum level, no additional transport of insulin will occur from serum to the CNS. CNS levels of insulin appear to closely follow those in blood serum (Greco et al. 1970; Woods and Porte 1977), and to date, there is no evidence of active transport of insulin from the CNS to serum, only from serum to the CNS (Banks et al. 2012; Cashion et al. 1996). Rather than regulating glucose levels in the CNS, insulin influences aspects of mood, cognition, and appetite (Banks et al. 2012). Many of the glucose transporters within the CNS are insensitive to insulin, including GLUT-1 (astrocytes), GLUT-3 (neurons), and GLUT-5 (microglia), yet these account for the majority of glucose uptake within the CNS (McEwen and Reagan 2004). Those transporters that do appear to be sensitive to insulin (e.g., GLUT-4) reside within the cerebellum, hypothalamus, and hippocampus (Grillo et al. 2009).

The sheer volume of glucose uptake performed by cells that are insensitive to insulin suggests that insulin must be playing a different role within the CNS, as compared to the periphery. In fact, there is clear evidence of insulin performing an antagonistic role once within the CNS, stimulating hunger, feeding, and the release of glucose (Bruning et al. 2000). In this respect, high levels of insulin within the CNS, which may indicate hypoglycemia given that the insulin will be derived from serum, will trigger responses to prevent hypoglycemia. In fact, insulin that is introduced directly into the CNS has the opposite effect to peripheral insulin, increasing blood glucose levels, decreasing feeding and body weight, and even decreasing blood insulin levels (Banks et al. 2012; Bruning et al. 2000; Strubbe and Mein 1977). Insulin also interacts with the brain circuits responsible for rewards and opiates, which are heavily involved in feeding behavior (Figlewicz and Sipols 2010).

Further to the above, insulin within the CNS appears to act as a growth factor, particularly in relation to synaptogenesis and nerve growth (Nelson et al. 2008). Hence, a lack of insulin or resistance to insulin could lead to cognitive decline, impaired learning, and neural plasticity and disorders such as Alzheimer's disease,

which is commonly associated with IR and diabetes (Chiu et al. 2007; Dou et al. 2005; Hoyer 2004; Valenciano et al. 2006). Insulin receptors are distributed throughout the CNS, but are highly concentrated in the olfactory bulb, cerebral cortex, hypothalamus, hippocampus, and cerebellum (Havrankova et al. 1978; Unger et al. 1989). Further, the rate of insulin uptake in these various tissues can be significantly different (Banks 2004), and it is proposed that IR can manifest to different degrees in different CNS tissues – mirroring the variability that occurs in resistance to thyroid hormones (Banks et al. 2012). The number of insulin receptors also decreases with age, suggesting a key role for insulin and IR in the aging process (Bosco et al. 2011; Chung et al. 2002). Such changes could also compound any effects of IR, as receptors would be both fewer in number and less responsive to insulin within the CNS.

One core mechanism through which insulin can be seen to regulate cognition, affect, and behavior is the hypothalamic-pituitary-adrenal (HPA) axis. Insulin signaling, as well as lipid sensing, in the hypothalamus triggers a negative feedback system to inhibit glucose production and appetite (Caspi et al. 2003; Schwartz and Porte 2005; Yue and Lam 2012). The HPA axis is a complex set of direct influences and feedback interactions among three endocrine glands: the hypothalamus, the pituitary gland, and the adrenal glands (small organs on top of the kidneys). The HPA axis is a central component in the neuroendocrine system's regulation of reactions to stress, regulating many body processes, including: digestion, the immune system, mood and emotions, and energy storage/expenditure.

Release of corticotropin-releasing hormone (CRH) from the hypothalamus is influenced by stress, physical activity, illness, blood cortisol levels, and the sleep/wake cycle (circadian rhythm). Typically, cortisol rises rapidly after wakening, peaking after 30–45 min, before falling over the course of the day, and then rising again in late afternoon. As nighttime approaches, cortisol levels fall in late evening, reaching a minimum in the middle of the night. Increased production of cortisol during times of stress increases the availability of glucose in order to facilitate the "fight-or-flight" response. As well as directly increasing glucose availability, cortisol also suppresses the metabolic processes of the immune system that would consume glucose, further increasing its availability (Besedovsky et al. 2008). As such, prolonged chronic stress can contribute to obesity, IR, and type 2 diabetes by disrupting the hormonal balance of the HPA axis (Gohil et al. 2001; Rosmond and Bjorntorp 2000; Tsigos and Chrousos 2002). A dysfunctional HPA axis causes high serum cortisol levels, which results in raising glucose and insulin levels, which in turn cause insulin-mediated effects on adipose tissue, ultimately promoting visceral adiposity and IR (Tsigos and Chrousos 2002). HPA-axis dysfunction and/or chronic psychological stress may explain the reported risk indication of abdominal obesity to cardiovascular disease (CVD), NIDDM, and stroke (Brunner et al. 2002; Rosmond and Bjorntorp 2000). With dense concentrations of insulin receptors in the hypothalamus and olfactory bulb, and the above-described close relationships between the HPA axis, insulin, and glucose, any chronic disorders of insulin regulation would appear to be extremely problematic.

Affective States: Affect, Mood, and Emotion

Affective states involve varying degrees of self-awareness and subjective experience, generally referring to the subjective evaluation of one's current experience (Hogg et al. 2010). Affective states vary in terms of (i) valence (positive versus negative), (ii) arousal (high versus low), (iii) the degree to which action is stimulated ("action tendency" or "motivational intensity"), (iv) the degree of cognitive evaluation, (v) generality versus specificity, and (vi) duration (acute versus chronic). It is possible to distinguish between different approaches to affective states by classifying concepts using these six criteria, with "affect," "mood," and "emotion" emerging as three distinguishable levels of analysis. That said, within any individual these three constructs should covary quite closely, so someone who is experiencing fatigue and exhaustion at the affective level – for example, through lack of sleep – is very likely to report similar evaluations of mood and emotion.

Pure *affect* is proposed as the simplest type of affective state, varying chiefly in terms of valence and arousal, but containing little or no cognitive evaluation, being highly generalized and relatively easy/quick to change. The role of action tendency (also termed motivational intensity) is less clear within affect, as arousal appears to be closely related to this impulse. Hence, for example, affect constituting high arousal and negative valence may reflect feelings of anger and agitation, whereas low arousal and positive valence may reflect the satisfied feeling from completing a difficult task. Studies of affect tend to focus on valence and arousal, for example, by asking participants to point to a location on a diagram mapping valence and arousal (Ekkekakis and Petruzzello 1999, 2000; Hall et al. 2002; Russell 1980). Hence, pure affect can be viewed in a two-by-two model: positive-high (e.g., energized), positive-low (relaxed/satisfied), negative-high (e.g., anger-frustration), and negative-low (e.g., depressed/exhausted) – cf. Russell 1980. In principle, affective states can change quite quickly, for example, in response to exercise, and are also more physiologically based. However, in a situation of relative homeostasis, affect is unlikely to change significantly over minutes or hours, without meaningful physiological stimulus. Thus affect is more likely to be influenced by sleep/fatigue, hydration, diet, exercise, etc. Pure affect should be difficult to influence using cognition, so "thinking positive" may not always lead to a difference in experienced energy levels (e.g., arousal). For this reason, pure affect is usually viewed as generalized, in that it has no clear cause or "target."

Mood can also be viewed as varying in terms of valence and arousal/energization, but it differs from pure affect because it is longer lasting (e.g., hours, days, weeks) (Schucman and Thetford 1975) and generally does involve some degree of cognitive mediation/evaluation (Brett 2003). To facilitate such cognitive evaluation, it means some sort of cause or "target" is involved, and so a mood can be more readily linked to something that is causing it, such as an imminent deadline or a recent event. However, mood remains relatively generalized and diffuse, lasting a long time, and thus it is not easy to consciously identify a specific target (i.e., people may simply forget what has caused a particular mood). In this respect, it remains

relatively difficult to influence mood using cognition; mood is relatively slow to change, and the cognitive component is usually viewed in terms of underlying beliefs and expectations (Batson et al. 1992), as opposed to explicit, deliberate, or conscious thoughts. As a result, mood arguably has the lowest action tendency of the three levels outlined, given that it has no clear focus (or a target that is very difficult to identify), is slow to change, and is difficult to deliberately influence. Thus, even deliberate and targeted attempts to influence mood can be problematic (Detweiler-Bedell et al. 2006; Heimpel et al. 2002). Mood is frequently measured using questionnaires, which is appropriate given its relative temporal stability and subjective accessibility. Common measures include the Profile of Mood States (POMS) (McNair et al. 1971; Pollock et al. 1979), the Brunel Mood Scale (BRUMS) (Terry et al. 1999, 2003), and the Positive and Negative Affect Schedule (PANAS) (Crawford and Henry 2004; Watson et al. 1988). Typically, these measures include subscales assessing tension-anxiety (all three), depression/sadness (all three), anger/hostility (all three), fatigue (all three), vigor/activation (BRUMS, POMS), and confusion (BRUMS, POMS), with the expanded PANAS also including guilt, surprise, joviality, self-assurance, attentiveness, and serenity (Thompson 2007). In this respect, it is clear that mood is more complex than affect, but closely related, because it contains similar concepts as well as many additions.

While mood reliably contains between 6 and 13 separable constructs, Hanin's (1999, 2000) reviews of various models of emotion identified 47 discrete emotions: ranging from fear and anger (i.e., consistent with affect and mood) to disgust, contempt, expectancy, acceptance, resignation, and more (Hanin 1999, 2000). Hence, emotions can be viewed as much more complex than affect and mood, varying in terms of valence and arousal, but also in terms of action tendency, generality, and cognitive appraisal. In fact, Hanin (1999) argued that this cognitive appraisal added additional considerations, such as whether the target/cause was in the past, present, or future, spatially close versus distant, and relating to the self versus another. Emotions are generally viewed as being shorter in duration and readily modified according to the changes in cognitive appraisal. Emotions are likely to be influenced, or biased, by current affect and mood. For example, a negative or flat mood may bias one's cognitive appraisal, and this may lead to a more negative emotional response. However, it is possible for an emotion to be experienced that is inconsistent with one's mood or affect. For example, one could be extremely tired and irritable after a day at work, but then be temporarily inspired or exhilarated when watching a television program. It is also possible for sustained or repeated emotional experiences to begin to influence mood, although this proposition may require further testing. The incredible variability of emotions combined with their temporal instability makes them relatively difficult to study. In light of this, much of the current chapter focuses on mood states and chronic affective disorders, which are both smaller in number and temporally consistent. Accordingly, there appears to be good potential for future research to progress from examining long-term and stable affective/mood states and instead explore how insulin, glucose, and related systems are related to more complex emotional states.

The Relationships between Insulin Resistance, Obesity, Glucose Regulation, and Mood

As noted in the preceding text, there are a number of important structures in the CNS that are affected by insulin and therefore a number of important functions that may be influenced too. Any effects on the HPA axis are likely to influence affect, moods, and feelings of stress, whereas any influences on cognition may affect our ability to perform the cognitive appraisals that precede emotions. As an example of a relatively direct effect, dopaminergic receptors in the ventral tegmental area (VTA) of the brain contain insulin receptors (Figlewicz et al. 2003), and insulin in this area regulates dopamine reuptake (Figlewicz et al. 1994). Mice with damaged insulin receptors in the VTA increase food intake and adiposity (Konner et al. 2011). In humans, these neural circuits play a key role in motivation and decision-making (DeLong and Wichmann 2010) as well as regulating a variety of motor control functions (Bjorklund and Dunnett 2007). The VTA is strongly associated with the experiencing of "rewards" following behaviors such as eating and sex, and stimulation of the area by drugs or electrodes is also reported to generate pleasurable experiences (Arias-Carrion and Poppel 2007; Wise 1996). However, in addition to simple "rewards," dopamine in the VTA is also associated with increased action tendencies and movement (Schultz 2002). Overall, dopamine appears to be important in both "reward" experiences and "seeking" tendencies, and so depending which specific circuits are more or less affected by insulin, appetite and/or enjoyment of eating may be influenced in this way. The amount of feeding as well as the nutritional constitution – glucose, carbohydrate, and lipids – will likely produce different impacts on mood. For example, fasting may gradually decrease CNS insulin, leading to a VTA-dopamine response that both motivates feeding and overestimates the likely pleasure/reward that will be derived (Schultz 2002). Feeding on foods that generate a lower-than-expected reward may decrease dopamine levels, whereas foods that produce a greater-than-expected reward may temporarily increase dopamine (the "prediction-error" hypothesis – cf. Schultz 2002). In fact, fMRI imaging studies have shown differences between the need to eat and the pleasure of eating within the VTA system (Tataranni and DelParigi 2003; Wang et al. 2001). Further, chronic stress, along with the accompanying chronic increases in neural glucocorticoids, appears to stimulate a preference for sweet and fatty foods, in a process believed to occur in the VTA-dopamine system (Lindley et al. 1999; Volkow et al. 2002; Wang et al. 2002). As such, any dysfunction or degradation of this system, such as IR or chronic hypo/hyperglycemia, may generate long-term problems for both mood/affect and obesity.

Following this line of reasoning, recent research has shown a longitudinal association between eating "palatable" food in order to cope (e.g., with stress or unhappiness) and subsequent increases in BMI in adults (Boggiano et al. 2015a; see also Boggiano et al. 2014; Burgess et al. 2014). In contrast, for adolescents perceptions of reward correlated most strongly with BMI, not coping motives (Boggiano et al. 2015b). These findings raise the possibility that eating highly

palatable foods to experience reward may subsequently catalyze such eating to cope and the development of obesity. This possibility is supported by the link between reward sensitivity and obesity in children (Faith et al. 2013; Graziano et al. 2010; Rollins et al. 2014). Hence, the development of IR may accompany and compound obesity by affecting the way humans both seek rewards and cope with negative affect, stimulating the overconsumption of highly palatable foods (i.e., high fat, high sugar, or high salt and calorie dense).

Obesity is known to impair the transit of insulin across the blood-brain barrier (Kaiyala et al. 2000), and IR – in the form of reduced effects on feeding and glucose regulation – is more pronounced in high-fat fed rodents (Clegg et al. 2011; Ono et al. 2008). The mechanism of impairment is proposed to be through interrupted insulin signaling in the hypothalamus (Belgardt and Bruning 2010; Clegg et al. 2011). Effectively, the high lipid levels and inflammation cause damage to the endoplasmic reticulum, and this leads to IR in both peripheral (Hotamisligil 2010) and CNS tissues (De Souza et al. 2005). Such increases in IR in both the periphery/liver and in the brain have been observed in both rats and dogs and would appear to constitute a vicious cycle of unhealthy eating triggering obesity, low mood, and further unhealthy eating (Yue and Lam 2012). Given the above descriptions of how insulin and IR may influence mood and affect, we should expect a clear association between obesity and mood disturbances.

Accordingly, in a study of children aged 5–13 years, depressive symptomatology at baseline was predictive of IR 6 years later, suggesting that low mood may be a key precursor to IR, obesity, and related disorders (Shomaker et al. 2011). This association was subsequently observed from early adolescence (mean age 12 years) into adulthood (mean age 33) in women, but not men (Pulkki-Raback et al. 2009). Associations have also been reported between depressive symptoms (and/or perceived stress) and IR in adults (Arroyo et al. 2004; Eaton et al. 1996; Everson-Rose et al. 2004; Golden et al. 2004; Kawakami et al. 1999; Suarez 2006). A relatively recent meta-analysis concluded that depressive symptoms were associated with a 37 % increased risk of subsequently developing NIDDM, independent of confounds such as body mass index (BMI) (Knol et al. 2006). Hence, chronic low mood and diminished affect appear to be good predictors of subsequent IR. Depressive symptomatology also accompanies diabetes and IR (Eckel et al. 2005; Okamura et al. 2000; Ramasubbu 2002; Timonen et al. 2005), particularly when comorbid cardiovascular disease is present (Engum et al. 2005; Gans 2006). It even seems that the degree of metabolic control maintained by diabetes patients plays an important role in determining whether depressive illness develops as a comorbidity (Lustman and Clouse 2005). This connection suggests a breakdown of a common system (or systems) that regulates glucose, insulin, and affective states with likely important roles for dyslipidemia and cortisol (Grundy et al. 2005).

IR and major depressive illness share several pathologies, including disorders of the HPA axis, the autonomic nervous system, platelets, and endothelial function (Gans 2006; Reagan 2007; Tamashiro et al. 2011). In fact, Gans (2006) outlined a range of possible pathways through which these symptoms may be

generated, including insulin resistance, HPA -axis dysfunction, autonomic nervous system imbalance, endothelial dysfunction, platelet overactivity, inflammation responses (too much inflammation or insufficient dampening), and chronic psychosocial distress. Any or all of these systems offer plausible explanations, and there is no reason to suppose that there is only one correct option from the seven listed. Evidence is accruing of a close linkage between the HPA axis, glycemic control, and cognitive performance (Bruehl et al. 2007). In this study, patients with type 2 diabetes exhibited increased basal levels of cortisol as well as increased cortisol following a dexamethasone suppression test – indicting hyperreactivity of the HPA axis. Further, neuroendocrine dysfunction was correlated with declarative memory performance in these patients. It has also been shown that acute insulin administration improves the declarative memory of Alzheimer's patients (Craft et al. 1996). Reagan (2007) has been quoted frequently in recent years, after describing the "striking similarities" (p. 635) between the neurological consequences of diabetes and depressive illness, including decreases in hippocampal formation volume (a vital component of memory function – see also: McEwan et al. 2002). In fact the hippocampus appears to be extremely sensitive to dysfunctional glucose regulation and/or insufficient insulin availability (or sensitivity), which triggers neural synaptic reorganization (Magariños and McEwen 2000) and increased astrocyte proliferation in diabetic rodents (Saravia et al. 2002). Remembering the importance of cognitive evaluation in emotions and, to a lesser extent, moods, these findings highlight the potential impact of impaired cognitive functioning on affective states. For example, a person faced with a stressful challenge and unable to bring to mind similar occasions when they coped successfully is likely to experience a more negative emotional and affective reaction. Glucose, and therefore insulin, appears to play important roles in memory function. For example, fasting has been shown to negatively correlate with episodic memory in healthy women (Rolandsson et al. 2008), and administering glucose has been shown to improve cognitive performance in humans and animals regardless of pre-existing cognitive impairments (Craft et al. 1996; Kaplan et al. 2000; Sunram-Lea et al. 2002). During tasks requiring hippocampal activity, extracellular glucose levels drop in rodents, implying uptake into the cells (McNay et al. 2000). Hence, we appear to face a situation where hypoglycemia impairs important aspects of brain function, but chronic or repeated hyperglycemia appears to cause lasting damage to the CNS (Perantie et al. 2007; Wrighten et al. 2009). This emphasizes the importance of maintaining glucose regulation, *euglycemia*, both for short-term CNS functioning and in the long-term maintenance of CNS health (Wrighten et al. 2009).

There is also increasing evidence of close associations between obesity and mood disorders such as depression, anxiety, panic disorder, and bipolar (Kloiber et al. 2007; McElroy et al. 2004; Novick et al. 2005; Simon et al. 2006; Singh 2014). Impairment in CNS function has been linked to obesity that in turn impacts mental and physical health (Allison et al. 2009; Duarte et al. 2010; Talen and Mann 2009). Obese individuals are at increased risk of developing depression and this risk is

doubled in the presence of diabetes (Anderson et al. 2001; de Groot et al. 2001; Labad et al. 2012). Depressed mood is also associated with abdominal obesity and poor diet (Dong et al. 2004; Hamer et al. 2012; Luppino et al. 2010; Roberts et al. 2003; Simon et al. 2006; Zhao et al. 2011). In animal models of mood disorders, a consistent link is found between obesity and depressive symptoms, again suggesting a common signaling pathway (Akubuiro et al. 2013; Chuang et al. 2011; Dallman 2010; Diz-Chaves 2011; Kumar et al. 2013; Maniam and Morris 2010; Spence and Courbasson 2012). As is the case throughout this field of research, the relationship does not appear to be one of linear causation (Singh 2014). As such, obesity can contribute to low mood (e.g., low energy, low self-esteem), but persistent low mood can contribute to obesity by prompting both increased feeding behavior and biasing food selection towards high-fat and high-sugar sources. Additionally, the IR, hyperglycemia, and chronic stress (i.e., HPA-axis activation) that often accompany obesity are likely to compound and propagate these issues. Hence, not only are IR and mood clearly linked, but so are obesity and mood, and there is clear evidence of the signaling pathways being closely related albeit complex.

One core issue for consideration is the role of pro-inflammatory cytokines from immune activity. Emerging evidence suggests an important link between increased production of these small proteins and neurochemical/neurotropic changes to the brain (Raison et al. 2006). When considered alongside their likely interactions with stress hormones and the endothelial membrane, cytokines stemming from autoimmune dysfunction and/or chronic stress appear strong candidates for further research (Craft et al. 1996; Reagan 2007). Likewise, chronic, or repeated episodes of, hyperglycemia may further compound this threat to the cell membranes of both the heart tissue (Rubin et al. 2012) and key neurological functions (Pais et al. 2007; Sommerfield et al. 2004). In fact, the administration of inflammatory cytokines such as IFN-α, IL-1, IL-2, IL-6, TNF-α, and C-reactive protein has been reliably shown to induce changes in mood, cognition, and behavior, similar to those observed in mood and anxiety disorders (Dantzer and Kelley 2007; Kent et al. 1992; Raison et al. 2006). Further still, blocking the receptors for these proteins has been shown to reduce sickness behavior and depressive symptoms in laboratory animals, even when the symptoms develop as a result of psychological stress (Milligan et al. 1998; Persoons et al. 2005; Tyring et al. 2006). Pro-inflammatory cytokines also have well-described effects on the HPA axis that are consistent with the changes seen in major depression and mood disorders (Raison et al. 2006). Specifically, increased production of CRH and cortisol as well as decreasing tissue sensitivity to glucocorticoid hormones (Hasler et al. 2004; Pace et al. 2007; Silverman et al. 2004). Pro-inflammatory cytokines also appear to mediate IR (Dandona et al. 2004; Shoelson et al. 2007). Hence, we have a developing picture of a system linking IR, obesity, and mood in complex and multifaceted ways, including the separate actions of insulin in the CNS and periphery, HPA-axis dysfunction, autoimmune responses, endothelial dysfunction, inflammatory responses, and chronic psychosocial distress (Gans 2006).

Clinical Implications

When facing such a complex and interactive system, we rarely deal in clear-cut diagnoses and treatment indications. Instead, we must observe the totality of the system, make measured and careful changes, and carefully monitor the effects. Further still, there is no reassurance that such a system will return to homeostasis if we remove a stimulus that has caused an unwanted change. We are faced with the famous "butterfly effect" problem, popularized by Lorenz (1963). There are relatively clear diagnostic tests and criteria for IR, metabolic syndrome, diabetes mellitus, mood disorders, and obesity. It is not clear, however, whether practitioners detecting one such disorder may wish to test for others in order to reach a more complete diagnosis of the evolving system. There is evidence that treating individual problems can also affect other aspects of the system, for example, antidepressant use appears to remove or attenuate inflammatory responses (Musselman et al. 2003; Yirmiya et al. 2001). Given the variability in how symptoms manifest and present, it seems sensible to approach issues on a case-by-case basis. There is no clear evidence to date that any specific aspect of the problem – obesity, IR, or mood disturbance – is primary in driving the pathology. Individual patients should arguably be assessed, evaluated, and treated in relation to their individual symptoms, while remaining cognizant of the potential comorbidities and developmental trajectories/prognoses.

Conclusions

This chapter has presented a brief but comprehensive overview of current knowledge in relation to IR, glucose regulation, obesity, and mood. Not only does this topic span disciplinary boundaries, but we also see an emerging picture of a complex regulatory system with no clean "directional causality." This situation challenges conventional approaches to science, which are often neatly segregated by topic area and which frequently assume a simple causal chain. However, by acknowledging both that our work must span disciplinary boundaries as well as addressing a highly complex phenomenon, we give ourselves the best chance of eventually understanding and even mastering an extremely important problem. The methods, analysis, training, and recruitment technique we adopt will therefore change accordingly. By developing specialists, researchers, and practitioners in this unique topic area, we may begin to construct a common understanding, and this approaches a clear consensus regarding best practice.

References

Akubuiro, A., Bridget Zimmerman, M., Boles Ponto, L. L., Walsh, S. A., Sunderland, J., McCormick, L., & Singh, M. (2013). Hyperactive hypothalamus, motivated and non-distractible chronic overeating in ADAR2 transgenic mice. *Genes, Brain and Behavior, 12*(3), 311–322. doi:10.1111/gbb.12020.

Allison, D. B., Newcomer, J. W., Dunn, A. L., Blumenthal, J. A., Fabricatore, A. N., Daumit, G. L., … Alpert, J. E. (2009). Obesity among those with mental disorders: A National Institute of Mental Health meeting report. *American Journal of Preventive Medicine, 36*(4), 341–350. doi:10.1016/j.amepre.2008.11.020.

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The prevalence of comorbid depression in adults with diabetes: A meta-analysis. *Diabetes Care, 24*(6), 1069–1078.

Arias-Carrion, O., & Poppel, E. (2007). Dopamine, learning, and reward-seeking behavior. *Acta Neurobiologiae Experimentalis (Warsaw), 67*(4), 481–488.

Aronoff, S. L., Berkowitz, K., Schreiner, B., & Want, L. (2004). Glucose metabolism and regulation: Beyond insulin and glucagon. *Diabetes Spectrum, 17*(3), 183–190.

Arroyo, C., Hu, F. B., Ryan, L. M., Kawachi, I., Colditz, G. A., Speizer, F. E., & Manson, J. (2004). Depressive symptoms and risk of type 2 diabetes in women. *Diabetes Care, 27*(1), 129–133.

Banks, W. A. (2004). The source of cerebral insulin. *European Journal of Pharmacology, 490* (1–3), 5–12. doi:10.1016/j.ejphar.2004.02.040.

Banks, W. A., Owen, J. B., & Erickson, M. A. (2012). Insulin in the brain: There and back again. *Pharmacology and Therapeutics, 136*(1), 82–93. doi:10.1016/j.pharmthera.2012.07.006.

Batson, C. D., Shaw, L. L., & Oleson, K. C. (1992). Differentiating affect, mood, and emotion: Toward functionally based conceptual distinctions. In M. S. Clark (Ed.), *Emotion. Review of personality and social psychology* (pp. 294–326). Thousand Oaks: Sage Publications.

Belgardt, B. F., & Bruning, J. C. (2010). CNS leptin and insulin action in the control of energy homeostasis. *Annals of the New York Academy of Sciences, 1212*, 97–113. doi:10.1111/j.1749-6632.2010.05799.x.

Besedovsky, H., Chrousos, G., & Rey, A. D. (2008). *The hypothalamus-pituitary-adrenal axis* (1st ed.). *Elsevier Science*. Amsterdam: Academic.

Bjorklund, A., & Dunnett, S. B. (2007). Dopamine neuron systems in the brain: An update. *Trends in Neurosciences, 30*(5), 194–202. doi:10.1016/j.tins.2007.03.006.

Boggiano, M. M., Burgess, E. E., Turan, B., Soleymani, T., Daniel, S., Vinson, L. D., Lokken, K. L., Wingo, B. C., & Morse, A. (2014). Motives for eating tasty foods associated with binge-eating. Results from a student and a weight loss seeking population. *Appetite, 83*, 160–166.

Boggiano, M. M., Wenger, L. E., Turan, B., Tatum, M. M., Morgan, P. R., & Sylvester, M. D. (2015a). Eating tasty food to cope. Longitudinal association with BMI. *Appetite, 87*, 365–370. doi:10.1016/j.appet.2015.01.008.

Boggiano, M. M., Wenger, L. E., Mrug, S., Burgess, E. E., & Morgan, P. R. (2015b). The kids-palatable eating motives scale: Relation to BMI and binge eating traits. *Eating Behaviors, 17*, 69–73.

Bosco, D., Fava, A., Plastino, M., Montalcini, T., & Pujia, A. (2011). Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. *Journal of Cellular and Molecular Medicine, 15*(9), 1807–1821. doi:10.1111/j.1582-4934.2011.01318.x.

Bratanova-Tochkova, T. K., Cheng, H., Daniel, S., Gunawardana, S., Liu, Y. J., Mulvaney-Musa, J., … Sharp, G. W. (2002). Triggering and augmentation mechanisms, granule pools, and biphasic insulin secretion. *Diabetes, 51*(Suppl 1), S83–S90.

Brett, M. A. S. (2003). The influence of gender on mood effects in advertising. *Psychology and Marketing, 20*(3), 249–273. doi:10.1002/mar.10070.

Bruehl, H., Rueger, M., Dziobek, I., Sweat, V., Tirsi, A., Javier, E., … Convit, A. (2007). Hypothalamic-pituitary-adrenal axis dysregulation and memory impairments in type 2 diabetes. *Journal of Clinical Endocrinology Metabolism, 92*(7), 2439–2445. doi:10.1210/jc.2006-2540.

Bruning, J. C., Gautam, D., Burks, D. J., Gillette, J., Schubert, M., Orban, P. C., … Kahn, C. R. (2000). Role of brain insulin receptor in control of body weight and reproduction. *Science, 289* (5487), 2122–2125.

Brunner, E. J., Hemingway, H., Walker, B. R., Page, M., Clarke, P., Juneja, M., ... Marmot, M. G. (2002). Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: Nested case-control study. *Circulation, 106*(21), 2659–2665.

Burgess, E. E., Turan, B., Lokken, K. L., Morse, A., & Boggiano, M. M. (2014). Profiling motives behind hedonic eating. Preliminary validation of the Palatable Eating Motives Scale. *Appetite, 72*, 66–72.

Cashion, M. F., Banks, W. A., & Kastin, A. J. (1996). Sequestration of centrally administered insulin by the brain: Effects of starvation, aluminum, and TNF-alpha. *Hormones and Behavior, 30*(3), 280–286. doi:10.1006/hbeh.1996.0034.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., ... Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386–389. doi:10.1126/science.1083968.

Chang, L., Chiang, S. H., & Saltiel, A. R. (2004). Insulin signaling and the regulation of glucose transport. *Molecular Medicine, 10*(7–12), 65–71. doi:10.2119/2005-00029.Saltiel.

Chisholm, D., Best, J., Frazer, I., Pawlak, D., Townsend, J., Twigg, S. (2010). Australian Type 1 diabetes research agenda – Parenting science, government and the community.

Chiu, H. K., Tsai, E. C., Juneja, R., Stoever, J., Brooks-Worrell, B., Goel, A., & Palmer, J. P. (2007). Equivalent insulin resistance in latent autoimmune diabetes in adults (LADA) and type 2 diabetic patients. *Diabetes Research and Clinical Practice, 77*(2), 237–244. doi:10.1016/j.diabres.2006.12.013.

Chuang, J. C., Perello, M., Sakata, I., Osborne-Lawrence, S., Savitt, J. M., Lutter, M., & Zigman, J. M. (2011). Ghrelin mediates stress-induced food-reward behavior in mice. *Journal of Clinical Investigation, 121*(7), 2684–2692. doi:10.1172/JCI57660.

Chung, Y. H., Shin, C. M., Joo, K. M., Kim, M. J., & Cha, C. I. (2002). Region-specific alterations in insulin-like growth factor receptor type I in the cerebral cortex and hippocampus of aged rats. *Brain Research, 946*(2), 307–313.

Clegg, D. J., Gotoh, K., Kemp, C., Wortman, M. D., Benoit, S. C., Brown, L. M., ... Woods, S. C. (2011). Consumption of a high-fat diet induces central insulin resistance independent of adiposity. *Physiology and Behavior, 103*(1), 10–16. doi:10.1016/j.physbeh.2011.01.010.

Craft, S., Newcomer, J., Kanne, S., Dagogo-Jack, S., Cryer, P., Sheline, Y., ... Alderson, A. (1996). Memory improvement following induced hyperinsulinemia in Alzheimer's disease. *Neurobiol Aging, 17*(1), 123–130.

Crawford, J. R., & Henry, J. D. (2004). The positive and negative affect schedule (PANAS): Construct validity, measurement properties and normative data in a large non-clinical sample. *British Journal of Clinical Psychology, 43*(Pt 3), 245–265. doi:10.1348/0144665031752934.

Dallman, M. F. (2010). Stress-induced obesity and the emotional nervous system. *Trends in Endocrinology and Metabolism, 21*(3), 159–165. doi:10.1016/j.tem.2009.10.004.

Dandona, P., Aljada, A., & Bandyopadhyay, A. (2004). Inflammation: The link between insulin resistance, obesity and diabetes. *Trends in Immunology, 25*(1), 4–7.

Daneman, D. (2006). Type 1 diabetes. *Lancet, 367*(9513), 847–858. doi:10.1016/S0140-6736(06)68341-4.

Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity, 21*(2), 153–160. doi:10.1016/j.bbi.2006.09.006.

de Groot, M., Anderson, R., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). Association of depression and diabetes complications: A meta-analysis. *Psychosomatic Medicine, 63*(4), 619–630.

de la Monte, S. M. (2014). Type 3 diabetes is sporadic Alzheimer's disease: Mini-review. *European Neuropsychopharmacology, 24*(12), 1954–1960. doi:10.1016/j.euroneuro.2014.06.008.

De Souza, C. T., Araujo, E. P., Bordin, S., Ashimine, R., Zollner, R. L., Boschero, A. C., Saad, M. J., & Velloso, L. A. (2005). Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. *Endocrinology, 146*, 4192–4199.

DeLong, M., & Wichmann, T. (2010). Changing views of basal ganglia circuits and circuit disorders. *Clinical EEG Neuroscience, 41*(2), 61–67. doi:10.1177/155005941004100204.

Detweiler-Bedell, B., Detweiler-Bedell, J. B., & Salovey, P. (2006). Mood-congruent perceptions of success depend on self-other framing. *Cognition & Emotion, 20*(2), 196–216. doi:10.1080/02699930500294996.

Diz-Chaves, Y. (2011). Ghrelin, appetite regulation, and food reward: Interaction with chronic stress. *International Journal of Peptides, 2011*, 898450. doi:10.1155/2011/898450.

Dong, C., Sanchez, L. E., & Price, R. A. (2004). Relationship of obesity to depression: A family-based study. *International Journal of Obesity and Related Metabolic Disorders, 28*(6), 790–795. doi:10.1038/sj.ijo.0802626.

Dou, J. T., Chen, M., Dufour, F., Alkon, D. L., & Zhao, W. Q. (2005). Insulin receptor signaling in long-term memory consolidation following spatial learning. *Learning and Memory, 12*(6), 646–655. doi:10.1101/lm.88005.

Duarte, C. S., Sourander, A., Nikolakaros, G., Pihlajamaki, H., Helenius, H., Piha, J., ... Must, A. (2010). Child mental health problems and obesity in early adulthood. *Journal of Pediatrics, 156*(1), 93–97. doi:10.1016/j.jpeds.2009.06.066.

Eaton, W. W., Armenian, H., Gallo, J., Pratt, L., & Ford, D. E. (1996). Depression and risk for onset of type II diabetes. A prospective population-based study. *Diabetes Care, 19*(10), 1097–1102.

Eckel, R. H., Grundy, S. M., & Zimmet, P. Z. (2005). The metabolic syndrome. *Lancet, 365*(9468), 1415–1428. doi:10.1016/S0140-6736(05)66378-7.

Edwardson, C. L., Gorely, T., Davies, M. J., Gray, L. J., Khunti, K., Wilmot, E. G., ... Biddle, S. J. (2012). Association of sedentary behaviour with metabolic syndrome: A meta-analysis. *PLoS One, 7*(4), e34916. doi:10.1371/journal.pone.0034916.

Ekkekakis, P., & Petruzzello, S. J. (1999). Acute aerobic exercise and affect: Current status, problems and prospects regarding dose-response. *Sports Medicine, 28*(5), 337–374.

Ekkekakis, P., & Petruzzello, S. J. (2000). Analysis of the affect measurement conundrum in exercise psychology: I. Fundamental issues. *Psychology of Sport & Exercise, 1*, 71–88.

Engum, A., Mykletun, A., Midthjell, K., Holen, A., & Dahl, A. A. (2005). Depression and diabetes: A large population-based study of sociodemographic, lifestyle, and clinical factors associated with depression in type 1 and type 2 diabetes. *Diabetes Care, 28*(8), 1904–1909.

Everson-Rose, S. A., Meyer, P. M., Powell, L. H., Pandey, D., Torrens, J. I., Kravitz, H. M., ... Matthews, K. A. (2004). Depressive symptoms, insulin resistance, and risk of diabetes in women at midlife. *Diabetes Care, 27*(12), 2856–2862.

Faith, M. S., Carnell, S., & Kral, T. V. (2013). Genetics of food intake self-regulation in childhood. Literature review and research opportunities. *Human Heredity, 75*, 80–89.

Figlewicz, D. P., & Sipols, A. J. (2010). Energy regulatory signals and food reward. *Pharmacology, Biochemistry, and Behavior, 97*(1), 15–24. doi:10.1016/j.pbb.2010.03.002.

Figlewicz, D. P., Szot, P., Chavez, M., Woods, S. C., & Veith, R. C. (1994). Intraventricular insulin increases dopamine transporter mRNA in rat VTA/substantia nigra. *Brain Research, 644*(2), 331–334.

Figlewicz, D. P., Evans, S. B., Murphy, J., Hoen, M., & Baskin, D. G. (2003). Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. *Brain Research, 964*(1), 107–115.

Gans, R. O. (2006). The metabolic syndrome, depression, and cardiovascular disease: Interrelated conditions that share pathophysiologic mechanisms. *The Medical Clinics of North America, 90*(4), 573–591. doi:10.1016/j.mcna.2006.05.002.

Giovannini, C., Sellini, M., Manzo, G., Barletta, C., & Scavo, D. (1982). The influence, in normal subjects, of a high-protein normocaloric diet on the response of cortisol, ACTH, GH, and PRL to insulin hypoglycemia. *Bollettino della Società Italiana di Biologia Sperimentale, 58*(3–4), 121–127.

Gohil, B. C., Rosenblum, L. A., Coplan, J. D., & Kral, J. G. (2001). Hypothalamic-pituitary-adrenal axis function and the metabolic syndrome X of obesity. *CNS Spectrums, 6*(7), 581–586, 589.

Golden, S. H., Williams, J. E., Ford, D. E., Yeh, H. C., Paton Sanford, C., Nieto, F. J., ... Atherosclerosis Risk in Communities, s. (2004). Depressive symptoms and the risk of type

2 diabetes: The Atherosclerosis Risk in Communities study. *Diabetes Care, 27*(2), 429–435.

Graziano, P. A., Calkins, S. D., & Keane, S. P. (2010). Toddler self-regulation skills predict risk for pediatric obesity. *International Journal of Obesity, 34*, 633–641.

Greco, A. V., Ghirlanda, G., Fedeli, G., & Gambassi, G. (1970). Insulin in the cerebrospinal fluid of man. *European Neurology, 3*(5), 303–307.

Grillo, C. A., Piroli, G. G., Hendry, R. M., & Reagan, L. P. (2009). Insulin-stimulated translocation of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent. *Brain Research, 1296*, 35–45. doi:10.1016/j.brainres.2009.08.005.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., ... Blood, I. (2005). Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation, 112* (17), 2735–2752. doi:10.1161/CIRCULATIONAHA.105.169404.

Hall, E. E., Ekkekakis, P., & Petruzzello, S. J. (2002). The affective beneficence of vigorous exercise revisited. *British Journal of Health Psychology, 7*(Pt 1), 47–66. doi:10.1348/135910702169358.

Hamer, M., Batty, G. D., & Kivimaki, M. (2012). Risk of future depression in people who are obese but metabolically healthy: The English longitudinal study of ageing. *Molecular Psychiatry, 17*(9), 940–945. doi:10.1038/mp.2012.30.

Hanin, Y. (1999). *Sports-specific emotion-motivational profiling: An individualized assessment programme*. Paper presented at the psychology of sport: Enhancing the quality of life. Proceedings of the 10th European congress of sport psychology. Part 1, Prague.

Hanin, Y. (2000). *Emotions in sport*. Champaign: Human Kinetics.

Harrison, C. L., Lombard, C. B., East, C., Boyle, J., & Teede, H. J. (2015). Risk stratification in early pregnancy for women at increased risk of gestational diabetes. *Diabetes Research and Clinical Practice, 107*(1), 61–68. doi:10.1016/j.diabres.2014.09.006.

Hasler, G., Drevets, W. C., Manji, H. K., & Charney, D. S. (2004). Discovering endophenotypes for major depression. *Neuropsychopharmacology, 29*(10), 1765–1781. doi:10.1038/sj.npp.1300506.

Havrankova, J., Roth, J., & Brownstein, M. (1978). Insulin receptors are widely distributed in the central nervous system of the rat. *Nature, 272*(5656), 827–829.

Hawkins, M., Hosker, M., Marcus, B. H., Rosal, M. C., Braun, B., Stanek, E. J., 3rd, ... Chasan-Taber, L. (2015). A pregnancy lifestyle intervention to prevent gestational diabetes risk factors in overweight Hispanic women: A feasibility randomized controlled trial. *Diabetes Medicine, 32*(1), 108–115. doi:10.1111/dme.12601.

Heimpel, S. A., Wood, J. V., Marshall, M. A., & Brown, J. D. (2002). Do people with low self-esteem really want to feel better? Self-esteem differences in motivation to repair negative moods. *Journal of Personality and Social Psychology, 82*(1), 128–147.

Hernandez, M., Mollo, A., Marsal, J. R., Esquerda, A., Capel, I., Puig-Domingo, M., ... Action, L. c. (2015). Insulin secretion in patients with latent autoimmune diabetes (LADA): Halfway between type 1 and type 2 diabetes: Action LADA 9. *BMC Endocrine Disorders, 15*(1), 1. doi:10.1186/1472-6823-15-1.

Hogg, M. A., Abrams, D., & Martin, G. N. (2010). *Social cognition and attitudes*. Harlow: Pearson Education Limited.

Hotamisligil, G. S. (2010). Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell, 140*(6), 900–917. doi:10.1016/j.cell.2010.02.034.

Hoyer, S. (2004). Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. *European Journal of Pharmacology, 490*(1–3), 115–125. doi:10.1016/j.ejphar.2004.02.049.

Isganaitis, E., & Lustig, R. H. (2005). Fast food, central nervous system insulin resistance, and obesity. *Arteriosclerosis, Thrombosis, and Vascular Biology, 25*(12), 2451–2462. doi:10.1161/01.ATV.0000186208.06964.91.

Kaiyala, K. J., Prigeon, R. L., Kahn, S. E., Woods, S. C., & Schwartz, M. W. (2000). Obesity induced by a high-fat diet is associated with reduced brain insulin transport in dogs. *Diabetes, 49*(9), 1525–1533.

Kaplan, R. J., Greenwood, C. E., Winocur, G., & Wolever, T. M. (2000). Cognitive performance is associated with glucose regulation in healthy elderly persons and can be enhanced with glucose and dietary carbohydrates. *American Journal of Clinical Nutrition, 72*(3), 825–836.

Kawakami, N., Takatsuka, N., Shimizu, H., & Ishibashi, H. (1999). Depressive symptoms and occurrence of type 2 diabetes among Japanese men. *Diabetes Care, 22*(7), 1071–1076.

Kent, S., Bluthe, R. M., Kelley, K. W., & Dantzer, R. (1992). Sickness behavior as a new target for drug development. *Trends in Pharmacological Sciences, 13*(1), 24–28.

Kloiber, S., Ising, M., Reppermund, S., Horstmann, S., Dose, T., Majer, M., . . . Lucae, S. (2007). Overweight and obesity affect treatment response in major depression. *Biological Psychiatry, 62*(4), 321–326. doi:10.1016/j.biopsych.2006.10.001.

Knol, M. J., Twisk, J. W., Beekman, A. T., Heine, R. J., Snoek, F. J., & Pouwer, F. (2006). Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia, 49*(5), 837–845. doi:10.1007/s00125-006-0159-x.

Komatsu, M., Takei, M., Ishii, H., & Sato, Y. (2013). Glucose-stimulated insulin secretion: A newer perspective. *Journal of Diabetes Investigation, 4*(6), 511–516. doi:10.1111/jdi.12094.

Konner, A. C., Hess, S., Tovar, S., Mesaros, A., Sanchez-Lasheras, C., Evers, N., . . . Bruning, J. C. (2011). Role for insulin signaling in catecholaminergic neurons in control of energy homeostasis. *Cell Metabolism, 13*(6), 720–728. doi:10.1016/j.cmet.2011.03.021.

Koyama, K., Chen, G., Lee, Y., & Unger, R. H. (1997). Tissue triglycerides, insulin resistance, and insulin production: Implications for hyperinsulinemia of obesity. *American Journal of Physiology, 273*(4 Pt 1), E708–E713.

Kumar, J., Chuang, J. C., Na, E. S., Kuperman, A., Gillman, A. G., Mukherjee, S., . . . Lutter, M. (2013). Differential effects of chronic social stress and fluoxetine on meal patterns in mice. *Appetite, 64*, 81–88. doi:10.1016/j.appet.2012.12.023.

Labad, J., Price, J. F., Strachan, M. W., Fowkes, F. G., Deary, I. J., Seckl, J. R., . . . Edinburgh Type 2 Diabetes Study, I. (2012). Leptin levels and depressive symptoms in people with type 2 diabetes: The edinburgh type 2 diabetes study. *Psychosomatic Medicine, 74*(1), 39–45. doi:10.1097/PSY.0b013e31823ba8af.

Lacroix, M. C., Badonnel, K., Meunier, N., Tan, F., Schlegel-Le Poupon, C., Durieux, D., . . . Caillol, M. (2008). Expression of insulin system in the olfactory epithelium: First approaches to its role and regulation. *Journal of Neuroendocrinology, 20*(10), 1176–1190. doi:10.1111/j.1365-2826.2008.01777.x.

Lindley, S. E., Bengoechea, T. G., Schatzberg, A. F., & Wong, D. L. (1999). Glucocorticoid effects on mesotelencephalic dopamine neurotransmission. *Neuropsychopharmacology, 21*(3), 399–407. doi:10.1016/S0893-133X(98)00103-1.

Lorenz, E. N. (1963). "The Predictability of Hydrodynamic Flow" (PDF). *Transactions of the New York Academy of Sciences 25*(4), 409–432.

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W., & Zitman, F. G. (2010). Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry, 67*(3), 220–229. doi:10.1001/archgenpsychiatry.2010.2.

Lustman, P. J., & Clouse, R. E. (2005). Depression in diabetic patients: The relationship between mood and glycemic control. *Journal of Diabetes and its Complications, 19*(2), 113–122. doi:10.1016/j.jdiacomp.2004.01.002.

Magariños, A. M., & McEwen, B. S. (2000). Experimental diabetes in rats causes hippocampal dendritic and synaptic reorganization and increased glucocorticoid reactivity to stress. *Proceedings of the National Academy of Science, 97*, 11056–11061.

Maniam, J., & Morris, M. J. (2010). Voluntary exercise and palatable high-fat diet both improve behavioural profile and stress responses in male rats exposed to early life stress: Role of

hippocampus. *Psychoneuroendocrinology, 35*(10), 1553–1564. doi:10.1016/j.psyneuen.2010.05.012.

Mayfield, J. (1998). Diagnosis and classification of diabetes mellitus: New criteria. *American Family Physician, 58*(6), 1355–1362, 1369–1370.

McElroy, S. L., Kotwal, R., Malhotra, S., Nelson, E. B., Keck, P. E., & Nemeroff, C. B. (2004). Are mood disorders and obesity related? A review for the mental health professional. *The Journal of Clinical Psychiatry, 65*(5), 634–651, quiz 730.

McEwen, B. S., & Reagan, L. P. (2004). Glucose transporter expression in the central nervous system: Relationship to synaptic function. *European Journal of Pharmacology, 490*(1–3), 13–24. doi:10.1016/j.ejphar.2004.02.041.

McEwen, B. S., Magarinos, A. M. & Reagan, L. P. (2002). Studies of hormone action in the hippocampal formation: possible relevance to depression and diabetes. *Journal of Psychocomatic Research, 53*(4), 883–890.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1971). *Manual for the profile of mood states*. San Diego: Educational and Industrial Testing Services.

McNay, E. C., Fries, T. M., & Gold, P. E. (2000). Decreases in rat extracellular hippocampal glucose concentration associated with cognitive demand during a spatial task. *Proceedings of the National Academy of Sciences of the United States of America, 97*(6), 2881–2885. doi:10.1073/pnas.050583697.

Milligan, G. N., Bernstein, D. I., & Bourne, N. (1998). T lymphocytes are required for protection of the vaginal mucosae and sensory ganglia of immune mice against reinfection with herpes simplex virus type 2. *Journal of Immunology, 160*(12), 6093–6100.

Morino, K., Petersen, K. F., & Shulman, G. I. (2006). Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. *Diabetes, 55*(Suppl 2), S9–S15. doi:10.2337/diabetes.

Muniyappa, R., Lee, S., Chen, H., & Quon, M. J. (2008). Current approaches for assessing insulin sensitivity and resistance in vivo: Advantages, limitations, and appropriate usage. *American Journal of Physiology, Endocrinology and Metabolism, 294*(1), E15–E26. doi:10.1152/ajpendo.00645.2007.

Musselman, D. L., Betan, E., Larsen, H., & Phillips, L. S. (2003). Relationship of depression to diabetes types 1 and 2: Epidemiology, biology, and treatment. *Biological Psychiatry, 54*(3), 317–329.

Myers, M. G., Cowley, M. A., & Munzberg, H. (2008). Mechanisms of leptin action and leptin resistance. *Annual Review of Physiology, 70*, 537–556. doi:10.1146/annurev.physiol.70.113006.100707.

Nelson, T. J., Sun, M. K., Hongpaisan, J., & Alkon, D. L. (2008). Insulin, PKC signaling pathways and synaptic remodeling during memory storage and neuronal repair. *European Journal of Pharmacology, 585*(1), 76–87. doi:10.1016/j.ejphar.2008.01.051.

Novick, J. S., Stewart, J. W., Wisniewski, S. R., Cook, I. A., Manev, R., Nierenberg, A. A., ... investigators, S. D. (2005). Clinical and demographic features of atypical depression in outpatients with major depressive disorder: Preliminary findings from STAR*D. *J Clin Psychiatry, 66*(8), 1002–1011.

Okamura, F., Tashiro, A., Utumi, A., Imai, T., Suchi, T., Tamura, D., ... Hongo, M. (2000). Insulin resistance in patients with depression and its changes during the clinical course of depression: Minimal model analysis. *Metabolism, 49*(10), 1255–1260. doi: 10.1053/meta.2000.9515.

Ono, H., Pocai, A., Wang, Y., Sakoda, H., Asano, T., Backer, J. M., ... Rossetti, L. (2008). Activation of hypothalamic S6 kinase mediates diet-induced hepatic insulin resistance in rats. *Journal of Clinical Investigation, 118*(8), 2959–2968. doi:10.1172/JCI34277.

Pace, T. W., Hu, F., & Miller, A. H. (2007). Cytokine-effects on glucocorticoid receptor function: Relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain, Behavior, and Immunity, 21*(1), 9–19. doi:10.1016/j.bbi.2006.08.009.

Pais, I., Hallschmid, M., Jauch-Chara, K., Schmid, S. M., Oltmanns, K. M., Peters, A., … Schultes, B. (2007). Mood and cognitive functions during acute euglycaemia and mild hyperglycaemia in type 2 diabetic patients. *Experimental and Clinical Endocrinology and Diabetes, 115*(1), 42–46. doi:10.1055/s-2007-957348.

Perantie, D. C., Wu, J., Koller, J. M., Lim, A., Warren, S. L., Black, K. J., … Hershey, T. (2007). Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. *Diabetes Care, 30*(9), 2331–2337. doi:10.2337/dc07-0351.

Persoons, P., Vermeire, S., Demyttenaere, K., Fischler, B., Vandenberghe, J., Van Oudenhove, L., … Rutgeerts, P. (2005). The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. *Alimentary Pharmacology and Therapeutics, 22*(2), 101–110. doi:10.1111/j.1365-2036.2005.02535.x.

Pollock, V., Cho, D. W., Reker, D., & Volavka, J. (1979). Profile of mood states: The factors and their physiological correlates. *Journal of Nervous and Mental Disease, 167*(10), 612–614.

Pulkki-Raback, L., Elovainio, M., Kivimaki, M., Mattsson, N., Raitakari, O. T., Puttonen, S., … Keltikangas-Jarvinen, L. (2009). Depressive symptoms and the metabolic syndrome in childhood and adulthood: A prospective cohort study. *Health Psychology, 28*(1), 108–116. doi: 10.1037/a0012646.

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology, 27*(1), 24–31. doi:10.1016/j.it.2005.11.006.

Ramasubbu, R. (2002). Insulin resistance: A metabolic link between depressive disorder and atherosclerotic vascular diseases. *Medical Hypotheses, 59*(5), 537–551.

Reagan, L. P. (2007). Insulin signaling effects on memory and mood. *Current Opinion in Pharmacology, 7*(6), 633–637. doi:10.1016/j.coph.2007.10.012.

Roberts, R. E., Deleger, S., Strawbridge, W. J., & Kaplan, G. A. (2003). Prospective association between obesity and depression: Evidence from the Alameda County Study. *International Journal of Obesity and Related Metabolic Disorders, 27*(4), 514–521. doi:10.1038/sj.ijo.0802204.

Roden, M., Price, T. B., Perseghin, G., Petersen, K. F., Rothman, D. L., Cline, G. W., & Shulman, G. I. (1996). Mechanism of free fatty acid-induced insulin resistance in humans. *Journal of Clinical Investigation, 97*(12), 2859–2865. doi:10.1172/JCI118742.

Rolandsson, O., Backestrom, A., Eriksson, S., Hallmans, G., & Nilsson, L. G. (2008). Increased glucose levels are associated with episodic memory in nondiabetic women. *Diabetes, 57*(2), 440–443. doi:10.2337/db07-1215.

Rollins, B. Y., Loken, E., Savage, J. S., & Birch, L. L. (2014). Measurement of food reinforcement in preschool children. Associations with food intake, BMI, and reward sensitivity. *Appetite, 72*, 21–27.

Rosmond, R., & Bjorntorp, P. (2000). The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. *Journal of Internal Medicine, 247*(2), 188–197.

Rubin, J., Matsushita, K., Ballantyne, C. M., Hoogeveen, R., Coresh, J., & Selvin, E. (2012). Chronic hyperglycemia and subclinical myocardial injury. *Journal of the American College of Cardiology, 59*(5), 484–489. doi:10.1016/j.jacc.2011.10.875.

Russell, J. A. (1980). A circumflex model of affect. *Journal of Personality and Social Psychology, 39*, 1161–1178.

Samuel, V. T., & Shulman, G. I. (2012). Mechanisms for insulin resistance: Common threads and missing links. *Cell, 148*(5), 852–871. doi:10.1016/j.cell.2012.02.017.

Saravia, F. E., Revsin, Y., Gonzalez Deniselle, M. C., Gonzalez, S. L., Roig, P., Lima, A., … De Nicola, A. F. (2002). Increased astrocyte reactivity in the hippocampus of murine models of type 1 diabetes: The nonobese diabetic (NOD) and streptozotocin-treated mice. *Brain Research, 957*(2), 345–353.

Schinner, S., Scherbaum, W. A., Bornstein, S. R., & Barthel, A. (2005). Molecular mechanisms of insulin resistance. *Diabetic Medicine, 22*(6), 674–682. doi:10.1111/j.1464-5491.2005.01566.x.

Schucman, H., & Thetford, C. (1975). *A course in miracle*. New York: Viking Penguin.
Schultz, W. (2002). Getting formal with dopamine and reward. *Neuron, 36*(2), 241–263.
Schwartz, M. W., & Porte, D., Jr. (2005). Diabetes, obesity, and the brain. *Science, 307*(5708), 375–379. doi:10.1126/science.1104344.
Shoelson, S. E., Herrero, L., & Naaz, A. (2007). Obesity, inflammation, and insulin resistance. *Gastroenterology, 132*(6), 2169–2180. doi:10.1053/j.gastro.2007.03.059.
Shomaker, L. B., Tanofsky-Kraff, M., Stern, E. A., Miller, R., Zocca, J. M., Field, S. E., … Yanovski, J. A. (2011). Longitudinal study of depressive symptoms and progression of insulin resistance in youth at risk for adult obesity. *Diabetes Care, 34*(11), 2458–2463. doi:10.2337/dc11-1131.
Silverman, M. N., Miller, A. H., Biron, C. A., & Pearce, B. D. (2004). Characterization of an interleukin-6- and adrenocorticotropin-dependent, immune-to-adrenal pathway during viral infection. *Endocrinology, 145*(8), 3580–3589. doi:10.1210/en.2003-1421.
Simon, G. E., Von Korff, M., Saunders, K., Miglioretti, D. L., Crane, P. K., van Belle, G., & Kessler, R. C. (2006). Association between obesity and psychiatric disorders in the US adult population. *Archives of General Psychiatry, 63*(7), 824–830. doi:10.1001/archpsyc.63.7.824.
Singh, M. (2014). Mood, food, and obesity. *Frontiers in Psychology, 5*, 925. doi:10.3389/fpsyg.2014.00925.
Sluijs, I., Beulens, J. W., van der A, D. L., Spijkerman, A. M., Grobbee, D. E., van der Schouw, Y. T. (2010). Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into cancer and nutrition (EPIC)-NL study. *Diabetes Care, 33*(1), 43–48. doi:10.2337/dc09-1321.
Sommerfield, A. J., Deary, I. J., & Frier, B. M. (2004). Acute hyperglycemia alters mood state and impairs cognitive performance in people with type 2 diabetes. *Diabetes Care, 27*(10), 2335–2340.
Spence, S., & Courbasson, C. (2012). The role of emotional dysregulation in concurrent eating disorders and substance use disorders. *Eating Behaviors, 13*(4), 382–385. doi:10.1016/j.eatbeh.2012.05.006.
Steen, E., Terry, B. M., Rivera, E. J., Cannon, J. L., Neely, T. R., Tavares, R., … de la Monte, S. M. (2005). Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – Is this type 3 diabetes? *Journal of Alzheimer's Disease, 7*(1), 63–80.
Strubbe, J. H., & Mein, C. G. (1977). Increased feeding in response to bilateral injection of insulin antibodies in the VMH. *Physiology and Behavior, 19*(2), 309–313.
Suarez, E. C. (2006). Sex differences in the relation of depressive symptoms, hostility, and anger expression to indices of glucose metabolism in nondiabetic adults. *Health Psychology, 25*(4), 484–492. doi:10.1037/0278-6133.25.4.484.
Sunram-Lea, S. I., Foster, J. K., Durlach, P., & Perez, C. (2002). Investigation into the significance of task difficulty and divided allocation of resources on the glucose memory facilitation effect. *Psychopharmacology, 160*(4), 387–397. doi:10.1007/s00213-001-0987-9.
Talen, M. R., & Mann, M. M. (2009). Obesity and mental health. *Primary Care, 36*(2), 287–305. doi:10.1016/j.pop.2009.01.012.
Tamashiro, K. L., Sakai, R. R., Shively, C. A., Karatsoreos, I. N., & Reagan, L. P. (2011). Chronic stress, metabolism, and metabolic syndrome. *Stress, 14*(5), 468–474. doi:10.3109/10253890.2011.606341.
Tataranni, P. A., & DelParigi, A. (2003). Functional neuroimaging: A new generation of human brain studies in obesity research. *Obesity Reviews, 4*(4), 229–238.
Terry, P. C., Lane, A. M., Lane, H. J., & Keohane, L. (1999). Development and validation of a mood measure for adolescents. *Journal of Sports Sciences, 17*(11), 861–872. doi:10.1080/026404199365425.
Terry, P. C., Lane, A. M., & Fogarty, G. J. (2003). Construct validity of the profile of mood states – Adolescents for use with adults. *Psychology of Sport and Exercise, 4*(2), 125–139. doi:10.1016/S1469-0292(01)00035-8.

Thompson, E. R. (2007). Development and validation of an internationally reliable short form of the positive and negative affect schedule (PANAS). *Journal of Consulting and Clinical Psychology, 38*(2), 227–242.

Timonen, M., Laakso, M., Jokelainen, J., Rajala, U., Meyer-Rochow, V. B., & Keinanen-Kiukaanniemi, S. (2005). Insulin resistance and depression: Cross sectional study. *BMJ, 330* (7481), 17–18. doi:10.1136/bmj.38313.513310.F71.

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research, 53*(4), 865–871.

Tyring, S., Gottlieb, A., Papp, K., Gordon, K., Leonardi, C., Wang, A., … Krishnan, R. (2006). Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomised phase III trial. *Lancet, 367*(9504), 29–35. doi:10.1016/S0140-6736(05)67763-X.

Unger, R. H., & Scherer, P. E. (2010). Gluttony, sloth and the metabolic syndrome: A roadmap to lipotoxicity. *Trends in Endocrinology and Metabolism, 21*(6), 345–352. doi:10.1016/j.tem.2010.01.009.

Unger, J., McNeill, T. H., Moxley, R. T., 3rd, White, M., Moss, A., & Livingston, J. N. (1989). Distribution of insulin receptor-like immunoreactivity in the rat forebrain. *Neuroscience, 31* (1), 143–157.

Valenciano, A. I., Corrochano, S., de Pablo, F., de la Villa, P., & de la Rosa, E. J. (2006). Proinsulin/insulin is synthesized locally and prevents caspase- and cathepsin-mediated cell death in the embryonic mouse retina. *Journal of Neurochemistry, 99*(2), 524–536. doi:10.1111/j.1471-4159.2006.04043.x.

Volkow, N. D., Fowler, J. S., Wang, G. J., Ding, Y. S., & Gatley, S. J. (2002). Role of dopamine in the therapeutic and reinforcing effects of methylphenidate in humans: Results from imaging studies. *European Neuropsychopharmacology, 12*(6), 557–566.

Wang, G. J., Volkow, N. D., Logan, J., Pappas, N. R., Wong, C. T., Zhu, W., … Fowler, J. S. (2001). Brain dopamine and obesity. *Lancet, 357*(9253), 354–357.

Wang, G. J., Volkow, N. D., & Fowler, J. S. (2002). The role of dopamine in motivation for food in humans: Implications for obesity. *Expert Opinion on Therapeutic Targets, 6*(5), 601–609. doi:10.1517/14728222.6.5.601.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063–1070.

Wilcox, G. (2005). Insulin and insulin resistance. *Clinical Biochemistry Reviews, 26*(2), 19–39.

Wise, R. A. (1996). Addictive drugs and brain stimulation reward. *Annual Review of Neuroscience, 19*, 319–340. doi:10.1146/annurev.ne.19.030196.001535.

Woods, S. C., & Porte, D., Jr. (1977). Relationship between plasma and cerebrospinal fluid insulin levels of dogs. *American Journal of Physiology, 233*(4), E331–E334.

Wrighten, S. A., Piroli, G. G., Grillo, C. A., & Reagan, L. P. (2009). A look inside the diabetic brain: Contributors to diabetes-induced brain aging. *Biochimica et Biophysica Acta, 1792*(5), 444–453. doi:10.1016/j.bbadis.2008.10.013.

Yirmiya, R., Pollak, Y., Barak, O., Avitsur, R., Ovadia, H., Bette, M., … Weidenfeld, J. (2001). Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. *Neuropsychopharmacology, 24*(5), 531–544. doi:10.1016/S0893-133X(00)00226-8.

Yue, J. T., & Lam, T. K. (2012). Lipid sensing and insulin resistance in the brain. *Cell Metabolism, 15*(5), 646–655. doi:10.1016/j.cmet.2012.01.013.

Zhao, G., Ford, E. S., Li, C., Tsai, J., Dhingra, S., & Balluz, L. S. (2011). Waist circumference, abdominal obesity, and depression among overweight and obese U.S. adults: National Health and Nutrition Examination Survey 2005–2006. *BMC Psychiatry, 11*, 130. doi:10.1186/1471-244X-11-130.

Zimmet, P., Alberti, K. G., & Shaw, J. (2001). Global and societal implications of the diabetes epidemic. *Nature, 414*(6865), 782–787. doi:10.1038/414782a.

Animal Models of Psychogenic Cardiovascular Disorders

Eugene Nalivaiko, Luca Carnevali, Angela J. Grippo, and Andrea Sgoifo

Contents

E. Nalivaiko (✉)
School of Biomedical Sciences Flinders Medical Centre, University of Newcastle, Callaghan, NSW, Australia

School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, NSW, Australia
e-mail: eugene.nalivaiko@newcastle.edu.au

L. Carnevali • A. Sgoifo
Department of Neuroscience, University of Parma, Parma, Italy

A.J. Grippo
Department of Psychology, Northern Illinois University, De Kalb, IL, USA

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_45

Abstract

Close causative relationship between psychological stresses and cardiovascular morbidity is now well documented. Research on humans has been attempting to unravel the significance of this association by investigating psychological and social characteristics in relation to cardiovascular health. However, this research is limited by the difficulty to control and standardize for the individual social history, the impossibility to apply psychosocial stress stimuli for mere experimental purposes, as well as the long time span of cardiovascular pathogenesis in humans. Animal studies controlling for social environment and adverse social episodes allow for partially overcoming these limitations. The aim of this review is to provide an up-to-date reference of the experimental evidence so far collected on the link between psychosocial factors and cardiovascular dysfunction in rodents, with special emphasis on modeling stress-induced sudden cardiac death, cardiac arrhythmias, stress cardiomyopathy, and psychogenic hypertension and with focusing on acute and chronic psychological and social stresses, aggressiveness, and negative mood states as causative factors.

Keywords

Stress • Arrhythmia • Social defeat • Depression • Hypertension

Introduction

The variety of psychosocial risk factors can be classified into three major categories, namely, the social environment, personality traits, and negative affect (von Kanel 2012). Numerous studies, both clinical/epidemiological and experimental in humans and animals, provide compelling evidence of a tight link between psychosocial factors and cardiovascular morbidity (Costoli et al. 2004; Krantz and McCeney 2002; Rozanski et al. 1999; Sgoifo et al. 2009; Verrier and Lown 1984). Factors such as anxiety and mood states, personality traits such as anger and hostility, coping strategies, socioeconomic status, acute and chronic psychological or social stressors, as well as the absence of significant social support have all been shown to modulate and interfere with cardiovascular health (Albus 2010; De Vogli et al. 2007; Steptoe et al. 2010; Van der Kooy et al. 2007). These psychosocial variables appear to be independent risk factors, as important as traditional ones (smoking, cholesterol levels, waist fat, body mass index, and poor physical activity), for the onset and progression of coronary artery disease, hypertension, myocardial stunning, stroke, and cardiac arrhythmias (Hemingway et al. 2001; Strike and Steptoe 2004; Wittstein et al. 2005).

An intrinsic limitation of research in humans lies in the difficulty to control and standardize for the individual social history preceding laboratory or clinical assessment. In addition, the application of psychosocial stress stimuli for experimental purposes is obviously limited by ethical concerns and regulations. It is here that animal studies become indispensible. Normal cardiovascular consequences of psychological stressors have been extensively studied in animals. Physiological mechanisms mediating such reactions are relatively well understood; this chapter focuses on psychogenic cardiovascular disturbances that cross the physiological homeostatic boundaries and lead to the state of disease. More specifically, it addresses animal models that provide insight into the mechanisms of stress-induced cardiovascular dysfunction. Based on the time scale of their development, psychogenic cardiovascular disturbances could be divided in two types – acute and chronic. Acute, immediate effects occur during or shortly (minutes/hours) after stressful events; stress-induced ventricular arrhythmias and stress (takotsubo) cardiomyopathy belong to this class. Sustained or enduring effects are provoked by chronic stressors and last for many days, months, or years; in humans, cardiovascular disturbances of this type are represented by psychogenic hypertension and depression-related cardiac disturbances.

Cardiac Disturbances Provoked by Acute Psychophysical Stressors

Causes of Sudden Cardiac Death

Psychological distress can provoke sudden death in humans. There is now solid clinical evidence that the principal cause of sudden death is ventricular arrhythmia, which is often preceded by acute psychological disturbances (Lampert et al. 2000; Reich et al. 1981; Rozanski et al. 1999). Other studies reinforce the importance of the link between psychological stress and cardiac arrhythmias (see Rozanski et al. (1999) for comprehensive review). Well-known examples are a sixfold increase in the sudden cardiac death rate on the day of Los Angeles (Northridge) earthquake in 1994 (Leor et al. 1996) and tripling of the incidence of arrhythmias in patients with implanted cardioverting defibrillators following the World Trade Center terrorist attack (Steinberg et al. 2004). An important question in the field of stress-induced cardiac arrhythmias is why some individuals are more susceptible to them than others. The causative role of myocardial electrical instability in the genesis of these arrhythmias is now firmly established, mainly due to extensive studies of patients with long QT syndrome. In these patients, sudden alerting stimuli may trigger polymorphic ventricular tachycardia, with a latency of just a few seconds (Wilde et al. 1999), indicating the neurogenic nature of these arrhythmias.

Heart Rate Is Not an Adequate Biomarker for Ventricular Changes

Animal studies of cardiac effects of acute stress employed various experimental paradigms. Similarly to laboratory or natural stressors in humans, psychological stressors (restraint, fear conditioning, loud noise, airjet, social defeat) consistently elevate heart rate in rats and mice. This tachycardia is a normal physiological response; it has been extensively studied, and its mechanisms are described elsewhere in great detail (see reviews by Bandler et al. 1991, Dampney et al. 2008, and Fontes et al. 2014). It was however rarely acknowledged that tachycardia (an index of autonomic influences at the cardiac pacemaker region) does not adequately reflect pro-arrhythmic status of the ventricular myocardium; in fact, it could be quite misleading. The sinoatrial node, the cardiac conducting system, and the ventricular myocardium may be controlled independently of each other (Nalivaiko et al. 2003, 2007). Consequently, an increase in HR does not necessarily predict neural influences in the myocardium. Furthermore, tachycardia by itself is cardioprotective as it reduces the duration of the ventricular diastolic period with enhanced electrical excitability (also called "ventricular vulnerable period"). These considerations emphasize that in animal studies of stress-induced cardiac dysfunction, *heart rate alone is not an adequate index of pro-arrhythmic effects* and that assessment of ventricular indices should be employed. Of the variety of such indices, we will focus on the following: (i) direct ECG signs of cardiac arrhythmia, (ii) invasive measurements of cardiac electrical stability, and (iii) radiographic assessment of ventricular wall motion.

Ventricular Arrhythmias in Stressed Animals with Predisposed Hearts

Several studies combined psychological stressors with mechanical or pharmacological intervention that altered the electrical stability of the myocardium prior to subjecting animals to stressors. In an early work performed in pigs (Skinner et al. 1975), an occluder was implanted in the left anterior descending coronary artery during preliminary surgery. After recovery, animals were stressed simply by immobilization and exposure to an unfamiliar environment. When coronary occlusion was performed during this stressor, it precipitated ventricular fibrillation (VF). In a subsequent study, authors demonstrated that crioblockade of the dorsomedial hypothalamus (or areas located just caudal to it) either prevented or markedly delayed the onset of VF after coronary occlusion (Skinner and Reed 1981). In a canine study conducted by Lown et al. (Corbalan et al. 1974), it was demonstrated that psychological stress reliably precipitated ventricular tachyarrhythmias in animals that had just recovered from myocardial infarction. The results of these two studies are complimentary as they both modeled situations in which stress is associated with the acute phase of myocardial infarction (Skinner and Reed 1981) or with the early post-infarct period (Corbalan et al. 1974).

Another way of unmasking arrhythmogenic effects of stressful interventions is presenting them to animals whose myocardial electrical stability is affected by pharmacological means. This approach was employed in early works of Natelson and colleagues who administered digitalis (a cardiac glycoside with well-known cardiotoxic properties) to their fear-conditioned guinea pigs. When a conditioned stimulus was presented to these animals, they developed more malignant arrhythmias and with higher incidence compared to digitalis-injected controls that were not subjected to fear conditioning (Natelson et al. 1978).

A major advance in understanding the mechanisms of sudden cardiac death in humans was the discovery and detailed characterization of the so-called long QT syndrome (LQTS) – a group of inherited (genetic) or acquired (drug-induced) cardiac channelopathies. A large part of these disorders is related to abnormal function of potassium channels expressed in cardiac myocytes; this results in a prolonged repolarization phase (hence "long QT" on the ECG) and elevated myocardial excitability. Patients with LQTS are prone to malignant ventricular tachyarrhythmias ("torsade de pointes") that may be triggered by either physical or psychological stressors. In rabbits, administration of dofetilide (a selective blocker of the rapid component of the delayed rectifier potassium current) mimics LQT2 type of the syndrome, and presentation of sudden alerting stimuli to these animals consistently triggered ventricular arrhythmias, including torsade-like events (Nalivaiko et al. 2004). The short latencies of these events suggested that they were neurally mediated, and sensitivity to beta-adrenergic blockade confirmed that they occurred due to increased cardiac sympathetic activity. These findings are in good accord with human data indicating that elevated cardiac sympathetic activity could be a principal cause of malignant ventricular tachyarrhythmias (Meredith et al. 1991).

The data presented above emphasize the importance of conducting animal stress studies in models that include provocations of electrical instability in the myocardium as animals with healthy hearts rarely exhibit overt ECG abnormalities. One of the first studies describing stress-induced arrhythmia in animals with intact hearts was conducted in guinea pigs (Natelson and Cagin 1979). While in resting conditions ectopic ventricular beats were only occasionally observed in some animals during 24-h ECG monitoring, restraint stress resulted in frequent occurrence of ectopics in all animals; additionally, in some of them, short periods of ventricular tachycardia were noted. In rat arrhythmia, vulnerability is even larger during social defeat compared to restraint because social defeat causes larger neuroendocrine activation compared to nonsocial stressors (Sgoifo et al. 1997).

Ventricular Electrical Events in Stressed Animals with Intact Hearts

Several cardiac electrophysiological protocols allow assessment of "silent" myocardial electrical stability, i.e., without obvious ECG signs of ventricular arrhythmias. These methods are invasive and require either implantation of cardiac pacing electrodes during preliminary surgery or, in larger animals, inserting them via the

femoral artery in acute studies. One way of cardiac electrophysiological assessment is to measure the threshold for ventricular fibrillation (minimal intensity of current that triggers VF). This technique, however, requires subsequent resuscitation of the animal, and it is preferable to measure the threshold for a repetitive ventricular response (repetitive extrasystole) (Lown et al. 1973). Lown and colleagues used this approach in a number of studies in conscious dogs. They found that psychological stress (anticipation of footshocks) substantially reduced the threshold for the repetitive ventricular response. Providing close correlation between this index and ventricular fibrillation threshold, the authors concluded that psychological stress is a potent predisposing/triggering factor for sudden cardiac death. They further demonstrated that sympathetic overactivity is the major mechanism affecting myocardial electrical stability (Matta et al. 1976) and that vagal stimulation counteracts this effect (Kolman et al. 1976).

Using repetitive extrasystole threshold as an index of ventricular vulnerability, in several follow-up studies, Lown and colleagues demonstrated cardioprotective properties of systemically administered serotonin (5-HT) precursors, agonists, or agents affecting central 5-HT levels (Blatt et al. 1979; Rabinowitz and Lown 1978). These cardioprotective effects were associated with an increase of 5-HT content in the cerebrospinal liquid and were largely mediated by reduced cardiac sympathetic nerve activity, unequivocally confirming that the effects were central (Lehnert et al. 1987). The authors thus concluded that altering central serotonergic neurotransmission is a promising therapeutic target for the prevention and treatment of ventricular tachyarrhythmias precipitated by stress. Only recently, this idea has been experimentally confirmed by Nalivaiko et al. (2009) who demonstrated that activation of 5-HT1A receptors with a selective agonist (8-OH-DPAT) virtually abolished stress-induced arrhythmias in rats subjected to social defeat. It is likely that the effect of the drug was due to the inhibition of cardiomotor presympathetic neurons in the medullary raphe, as local microinjection of 8-OH-DPAT into this area efficiently suppressed stress-induced tachycardia in rats and rabbits (Nalivaiko et al. 2005; Ngampramuan et al. 2008). Involvement of central serotonergic neurotransmission has been extensively studied during recent decades (see McCall and Clement 1994, Nalivaiko and Sgoifo 2009, Ramage 2001, and Ramage and Villalon 2008 for reviews), and the above-described experiments are in good agreement with the generally established view that 5-HT1A receptors possess central sympatholytic and vagomimetic properties.

Animal Models of Stress Cardiomyopathy

Stress cardiomyopathy (also known as "apical ballooning," "takotsubo cardiomyopathy," or "broken heart syndrome") was first described by Japanese cardiologists nearly 10 years ago (Satoda et al. 1995); see also relevant chapter in this book. Clinically, the dysfunction mimics myocardial infarction, with symptoms such as chest pain and with ECG abnormalities, but without concomitant coronary spasm or ischemia-induced enzymatic release from the myocardium. Stress cardiomyopathy

prevails in postmenopausal women and is usually triggered by potent emotional stressors. The most distinctive feature of this disorder is ventricular wall dysfunction, predominantly in the apical region (Akashi et al. 2010).

A naturalistic animal model of stress cardiomyopathy was developed by Ueyama and colleagues (2002). They found that rats subjected to immobilization stress developed transient left ventricular dysfunction very similar to that observed in humans. The effect was mediated by catecholamines as it was sensitive to pharmacological blockade of adrenoreceptors. This is an interesting example of animal study preceding similar findings in humans: in 2005 Wittstein and colleagues (2005) reported that in patients with stress cardiomyopathy, the levels of plasma catecholamines were dramatically elevated. Using their rat model, Ueyama and colleagues substantially contributed to the understanding of the pathophysiology of the stress cardiomyopathy. They demonstrated that during immobilization stress, activation of adrenoreceptors causes upregulation of immediate early genes in cardiac tissues (Ueyama 2004); potential molecular consequences of this effect are discussed in detail by Akashi et al. (2010).

Rat studies also provided potential explanation of why stress cardiomyopathy occurs more frequently in postmenopausal women. During menopause, a lack of estrogen resulted in cardiac vulnerability to stress; a relevant model approach for this situation is ovariectomized rats. In such animals, estrogen supplementation attenuated immobilization-induced cardiomyopathy (Ueyama et al. 2007). Additionally, it was found that the cardioprotective properties of estrogens could be mediated both at the level of the brain and at the level of end-organs heart and adrenal medulla (Ueyama et al. 2006, 2007).

Importance of Social Factor and Cardiac Disturbances Provoked by Acute Social Stressors

In humans, various forms of inadequate social interaction could be the most relevant stress factor for the onset and progression of stress-related disorders, both psychosomatic (such as cardiovascular pathologies) and psychological (e.g., anxiety and depression) (Bjorkqvist 2001). Social stress episodes do not necessarily imply overt aggressive acts; rather, they usually follow verbal and psychological pathways (Pico-Alfonso et al. 2007). In animals, disputes for territory control, food resources, and sexual partners can be harsh and frequent and may produce severe physical and psychological damage. For many years, stress biologists implemented a variety of experimental paradigms with the aim of understanding the physiological and behavioral features of stress responses and the mechanisms underlying stress-related disturbances. Paradigms that are traditionally used in rodent psychophysical stress procedures (e.g., immobilization or electric shock) bear limited ethological relevance (Sgoifo et al. 2005). More recent research benefited from the use of highly translational, naturalistic stress models such as social conflict, subordination, and long-term social isolation.

Acute and Chronic Effects of Social Defeat

In rodents, a single episode of social defeat has a strong physiological and behavioral impact. Social defeat is obtained by means of the resident-intruder test, which consists in introducing the experimental animal in the territory of a conspecific dominant male. Defeat is the outcome of repeated attacks by the resident rat, and the declaration of subordination by the intruder is clearly detectable on the basis of characteristic behavioral patterns (Koolhaas et al. 2013). In the short term (minutes to hours), defeat produces tachycardia, vagal withdrawal, cardiac arrhythmias, hypertension, hyperthermia, and elevated plasma levels of glucocorticoids and catecholamines (Sgoifo et al. 1999). Interestingly, 8-OH-DPAT (a 5-HT1A receptor agonist) attenuates defeat-induced tachycardia and arrhythmogenesis, due to suppression of both cardiac sympathetic drive and vagal withdrawal (Nalivaiko et al. 2009).

In the long term (days/weeks), social defeat dramatically affects animals' behavior (McGrady 1984; Meerlo et al. 1996a; Ruis et al. 1999), memory (Von Frijtag et al. 2000), and neuroendocrine and immune function (Buwalda et al. 1999; Engler et al. 2004; Meerlo et al. 1996b; Stefanski and Engler 1998). In particular, social defeat may result in severe perturbations of circadian rhythms of heart rate (Meerlo et al. 1999), which consist mainly in a dampening of the rhythm amplitude that may be due to an increase in the resting phase values and/or a decrease in the active phase ones (Meerlo et al. 2002). These alterations could persist for up to 2 weeks after challenge termination (Meerlo et al. 1999; Tornatzky and Miczek 1993).

When social subordination becomes a chronic state, consequences can be irreversible. For instance, repeated defeat episodes associated with the threat represented by the constant vicinity of the aggressor were shown to produce permanent cardiac anatomical alterations (Costoli et al. 2004). Specifically, when a male mouse was exposed for 2 weeks to a daily episode of aggression and was permanently maintained under the threat of further attacks, a structural damage at the level of the heart was observed, with substantial accumulation of fibrotic tissue – a well-documented substrate for the development of cardiac arrhythmias (Costoli et al. 2004). The outcome of this experiment supports the hypothesis that the physiological responses to an intermittent homotypic stressor, although allowing short-term adaptation and gradually fading in intensity across days, can bring about an overload for the organism in the long term and contribute to permanent pathological alterations (McEwen 1998). The precise mechanisms underlying these alterations are currently unknown; they may include massive release of catecholamines in response to the persistent social threat condition.

When a similar chronic psychosocial stress protocol was applied to mice lacking 1A serotonin receptors (5-HT1A KO mice), a quarter of the animals died from cardiac arrest (Carnevali et al. 2012a). Indeed, genetic lack of 5-HT_{1A} receptors appears to be detrimental for cardiovascular health, by increasing the risk of fatal cardiac events in mice undergoing chronic stress. This evidence corroborates the protective role of these receptors for cardiovascular stress homeostasis, as

previously described for acute anti-arrhythmogenic and anti-tachycardic effects of serotonin 1A agonists in a social defeat context (Nalivaiko et al. 2009; Nalivaiko and Sgoifo 2009). Similar cardioprotective role of central 5-HT1A receptors has been reported in cynomolgus monkeys exposed to social stress (Shively et al. 2006).

Another contribution to the elucidation of the neurobiological mechanisms underlying social stress-induced autonomic imbalance came from a recent study by Sevoz-Couche and colleagues (2013). They found that rats exposed to four consecutive days of social defeat sessions developed reduced heart rate variability (HRV), cardiac sympathetic prevalence, and reduced baroreflex gain. The inhibition of the dorsomedial hypothalamus with muscimol and the blockade of the nucleus tractus solitarii 5-HT3 receptors with granisetron reversed these cardiovascular alterations and highlighted the role of these regions in cardiovascular autonomic adaptation following repeated social challenge.

Effects of Social Isolation

Deleterious effect of another social challenge – social isolation – has been extensively studied by Grippo and colleagues in prairie voles (*Microtus ochrogaster*) (see for instance Grippo 2009; Grippo et al. 2011). The advantage of this animal species is in their stable monogamous social relationships and engagement in the surrounding social context (Carter et al. 2008; Young and Wang 2004) These unique features of sociality make this animal model extremely interesting in translational terms. Female and male prairie voles are sensitive to long-term deprivation of social contact from a sexual partner or a family member, with significant behavioral and physiological consequences including anxious and depressive behavior, as well as autonomic, neuroendocrine, and cardiac dysfunctions (Grippo et al. 2011, 2012; McNeal et al. 2014).

Chronic Social Stressors and Interaction Between Depression and Cardiac Disorders

Assessment of Depression-Like State in Experimental Animals

Both experimental and clinical evidence points to a robust bidirectional link between depressive disorders and cardiovascular dysfunction. In particular, depressed patients have a markedly higher risk of cardiac morbidity (Khawaja et al. 2009; Lippi et al. 2009), independently from traditional risk factors such as hypertension, smoking, elevated cholesterol, physical inactivity, and elevated body mass index (Sowden and Huffman 2009; Whooley 2006). Although many studies highlighted the association between depression and heart disease, common underlying substrates are only partially understood. The major difficulty in conducting animal studies related to depression is the extreme paucity of objective

pro-depressive indices; the two most commonly used are the sucrose preference and the immobility in the forced swimming test. The former is based on reduced animals' normal preference for sugar-sweetened water; this is believed to reflect anhedonia, a classical symptom of depression. In the latter test, reduced swimming activity is believed to reflect despair, another feature of depression in humans. Cardiovascular measures thus are of substantial value here as they can be objectively measured. One possible pathophysiological mechanistic link between depression and cardiac health appears to be an alteration of cardiac sympathovagal balance, due to elevated cardiac sympathetic and/or reduced cardiac vagal tone (Barton et al. 2007; Carney et al. 1988; Kemp et al. 2010; Pitzalis et al. 2001; Rechlin et al. 1994). Perturbations of the autonomic nervous system may result in ventricular tachyarrhythmias and sudden cardiac death, the latter being one of the leading causes of cardiovascular mortality (Zipes and Wellens 1998).

Mechanistic Links Between Depression-Like State and Cardiac Disorders

Social stress is a critical environmental factor for the development of both clinical depression (Kendler et al. 1999) and cardiovascular disease (Steptoe and Brydon 2009). Major social life events, such as job strain, the loss of a family member, and social isolation, may sensitize individuals to subsequent stress and thereby increase the risk of developing such disorders (Post 1992). To understand the associations among social stress, depression, and cardiovascular dysfunction, various experimental approaches have been used (Nestler and Hyman 2010). Among them, social challenge based on a single episode of social defeat followed by a period of isolation is an experimental paradigm that relies on robust theoretical prerequisites to meet construct and etiological validity. As previously summarized, social defeat and social isolation separately induce acute and long-lasting behavioral and physiological changes that well resemble core aspects of mood disorders in humans. Using this combined social defeat/social isolation paradigm in rats, Carnevali and colleagues (2012b) recently found that this challenge induced behavioral signs of depression, functional and structural changes of the hypothalamic-pituitary-adrenocortical axis, and increased anxiety levels. The cardiovascular consequences consisted of transitory heart rate circadian rhythm alterations and moderate cardiac hypertrophy.

Only a few studies assessed mechanistic links between chronic social stress and cardiac malfunction. In one of them, Carnevali and colleagues (2013) demonstrated that subjecting rats to repetitive social defeats over 3 weeks results not only in behavioral (reduced sucrose preference) and biological (loss of body weight and alterations in circadian rhythm amplitudes) pro-depression signs but also caused pro-arrhythmic effect on cardiac electrophysiological variables. The high-density epicardial mapping analysis revealed a significant decrease in transversal conduction velocity of the electrical wavefront, a shortening of the effective refractory

period and an increase in myocardial excitability in the ventricles of stressed animals compared to controls, conditions that are generally considered as important determinants of arrhythmogenesis (Carnevali et al. 2013).

Behavioral Coping Style and Cardiac Vulnerability

In humans it is now well established that certain patterns of behavior are associated with elevated cardiovascular risk. Specifically, individuals with so-called "type A" behavior (aggressive, hostile, impatient, competitive, achievement striving) are more vulnerable to heart disease than type B counterparts (relative absence of type A characteristics) (Betensky and Contrada 2010; Friedman and Rosenman 1959; Kop 1999; Rozanski et al. 1999; Smith 1992; Smith et al. 2004). Putative pathophysiological mechanisms that mediate this link may include an impairment of autonomic nervous system control over cardiac function. Abundant evidence demonstrates that reduced autonomic modulation of the heart, as shown by HRV measurements, predicts the development of heart disease in initially healthy subjects (Liao et al. 1997; Tsuji et al. 1996), as well as poorer survival rate in patients with myocardial infarction or heart failure (Bigger et al. 1992; La Rovere et al. 1998, 2003). A deeper insight into the underlying mechanisms might be gained by the use of animal models, since most described behavioral traits in humans are identifiable in animals as well. In rats, the extent of the trait level of aggressiveness could be assessed on the basis of the latency time to attack a male intruder in a classical resident-intruder test (Koolhaas et al. 2013). In line with the characterization of personality in many other animal species (Bell and Sih 2007; Groothuis and Carere 2005; Reale et al. 2007; Sih et al. 2004), high levels of aggression in rodents are considered an important indicator and component of a more general proactive coping style, whereas low levels of aggression are believed to be a reflection of a reactive coping style (Koolhaas 2008; Koolhaas et al. 1999). These divergent behavioral coping styles have frequently been associated with different patterns of both autonomic nervous and endocrine (re)activity (de Boer et al. 2003; Koolhaas et al. 1999). However, the investigation of the cardiac autonomic control of these distinct behavioral and physiological coping styles has been conducted only sporadically and provided inconclusive evidence (Sgoifo et al. 2005, 1996). In a recent rat study specifically addressing this issue, Catnevali and colleagues (2013) found that high-aggressive rats had reduced resting heart rate variability, mostly in terms of lower vagal modulation, compared to nonaggressive animals. Most importantly, high-aggressive rats had higher incidence of ventricular tachyarrhythmias during stress or during pharmacological beta-adrenergic stimulation. These findings are consistent with the view that high levels of aggressive behavior in rats are associated with signs of cardiac autonomic impairment and increased arrhythmogenic susceptibility that may predict vulnerability to cardiac morbidity and mortality.

Psychogenic Hypertension

Epidemiological Evidence of Psychogenic Hypertension

Numerous epidemiological studies provide compelling evidence for the causative role of psychosocial factors in developing essential hypertension in humans (Henry and Cassel 1969; Steptoe 2000). One of the best known is a longitudinal study of more than a hundred Italian nuns living monastic life: in the course of this study (20 years), there were virtually no changes in their values of systolic and diastolic arterial pressure (AP). Conversely, in age-matched laywomen, AP substantially and significantly increased over the same period (Timio et al. 1988). In a later paper, the authors confirmed their initial finding by describing another 12 years of the follow-up and presented arguments suggesting that other lifestyle differences between nuns and laywomen did not contribute to the AP differences found between the two groups (Timio et al. 2001). "Job strain" (professional activities associated with high demand and low perceived control) is now a recognized lifestyle risk factor for developing hypertension, as demonstrated by many carefully designed studies (e.g., Pickering 2004; Schnall et al. 1990).

Early Animal Models of Psychogenic Hypertension

Not surprisingly, numerous attempts were made to establish an animal model of stress-induced hypertension, and the aim of this section is to provide a critical review of the most relevant studies in this area. "Stress-induced hypertension" here is defined as long-term, sustained elevation of the AP that lasts well beyond the duration of stressors; the acute pressor effects of psychological stressors are very well documented, extensively studied, and broadly described elsewhere. One major conclusion that could be made on the basis of existing studies is that their results are often conflicting and contradictory. Various factors that potentially contributed to this controversy may include different kind of stress protocols, duration of their presentation, animals' age and their strain, and, most importantly, the method used to assess AP.

In two early rat studies, animals were subjected to unpredictable noxious sensory stimuli (flashing lights, loud sounds, shaking cages) three times a week for 12–20 weeks (Cox et al. 1985; Smookler and Buckley 1969). Substantial hypertension was found starting from the second week of stress and lasted throughout the entire stress period. In one of these studies, animals were monitored for 20 weeks after the termination of the stress protocol, and during all this period, AP remained high.

Role of Genetic Makeup in Psychogenic Hypertension

Some researchers were particularly interested in the potential genetic predisposition in the rats' sensitivity to stressors. To address this issue, Lawler (Lawler et al. 1981)

set up a novel animal model called borderline hypertensive rats (BHR, a - first-generation offspring of SHR and Wistar-Kyoto rats) that had mildly elevated AP, without frank hypertension. It was suggested that such prehypertensive animals would be more susceptible to psychological stressors in terms of developing sustained hypertension. When BHR were subjected to a complex stress paradigm (conditioned footshock avoidance) on a daily basis, they developed elevated blood pressure within 2–3 weeks; this hypertension persisted during the entire stress period (3–4 months) as well as during the post-stress phase (Lawler et al. 1981, 1984). Interestingly, substantial inconsistencies were reported even in studies performed in the same laboratory and using the same animal strain and stress paradigm: in the first study (Lawler et al. 1981), AP steadily increased in the course of the experiment reaching a difference of 40 mmHg, while in the second study, the pressor effect was smaller (20–25 mmHg), reached plateau during 2–3 weeks, and did not increase further (Lawler et al. 1984). It is important to note that in all studies mentioned so far, AP was determined indirectly, using the tail-cuff method.

BHR rats were used in several later experiments employing less complex stressors such as inescapable footshocks (Cox et al. 1985), restraint with airjet (Hatton et al. 1993), or social crowding (Muller et al. 2001), all producing variable pressor effects (10–30 mmHg). Tail-cuff method was used in all of these studies, and in two of them, AP was additionally measured at the end of stress period directly, using catheters implanted into the aorta (Cox et al. 1985; Hatton et al. 1993). Later, Mansi and Drolet (1997) reported mild hypertension in BHR subjected to 8-week restraint/airjet stress. Finally, in two other studies where AP in BHR was assessed using biotelemetry, no signs of stress-induced hypertension were found (Mansi and Drolet 1997; Muller et al. 2001).

Another approach for assessing the effect of genetic predisposition on psychogenic hypertension was based on breeding two rat lines based on their AP response to salt ingestion. These lines are known as Dahl-sensitive and Dahl-resistant rats. Aversive Pavlovian conditioning did not provoke hypertension in these rats (Dahl et al. 1968), but when they were subjected to a highly noxious footshock/food conflict (in order to obtain food pellet, rats had to press a lever that triggered a footshock), Dahl-sensitive rats had developed hypertension that persisted for the entire 25-week stress period (Friedman and Iwai 1976). The hypertensive effect of stress was also present in Dahl-resistant animals, but developed slower and was less prominent.

Controversy in the Research on Psychogenic Hypertension in Animals and Potential Causes of This Controversy

A good example of unexplained controversy in chronic stress/hypertension animal studies could be illustrated by the following sequence of experimental works.

Initially, Henry and Cassel (1969) presented evidence that various stressors (social crowding, exposure to a cat odor, and territorial fights) provoke considerable sustained elevation in the AP in mice (65). This finding was reproduced in rats by

Wexler and Greenberg (1978) who also found that maintaining an unstable social hierarchy, by frequently moving males from one communal cage to another, provokes dramatic hypertension (+80 mmHg), even in normotensive Sprague-Dawley rats. Several years after, however, Harrap et al. (1984) put these findings under serious doubt by demonstrating that a similar chronic stress paradigm had absolutely no effect on AP, not only in normotensive SD and WKY but also in BHR rats. In response, Henry conducted a very detailed and prolonged (6-month) study using exactly the same stress protocol as Wexler and found that, indeed, AP remains unaffected in WKY rats, is slightly elevated (~10 mmHg) during some measuring monthly points in SD rats, and slowly raises in Long-Evans rats (Henry et al. 1993). Authors explain this interstrain difference by the higher levels of aggression and more frequent fights displayed by Long-Evans rats. It remained however entirely unexplained why identical stress procedures applied to the same strain (Sprague-Dawley) provoked rapid and dramatic hypertensive effects within 1 month in the first study (Wexler and Greenberg 1978), but had only very mild and delayed action in the later one (Henry et al. 1993).

It must be noted that in most of the above-cited studies, AP was assessed using the tail-cuff method – a simple noninvasive technique based on the same principle as indirect measurement of arterial pressure in humans. However, tail-cuff measurement has some serious limitations. Firstly, the tail vascular bed is thermoregulatory in rats and mice, and at normal laboratory ambient temperatures of 20–25 °C, tail blood flow varies very significantly, sometimes falling near zero (Blessing 2005; Garcia et al. 2001). Thus, in order to maintain it at a constant and measurable level, animals should be kept in a warm environment (33–38 °C) before and during the measurements. Secondly, animals should be restrained, and restrainers used for this purpose – plastic cylinders – are not dissimilar to those used for provoking restraint stress. Thirdly, it is not widely recognized that the tail vascular bed is controlled separately from other vasculatures, and even mild stressors can provoke dramatic selective vasoconstriction in the tail vascular bed (Blessing 2005). Thus, it is questionable whether AP measures taken by means of tail cuff represent true resting values. Indeed, several recent studies where AP was assessed telemetrically during tail-cuff procedure support this doubts: Van Acker et al. (2001) found that tail-cuff measurement provokes substantial increases in both AP and heart rate. In another carefully designed study, it was convincingly demonstrated that even after 3 weeks (nine sessions) of habituation, restraint and heating still provoked dramatic pressor and tachycardic responses, as well as elevation in plasma noradrenaline and angiotensin II concentrations (Grundt et al. 2009). Finally, handling alone, as well as handling and restraint, provoke substantial rises in AP and heart rate, and these responses do not habituate even after ten sessions (McDougall et al. 2005).

Biotelemetry is a "gold standard" for assessing cardiovascular parameters in conscious unrestrained animals. So far there are four published studies that used this method in order to determine whether chronic stress has any sustained effects on AP (Bobrovskaya et al. 2013; Gelsema et al. 1994; Lemaire and Mormede 1995; Muller et al. 2001). Together, these studies involved four rat strains, including BHR and

SHR, and employed the same stress paradigms that caused hypertension in previous studies using tail-cuff measurements. Marginal elevation of AP was found in only one of them (Bobrovskaya et al. 2013); in three other instances, AP remained consistently stable.

In summary, it appears that experimenters using tail-cuff measurements succeeded in demonstrating that only *some* stressors evoke rise in AP in only *some* rat strains, whereas most biotelemetric studies failed to demonstrate any effect on the blood pressure of any stressor in any strain. It is thus most likely that the major cause of such dramatic discrepancies is the intrusiveness of the tail-cuff method, with associated restraint: values measured in this case may reflect the animal's reaction to the measurement procedure rather than the basal levels of AP in the undisturbed state. This most probably happened at least in those cases where these measurements were performed only once a week (Lawler et al. 1984; Wexler and Greenberg 1978) or even once a month (Henry et al. 1993), without any preliminary habituation. It could be that previously stressed animals responded more vigorously to the tail-cuff procedure compared to unstressed controls. While manufacturers recommend that prior to the tail-cuff measurements, the animals should be habituated to measurement conditions, it is currently not clear how many habituation sessions are sufficient.

Tail cuff is still widely used, and several more recent studies employed it to document the hypertensive effects of chronic stress in normotensive rat strains (Andrews et al. 2003; Blake et al. 1995); in one instance, this was confirmed by direct measurements as well (Alkadhi et al. 2005). The dynamics of developing hypertension in this later study (plateau at +40 mmHg in just 4 days) is in sharp contrast with several other previous reports where pressor changes required 2–3 weeks of stress exposure. Presented above considerations suggest that positive pressor effects of prolonged stressors must be taken with some caution.

It may be that factors other than the method of AP assessment contributed to discrepancies in results from different studies as well as to inconsistencies between animal models of psychogenic hypertension and the actual condition in humans. In his seminal review, when discussing psycho-emotional causes of hypertension, Folkow (1982) suggested that if pressor-inducing stress episodes are repeated frequently enough, this may lead to sustained elevation of AP. In most works reviewed here, stressful procedures were either performed daily or were lasting permanently, and further increasing the frequency of stressful interventions does not seem to be a promising idea. Another issue that could contribute to the conflicting results in animal models of psychogenic hypertension is the type of stressor that is employed. It is now accepted in the field of stress research that a critical determinant for a stressor to induce adverse consequences is the ability of the animal to exert control over these events (Maier 1984). Having actual or perceived control over a stressful situation powerfully reduces its negative physiological consequences. It is likely that animals exposed to chronic or repetitive aversive stressors develop effective coping strategies to these putative adverse events that somehow combat the deleterious effects of these stressors. It thus

follows that future animal studies targeting psychogenic hypertension must develop and employ new stress protocols specifically focusing on uncontrollability and unpredictability of stressors.

Conclusions and Clinical Implications

From the data summarized in this chapter, it is evident that animal models of acute and chronic stress-induced cardiac disturbances are extremely useful. They allowed researchers to reproduce human clinical conditions, provided insight into pathogenesis, and also suggested new therapeutic strategies. In some instances, they preceded and predicted clinical findings made in humans. It is likely that by following this research direction with rodent models, it will be possible to obtain not only clearer insights into the physiological/neural/behavioral substrates of psychological and social stress-related psychosomatic disorders but also the biological evidence of the beneficial effects of social support and, more generally speaking, of positive social relationships.

References

Akashi, Y. J., Nef, H. M., Mollmann, H., & Ueyama, T. (2010). Stress cardiomyopathy. *Annual Review of Medicine, 61*, 271–286.

Albus, C. (2010). Psychological and social factors in coronary heart disease. *Annals of Medicine, 42*(7), 487–494. doi:10.3109/07853890.2010.515605.

Alkadhi, K. A., Alzoubi, K. H., Aleisa, A. M., Tanner, F. L., & Nimer, A. S. (2005). Psychosocial stress-induced hypertension results from in vivo expression of long-term potentiation in rat sympathetic ganglia. *Neurobiology of Disease, 20*(3), 849–857.

Andrews, E., Jenkins, C., Seachrist, D., Dunphy, G., & Ely, D. (2003). Social stress increases blood pressure and cardiovascular pathology in a normotensive rat model. *Clinical and Experimental Hypertension, 25*(2), 85–101.

Bandler, R., Carrive, P., & Zhang, S. P. (1991). Integration of somatic and autonomic reactions within the midbrain periaqueductal grey: Viscerotopic, somatotopic and functional organization. *Progress in Brain Research, 87*, 269–305.

Barton, D. A., Dawood, T., Lambert, E. A., Esler, M. D., Haikerwal, D., Brenchley, C.,... Lambert, G. W. (2007). Sympathetic activity in major depressive disorder: Identifying those at increased cardiac risk? *Journal of Hypertension, 25*(10), 2117–2124.

Bell, A. M., & Sih, A. (2007). Exposure to predation generates personality in threespined sticklebacks (Gasterosteus aculeatus). *Ecology Letters, 10*(9), 828–834. doi:10.1111/j.1461-0248.2007.01081.x.

Betensky, J. D., & Contrada, R. J. (2010). Depressive symptoms, trait aggression, and cardiovascular reactivity to a laboratory stressor. *Annals of Behavioral Medicine, 39*(2), 184–191. doi:10.1007/s12160-010-9176-6.

Bigger, J. T., Jr., Fleiss, J. L., Steinman, R. C., Rolnitzky, L. M., Kleiger, R. E., & Rottman, J. N. (1992). Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation, 85*(1), 164–171.

Bjorkqvist, K. (2001). Social defeat as a stressor in humans. *Physiology and Behavior, 73*(3), 435–442.

Blake, M. J., Klevay, L. M., Halas, E. S., & Bode, A. M. (1995). Blood pressure and heat shock protein expression in response to acute and chronic stress. *Hypertension, 25*(4 Pt 1), 539–544.

Blatt, C. M., Rabinowitz, S. H., & Lown, B. (1979). Central serotonergic agents raise the repetitive extrasystole threshold of the vulnerable period of the canine ventricular myocardium. *Congressional Record, 44*(5), 723–730.

Blessing, W. W. (2005). Clozapine increases cutaneous blood flow and reduces sympathetic cutaneous vasomotor alerting responses (SCVARs) in rats: Comparison with effects of haloperidol. *Psychopharmacology, 181*(3), 518–528.

Bobrovskaya, L., Beard, D., Bondarenko, E., Beig, M. I., Jobling, P., Walker, F. R.,... Nalivaiko, E. (2013). Does exposure to chronic stress influence blood pressure in rats? *Autonomic Neuroscience, 177*(2), 217–223. doi:10.1016/j.autneu.2013.05.001.

Buwalda, B., de Boer, S., ED, S., Felszeghy, K., Nyakas, C., A, S.,... Koolhaas, J. (1999). Long-lasting deficient dexamethasone suppression of hypothalamic-pituitary-adrenocortical activation following peripheral CRF challenge in socially defeated rats. *Journal of Neuroendocrinology, 11*(7), 513–520.

Carnevali, L., Mastorci, F., Audero, E., Graiani, G., Rossi, S., Macchi, E.,... Sgoifo, A. (2012a). Stress-induced susceptibility to sudden cardiac death in mice with altered serotonin homeostasis. *PLoS One, 7*(7), e41184. doi:10.1371/journal.pone.0041184, [pii] PONE-D-12-09604.

Carnevali, L., Mastorci, F., Graiani, G., Razzoli, M., Trombini, M., Pico-Alfonso, M. A.,... Sgoifo, A. (2012b). Social defeat and isolation induce clear signs of a depression-like state, but modest cardiac alterations in wild-type rats. *Physiology and Behavior, 106*(2), 142–150. doi:10.1016/j.physbeh.2012.01.022.

Carnevali, L., Trombini, M., Porta, A., Montano, N., de Boer, S. F., & Sgoifo, A. (2013a). Vagal withdrawal and susceptibility to cardiac arrhythmias in rats with high trait aggressiveness. *PLoS One, 8*(7), e68316. doi:10.1371/journal.pone.0068316.

Carnevali, L., Trombini, M., Rossi, S., Graiani, G., Manghi, M., Koolhaas, J. M.,... Sgoifo, A. (2013). Structural and electrical myocardial remodeling in a rodent model of depression. *Psychosomatic Medicine, 75*(1), 42–51. doi:10.1097/PSY.0b013e318276cb0d, [pii] PSY.0b013e318276cb0d.

Carney, R. M., Rich, M. W., teVelde, A., Saini, J., Clark, K., & Freedland, K. E. (1988). The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. *Journal of Psychosomatic Research, 32*(2), 159–164.

Carter, C. S., Grippo, A., Pournajafi-Nazarloo, H., Ruscio, M. G., & Porges, S. W. (2008). Oxytocin, vasopressin and sociality. Prog. in brain res (Vol. 170, pp. 331–336).

Corbalan, R., Verrier, R., & Lown, B. (1974). Psychological stress and ventricular arrhythmias during myocardial infarction in the conscious dog. *Congressional Record, 34*(6), 692–696.

Costoli, T., Bartolomucci, A., Graiani, G., Stilli, D., Laviola, G., & Sgoifo, A. (2004). Effects of chronic psychosocial stress on cardiac autonomic responsiveness and myocardial structure in mice. *American Journal of Physiology – Heart and Circulatory Physiology, 286*(6), H2133–H2140. doi:10.1152/ajpheart.00869.2003.

Cox, R. H., Hubbard, J. W., Lawler, J. E., Sanders, B. J., & Mitchell, V. P. (1985). Exercise training attenuates stress-induced hypertension in the rat. *Congressional Record, 7*(5), 747–751.

Dahl, L. K., Knudsen, K. D., Heine, M., & Leitl, G. (1968). Hypertension and stress. *Nature, 219* (5155), 735–736.

Dampney, R., Horiuchi, J., & McDowall, L. (2008). Hypothalamic mechanisms coordinating cardiorespiratory function during exercise and defensive behaviour. *Autonomic Neuroscience, 142*, 3–10.

de Boer, S. F., van der Vegt, B. J., & Koolhaas, J. M. (2003). Individual variation in aggression of feral rodent strains: A standard for the genetics of aggression and violence? *Behavior Genetics, 33*(5), 485–501.

De Vogli, R., Chandola, T., & Marmot, M. G. (2007). Negative aspects of close relationships and heart disease. *Archives of Internal Medicine, 167*(18), 1951–1957. doi:10.1001/archinte.167.18.1951.

Engler, H., Dawils, L., Hoves, S., Kurth, S., Stevenson, J. R., Schauenstein, K., & Stefanski, V. (2004). Effects of social stress on blood leukocyte distribution: The role of alpha- and beta-adrenergic mechanisms. *Journal of Neuroimmunology, 156*(1–2), 153–162. doi:10.1016/j.jneuroim.2004.08.005.

Folkow, B. (1982). Physiological aspects of primary hypertension. *Congressional Record, 62*(2), 347–504.

Fontes, M. A., Xavier, C. H., Marins, F. R., Limborco-Filho, M., Vaz, G. C., Muller-Ribeiro, F. C., & Nalivaiko, E. (2014). Emotional stress and sympathetic activity: Contribution of dorsomedial hypothalamus to cardiac arrhythmias. *Brain Research, 1554*, 49–58. doi:10.1016/j.brainres.2014.01.043.

Friedman, R., & Iwai, J. (1976). Genetic predisposition and stress-induced hypertension. *Congressional Record, 193*(4248), 161–162.

Friedman, M., & Rosenman, R. H. (1959). Association of specific overt behavior pattern with blood and cardiovascular findings; blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease. *Journal of the American Medical Association, 169*(12), 1286–1296.

Garcia, J. N., Pedersen, N. P., Nalivaiko, E., & Blessing, W. W. (2001). Tail artery blood flow measured by chronically implanted Doppler ultrasonic probes in unrestrained conscious rats. *Journal of Neuroscience Methods, 104*(2), 209–213.

Gelsema, A. J., Schoemaker, R. G., Ruzicka, M., & Copeland, N. E. (1994). Cardiovascular effects of social stress in borderline hypertensive rats. *Journal of Hypertension, 12*(9), 1019–1028.

Grippo, A. J. (2009). Mechanisms underlying altered mood and cardiovascular dysfunction: The value of neurobiological and behavioral research with animal models. *Neuroscience and Biobehavioral Reviews, 33*(2), 171–180. doi:10.1016/j.neubiorev.2008.07.004.

Grippo, A. J., Carter, C. S., McNeal, N., Chandler, D. L., Larocca, M. A., Bates, S. L., & Porges, S. W. (2011). 24-hour autonomic dysfunction and depressive behaviors in an animal model of social isolation: Implications for the study of depression and cardiovascular disease. *Psychosomatic Medicine, 73*(1), 59–66. doi:10.1097/PSY.0b013e31820019e4.

Grippo, A. J., Moffitt, J. A., Sgoifo, A., Jepson, A. J., Bates, S. L., Chandler, D. L.,... Preihs, K. (2012). The integration of depressive behaviors and cardiac dysfunction during an operational measure of depression: Investigating the role of negative social experiences in an animal model. *Psychosomatic Medicine, 74*(6), 612–619. doi:10.1097/PSY.0b013e31825ca8e5.

Groothuis, T. G., & Carere, C. (2005). Avian personalities: Characterization and epigenesis. *Neuroscience and Biobehavioral Reviews, 29*(1), 137–150. doi:10.1016/j.neubiorev.2004.06.010.

Grundt, A., Grundt, C., Gorbey, S., Thomas, M. A., & Lemmer, B. (2009). Strain-dependent differences of restraint stress-induced hypertension in WKY and SHR. *Physiology and Behavior, 97*(3–4), 341–346.

Harrap, S. B., Louis, W. J., & Doyle, A. E. (1984). Failure of psychosocial stress to induce chronic hypertension in the rat. *Journal of Hypertension, 2*(6), 653–62.

Hatton, D. C., DeMerritt, J., Coste, S. C., & McCarron, D. A. (1993). Stress-induced hypertension in the borderline hypertensive rat: Stimulus duration. *Congressional Record, 53*(4), 635–641.

Hemingway, H., Malik, M., & Marmot, M. (2001). Social and psychosocial influences on sudden cardiac death, ventricular arrhythmia and cardiac autonomic function. *European Heart Journal, 22*(13), 1082–1101. doi:10.1053/euhj.2000.2534.

Henry, J. P., & Cassel, J. C. (1969). Psychosocial factors in essential hypertension. Recent epidemiologic and animal experimental evidence. *Congressional Record, 90*(3), 171–200.

Henry, J. P., Liu, Y. Y., Nadra, W. E., Qian, C. G., Mormede, P., Lemaire, V.,... Hendley, E. D. (1993). Psychosocial stress can induce chronic hypertension in normotensive strains of rats. *Hypertension, 21*(5), 714–723.

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., & Gatt, J. M. (2010). Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. *Biological Psychiatry, 67*(11), 1067–1074. doi:10.1016/j.biopsych.2009.12.012.

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *The American Journal of Psychiatry, 156*(6), 837–841.

Khawaja, I. S., Westermeyer, J. J., Gajwani, P., & Feinstein, R. E. (2009). Depression and coronary artery disease: The association, mechanisms, and therapeutic implications. *Psychiatry (Edgmont), 6*(1), 38–51.

Kolman, B. S., Verrier, R. L., & Lown, B. (1976). Effect of vagus nerve stimulation upon excitability of the canine ventricle. Role of sympathetic-parasympathetic interactions. *American Journal of Cardiology, 37*(7), 1041–1045.

Koolhaas, J. M. (2008). Coping style and immunity in animals: Making sense of individual variation. *Brain, Behavior, and Immunity, 22*(5), 662–667. doi:10.1016/j.bbi.2007.11.006.

Koolhaas, J. M., Korte, S. M., De Boer, S. F., Van Der Vegt, B. J., Van Reenen, C. G., Hopster, H.,... Blokhuis, H. J. (1999). Coping styles in animals: Current status in behavior and stress-physiology. *Neuroscience and Biobehavioral Reviews, 23*(7), 925–935.

Koolhaas, J. M., Coppens, C. M., de Boer, S. F., Buwalda, B., Meerlo, P., & Timmermans, P. J. (2013). The resident-intruder paradigm: A standardized test for aggression, violence and social stress. *Journal of Visualized Experiments, 77*, e4367. doi:10.3791/4367.

Kop, W. J. (1999). Chronic and acute psychological risk factors for clinical manifestations of coronary artery disease. *Psychosomatic Medicine, 61*(4), 476–487.

Krantz, D. S., & McCeney, M. K. (2002). Effects of psychological and social factors on organic disease: A critical assessment of research on coronary heart disease. *Annual Review of Psychology, 53*, 341–369. doi:10.1146/annurev.psych.53.100901.135208.

La Rovere, M. T., Bigger, J. T., Jr., Marcus, F. I., Mortara, A., & Schwartz, P. J. (1998). Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet, 351*(9101), 478–484.

La Rovere, M. T., Pinna, G. D., Maestri, R., Mortara, A., Capomolla, S., Febo, O.,... Cobelli, F. (2003). Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation, 107*(4), 565–570.

Lampert, R., Jain, D., Burg, M. M., Batsford, W. P., & McPherson, C. A. (2000). Destabilizing effects of mental stress on ventricular arrhythmias in patients with implantable cardioverter-defibrillators. *Circulation, 101*(2), 158–164.

Lawler, J. E., Barker, G. F., Hubbard, J. W., & Schaub, R. G. (1981). Effects of stress on blood pressure and cardiac pathology in rats with borderline hypertension. *Congressional Record, 3*(4), 496–505.

Lawler, J. E., Barker, G. F., Hubbard, J. W., Cox, R. H., & Randall, G. W. (1984). Blood-pressure and plasma-renin activity responses to chronic stress in the borderline hypertensive rat. *Physiology & Behavior, 32*(1), 101–105.

Lehnert, H., Lombardi, F., Raeder, E. A., Lorenzo, A. V., Verrier, R. L., Lown, B., & Wurtman, R. J. (1987). Increased release of brain serotonin reduces vulnerability to ventricular fibrillation in the cat. *Journal of Cardiovascular Pharmacology, 10*(4), 389–397.

Lemaire, V., & Mormede, P. (1995). Telemetered recording of blood pressure and heart rate in different strains of rats during chronic social stress. *Physiology and Behavior, 58*(6), 1181–1188.

Leor, J., Poole, W. K., & Kloner, R. A. (1996). Sudden cardiac death triggered by an earthquake. *New England Journal of Medicine, 334*(7), 413–419.

Liao, D., Cai, J., Rosamond, W. D., Barnes, R. W., Hutchinson, R. G., Whitsel, E. A.,... Heiss, G. (1997). Cardiac autonomic function and incident coronary heart disease: A population-based case-cohort study. The ARIC Study. Atherosclerosis Risk in Communities Study. *American Journal of Epidemiology. 145*(8), 696–706.

Lippi, G., Montagnana, M., Favaloro, E. J., & Franchini, M. (2009). Mental depression and cardiovascular disease: A multifaceted, bidirectional association. *Seminars in Thrombosis and Hemostasis, 35*(3), 325–336. doi:10.1055/s-0029-1222611.

Lown, B., Corbalan, R., & Verrier, R. L. (1973). Psychologic stress and threshold for repetitive ventricular response. *Congressional Record, 182*(114), 834–836.

Maier, S. F. (1984). Learned helplessness and animal models of depression. *Progress in Neuropsychopharmacology and Biological Psychiatry, 8*(3), 435–446.

Mansi, J. A., & Drolet, G. (1997). Chronic stress induces sensitization in sympathoadrenal responses to stress in borderline hypertensive rats. *Congressional Record, 272*(3 Pt 2), R813–820.

Matta, R. J., Lawler, J. E., & Lown, B. (1976). Ventricular electrical instability in the conscious dog: Effects of psychologic stress and beta adrenergic blockade. *American Journal of Cardiology, 38*(5), 594–598.

McCall, R. B., & Clement, M. E. (1994). Role of serotonin1A and serotonin2 receptors in the central regulation of the cardiovascular system. *Pharmacological Reviews, 46*(3), 231–243.

McDougall, S. J., Lawrence, A. J., & Widdop, R. E. (2005). Differential cardiovascular responses to stressors in hypertensive and normotensive rats. *Experimental Physiology, 90*(1), 141–150.

McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine, 338*(3), 171–179.

McGrady, A. V. (1984). Effects of psychological stress on male reproduction: A review. *Archives of Andrology, 13*(1), 1–7.

Meerlo, P., De Boer, S. F., Koolhaas, J. M., Daan, S., & Van den Hoofdakker, R. H. (1996a). Changes in daily rhythms of body temperature and activity after a single social defeat in rats. *Physiology and Behavior, 59*(4–5), 735–739.

Meerlo, P., Overkamp, G. J., Benning, M. A., Koolhaas, J. M., & Van den Hoofdakker, R. H. (1996b). Long-term changes in open field behaviour following a single social defeat in rats can be reversed by sleep deprivation. *Physiology and Behavior, 60*(1), 115–119.

Meerlo, P., Sgoifo, A., De Boer, S. F., & Koolhaas, J. M. (1999). Long-lasting consequences of a social conflict in rats: Behavior during the interaction predicts subsequent changes in daily rhythms of heart rate, temperature, and activity. *Behavioral Neuroscience, 113*(6), 1283–1290.

Meerlo, P., Sgoifo, A., & Turek, F. W. (2002). The effects of social defeat and other stressors on the expression of circadian rhythms. *Stress, 5*(1), 15–22. doi:10.1080/102538902900012323.

Meredith, I. T., Broughton, A., Jennings, G. L., & Esler, M. D. (1991). Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. *Congressional Record, 325*(9), 618–624.

Muller, J. R., Le, K. M., Haines, W. R., Gan, Q., & Knuepfer, M. M. (2001). Hemodynamic response pattern predicts susceptibility to stress-induced elevation in arterial pressure in the rat. *Congressional Record, 281*(1), R31–37.

Nalivaiko, E., & Sgoifo, A. (2009). Central 5-HT receptors in cardiovascular control during stress. *Neuroscience and Biobehavioral Reviews, 33*(2), 95–106. doi:10.1016/j.neubiorev.2008.05.026. [pii] S0149-7634(08)00094-8.

Nalivaiko, E., De Pasquale, C. G., & Blessing, W. W. (2003). Electrocardiographic changes associated with the nasopharyngeal reflex in conscious rabbits: Vago-sympathetic co-activation. *Autonomic Neuroscience, 105*(2), 101–104. doi:10.1016/S1566-0702(03)00048-1. [pii] S1566-0702(03)00048-1.

Nalivaiko, E., De Pasquale, C. G., & Blessing, W. W. (2004). Ventricular arrhythmias triggered by alerting stimuli in conscious rabbits pre-treated with dofetilide. *Basic Research in Cardiology, 99*(2), 142–151. doi:10.1007/s00395-003-0448-1.

Nalivaiko, E., Ootsuka, Y., & Blessing, W. W. (2005). Activation of 5-HT1A receptors in the medullary raphe reduces cardiovascular changes elicited by acute psychological and inflammatory stresses in rabbits. *American Journal of Physiology – Regulatory Integrative & Comparative Physiology, 289*(2), R596–R604.

Nalivaiko, E., Catcheside, P. G., Adams, A., Jordan, A. S., Eckert, D. J., & McEvoy, R. D. (2007). Cardiac changes during arousals from non-REM sleep in healthy volunteers. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology, 292*(3), R1320–R1327. doi:10.1152/ajpregu.00642.2006. [pii] 00642.2006.

Nalivaiko, E., Mastorci, F., & Sgoifo, A. (2009). 8-OH-DPAT prevents cardiac arrhythmias and attenuates tachycardia during social stress in rats. *Physiology and Behavior, 96*(2), 320–327.

Natelson, B. H., & Cagin, N. A. (1979). Stress-induced ventricular arrhythmias. *Congressional Record, 41*(3), 259–262.

Natelson, B. H., Cagin, N. A., Donner, K., & Hamilton, B. E. (1978). Psychosomatic digitalis-toxic arrhythmias in guinea pigs. *Congressional Record, 22*(24), 2245–2250.

Nestler, E. J., & Hyman, S. E. (2010). Animal models of neuropsychiatric disorders. *Nature Neuroscience, 13*(10), 1161–1169. doi:10.1038/nn.2647.

Ngampramuan, S., Baumert, M., Beig, M. I., Kotchabhakdi, N., & Nalivaiko, E. (2008). Activation of 5-HT(1A) receptors attenuates tachycardia induced by restraint stress in rats. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 294*(1), R132–R141. doi:10.1152/ajpregu.00464.2007. [pii] 00464.2007.

Pickering, T. G. (2004). Reflections in hypertension: Work and blood pressure. *Congressional Record, 6*(7), 403–405.

Pico-Alfonso, M. A., Mastorci, F., Ceresini, G., Ceda, G. P., Manghi, M., Pino, O.,... Sgoifo, A. (2007). Acute psychosocial challenge and cardiac autonomic response in women: The role of estrogens, corticosteroids, and behavioral coping styles. *Psychoneuroendocrinology, 32*(5), 451–463. doi:10.1016/j.psyneuen.2007.02.009.

Pitzalis, M. V., Iacoviello, M., Todarello, O., Fioretti, A., Guida, P., Massari, F.,... Rizzon, P. (2001). Depression but not anxiety influences the autonomic control of heart rate after myocardial infarction. *American Heart Journal, 141*(5), 765–771. doi:10.1067/mhj.2001.114806.

Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *The American Journal of Psychiatry, 149*(8), 999–1010.

Rabinowitz, S. H., & Lown, B. (1978). Central neurochemical factors related to serotonin metabolism and cardiac ventricular vulnerability for repetitive electrical activity. *American Journal of Cardiology, 41*(3), 516–522.

Ramage, A. G. (2001). Central cardiovascular regulation and 5-hydroxytryptamine receptors. *Brain Research Bulletin, 56*(5), 425–439.

Ramage, A. G., & Villalon, C. M. (2008). 5-Hydroxytryptamine and cardiovascular regulation. *Trends in Pharmacological Sciences, 29*, 472–481.

Reale, D., Reader, S. M., Sol, D., McDougall, P. T., & Dingemanse, N. J. (2007). Integrating animal temperament within ecology and evolution. *Biological Reviews of the Cambridge Philosophical Society, 82*(2), 291–318. doi:10.1111/j.1469-185X.2007.00010.x.

Rechlin, T., Weis, M., Spitzer, A., & Kaschka, W. P. (1994). Are affective disorders associated with alterations of heart rate variability? *Journal of Affective Disorders, 32*(4), 271–275.

Reich, P., DeSilva, R. A., Lown, B., & Murawski, B. J. (1981). Acute psychological disturbances preceding life-threatening ventricular arrhythmias. *JAMA, 246*, 233–235.

Rozanski, A., Blumenthal, J. A., & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation, 99*(16), 2192–2217.

Ruis, M. A., te Brake, J. H., Buwalda, B., De Boer, S. F., Meerlo, P., Korte, S. M.,... Koolhaas, J. M. (1999). Housing familiar male wildtype rats together reduces the long-term adverse behavioural and physiological effects of social defeat. *Psychoneuroendocrinology, 24*(3), 285–300.

Satoda, T., Takahashi, O., Uchida, T., & Mizuno, N. (1995). An anterograde-retrograde labeling study of the carotid sinus nerve of the Japanese monkey (Macaca fuscata). *Neuroscience Research, 22*, 381–387.

Schnall, P. L., Pieper, C., Schwartz, J. E., Karasek, R. A., Schlussel, Y., Devereux, R. B.,... Pickering, T. G. (1990). The relationship between 'job strain,' workplace diastolic blood pressure, and left ventricular mass index. Results of a case-control study. *JAMA, 263*(14), 1929–1935.

Sevoz-Couche, C., Brouillard, C., Camus, F., Laude, D., De Boer, S. F., Becker, C., & Benoliel, J. J. (2013). Involvement of the dorsomedial hypothalamus and the nucleus tractus solitarii in chronic cardiovascular changes associated with anxiety in rats. *Journal of Physiology, 591* (Pt 7), 1871–1887. doi:10.1113/jphysiol.2012.247791. [pii] jphysiol.2012.247791.

Sgoifo, A., de Boer, S. F., Haller, J., & Koolhaas, J. M. (1996). Individual differences in plasma catecholamine and corticosterone stress responses of wild-type rats: Relationship with aggression. *Physiology and Behavior, 60*(6), 1403–1407.

Sgoifo, A., de Boer, S. F., Westenbroek, C., Maes, F. W., Beldhuis, H., Suzuki, T., & Koolhaas, J. M. (1997). Incidence of arrhythmias and heart rate variability in wild-type rats exposed to social stress. *American Journal of Physiology, 273*(4 Pt 2), H1754–H1760.

Sgoifo, A., Koolhaas, J. M., De Boer, S. F., Musso, E., Stilli, D., Buwalda, B., & Meerlo, P. (1999). Social stress, autonomic neural activation, and cardiac activity in rats. *Neuroscience and Biobehavioral Reviews, 23*(7), 915–923.

Sgoifo, A., Costoli, T., Meerlo, P., Buwalda, B., Pico'-Alfonso, M. A., De Boer, S.,... Koolhaas, J. (2005). Individual differences in cardiovascular response to social challenge. *Neuroscience and Biobehavioral Reviews, 29*(1), 59–66. doi:10.1016/j.neubiorev.2004.07.001.

Sgoifo, A., Montano, N., Shively, C., Thayer, J., & Steptoe, A. (2009). The inevitable link between heart and behavior: New insights from biomedical research and implications for clinical practice. *Neuroscience and Biobehavioral Reviews, 33*(2), 61–62. doi:10.1016/j.neubiorev.2008.10.007.

Shively, C. A., Friedman, D. P., Gage, H. D., Bounds, M. C., Brown-Proctor, C., Blair, J. B.,... Buchheimer, N. (2006). Behavioral depression and positron emission tomography-determined serotonin 1A receptor binding potential in cynomolgus monkeys. *Archives of General Psychiatry, 63*(4), 396–403.

Sih, A., Bell, A. M., Johnson, J. C., & Ziemba, R. E. (2004). Behavioral syndromes: An integrative overview. *Quarterly Review of Biology, 79*(3), 241–277.

Skinner, J. E., & Reed, J. C. (1981). Blockade of frontocortical-brain stem pathway prevents ventricular fibrillation of ischemic heart. *American Journal of Physiology, 240*(2), H156–H163.

Skinner, J. E., Lie, J. T., & Entman, M. L. (1975). Modification of ventricular fibrillation latency following coronary artery occlusion in the conscious pig. *Circulation, 51*(4), 656–667.

Smith, T. W. (1992). Hostility and health: Current status of a psychosomatic hypothesis. *Health Psychology, 11*(3), 139–150.

Smith, T. W., Glazer, K., Ruiz, J. M., & Gallo, L. C. (2004). Hostility, anger, aggressiveness, and coronary heart disease: An interpersonal perspective on personality, emotion, and health. *Journal of Personality, 72*(6), 1217–1270. doi:10.1111/j.1467-6494.2004.00296.x

Smookler, H. H., & Buckley, J. P. (1969). Relationships between brain catecholamine synthesis, pituitary adrenal function and the production of hypertension during prolonged exposure to environmental stress. *Congressional Record, 8*(1), 33–41.

Sowden, G. L., & Huffman, J. C. (2009). The impact of mental illness on cardiac outcomes: A review for the cardiologist. *International Journal of Cardiology, 132*(1), 30–37. doi:10.1016/j.ijcard.2008.10.002.

Stefanski, V., & Engler, H. (1998). Effects of acute and chronic social stress on blood cellular immunity in rats. *Physiology and Behavior, 64*(5), 733–741.

Steinberg, J. S., Arshad, A., Kowalski, M., Kukar, A., Suma, V., Vloka, M.,... Rozanski, A. (2004). Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. *Journal of the American College of Cardiology, 44*(6), 1261–1264.

Steptoe, A. (2000). Psychosocial factors in the development of hypertension. *Annals of Medicine, 32*, 371–375.

Steptoe, A., & Brydon, L. (2009). Emotional triggering of cardiac events. *Neuroscience and Biobehavioral Reviews, 33*(2), 63–70. doi:10.1016/j.neubiorev.2008.04.010.

Steptoe, A., Hamer, M., O'Donnell, K., Venuraju, S., Marmot, M. G., & Lahiri, A. (2010). Socioeconomic status and subclinical coronary disease in the Whitehall II epidemiological study. *PLoS One, 5*(1), e8874. doi:10.1371/journal.pone.0008874.

Strike, P. C., & Steptoe, A. (2004). Psychosocial factors in the development of coronary artery disease. *Progress in Cardiovascular Diseases, 46*(4), 337–347.

Timio, M., Verdecchia, P., Venanzi, S., Gentili, S., Ronconi, M., Francucci, B., Montanari, M., & Bichisao, E. (1988). Age and blood pressure changes. A 20-year follow-up study in nuns in a secluded order. *Congressional Record, 12*(4), 457–461.

Timio, M., Saronio, P., Verdura, C., Schiaroli, M., Timio, F., & Monarca, C. (2001). A link between psychosocial factors and blood pressure trend in women. *Congressional Record, 73* (3), 359–363.

Tornatzky, W., & Miczek, K. A. (1993). Long-term impairment of autonomic circadian rhythms after brief intermittent social stress. *Physiology and Behavior, 53*(5), 983–993.

Tsuji, H., Larson, M. G., Venditti, F. J., Jr., Manders, E. S., Evans, J. C., Feldman, C. L., & Levy, D. (1996). Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation, 94*(11), 2850–2855.

Ueyama, T. (2004). Emotional stress-induced Tako-tsubo cardiomyopathy: Animal model and molecular mechanism. *Annals of the New York Academy of Sciences, 1018*, 437–444.

Ueyama, T., Kasamatsu, K., Hano, T., Yamamoto, K., Tsuruo, Y., & Nishio, I. (2002). Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: A possible animal model of 'tako-tsubo' cardiomyopathy. *Circulation Journal, 66*(7), 712–713.

Ueyama, T., Tanioku, T., Nuta, J., Kujira, K., Ito, T., Nakai, S., & Tsuruo, Y. (2006). Estrogen alters c-Fos response to immobilization stress in the brain of ovariectomized rats. *Brain Research, 1084*(1), 67–79.

Ueyama, T., Ishikura, F., Matsuda, A., Asanuma, T., Ueda, K., Ichinose, M.,... Beppu, S. (2007). Chronic estrogen supplementation following ovariectomy improves the emotional stress-induced cardiovascular responses by indirect action on the nervous system and by direct action on the heart. *Circulation Journals, 71*(4), 565–573.

Van Acker, S. A., Fluttert, M. F., Sibug, R. M., & De Kloet, E. R. (2001). Intracerebroventricular administration of a glucocorticoid receptor antagonist enhances the cardiovascular responses to brief restraint stress. *Congressional Record, 430*(1), 87–91.

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. *International Journal of Geriatric Psychiatry, 22*(7), 613–626. doi:10.1002/gps.1723.

Verrier, R. L., & Lown, B. (1984). Behavioral stress and cardiac arrhythmias. *Congressional Record, 46*, 155–176.

Von Frijtag, J. C., Reijmers, L. G., Van der Harst, J. E., Leus, I. E., Van den Bos, R., & Spruijt, B. M. (2000). Defeat followed by individual housing results in long-term impaired reward- and cognition-related behaviours in rats. *Behavioural Brain Research, 117*(1–2), 137–146.

von Kanel, R. (2012). Psychosocial stress and cardiovascular risk: Current opinion. *Swiss Medical Weekly, 142*, w13502. doi:10.4414/smw.2012.13502.

Wexler, B. C., & Greenberg, B. P. (1978). Pathophysiological differences between paired and communal breeding of male and female Sprague-Dawley rats. *Congressional Record, 42*(1), 126–135.

Whooley, M. A. (2006). Depression and cardiovascular disease: Healing the broken-hearted. *JAMA, 295*(24), 2874–2881. doi:10.1001/jama.295.24.2874.

Wilde, A., Jongbloed, R., Doevendans, P., Duren, D., Hauer, R., van Langen, I.,... Geelen, J. (1999). Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *Journal of the American College of Cardiology, 33*(2), 327–332.

Wittstein, I. S., Thiemann, D. R., Lima, J. A., Baughman, K. L., Schulman, S. P., Gerstenblith, G.,... Champion, H. C. (2005). Neurohumoral features of myocardial stunning due to sudden emotional stress. *New England Journal of Medicine, 352*(6), 539–548.

Young, L. J., & Wang, Z. (2004). The neurobiology of pair bonding. *Nature Neuroscience, 7*(10), 1048–1054. doi:10.1038/nn1327.

Zipes, D. P., & Wellens, H. J. (1998). Sudden cardiac death. *Circulation, 98*(21), 2334–2351.

McNeal, N., Scotti, M. A., Wardwell, J., Chandler, D. L., Bates, S. L., Larocca, M.,... Grippo, A. J. (2014). Disruption of social bonds induces behavioral and physiological dysregulation in male and female prairie voles. *Autonomic Neuroscience, 180*, 9–16. doi:10.1016/j.autneu.2013.10.001.

Nonlinear Analyses of Data in Cardiovascular Physiology and Epidemiology

Robert A. M. Gregson

Contents

Abstract

The nonlinear dynamics of heart action are such as to generate and to support irregular nonrandom variations in the main output parameters of pulse and

Notes: I am indebted to Prof. Don Byrne for drawing my attention to a diversity of valuable sources on anxiety and heart function, including his own work. The mathematical interpretations are mostly my own.

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7, May 2003, in the USA) introduced the notion of prehypertension. If this condition is defined by a single threshold value for SAP (120–139 mmHg is suggested), then logically, given the nonlinear variability of cardiac function, virtually all persons over a cutoff age of around 50 years will be at some times prehypertensive, and for them medical intervention is commended, including the reduced use of sodium in diet and at least to advise on lifestyle. It has been noted (www.medscape.com) that most of the authors of the report have extensive financial disclosures with numerous pharmaceutical companies. It must be emphasized that the recommendations of JNC7 have been strongly criticized, based in part on findings from the Second Australian National Blood Pressure Study (Wing et al. 2003). Some medical specialists, not starting from a base of nonlinear cardiac dynamics, but considering high plasma renin levels, have ridiculed the very existence of prehypertension.

R.A.M. Gregson (✉)
Research School of Psychology, Australian National University, Canberra, ACT, Australia
e-mail: ramgdd@bigpond.com

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_46

pressure, in response to external stimulation such as stressors (Pearson 1972; Gregson 2009; Herbert 1995; Mezentseva et al. 2002; Rao and Yeragani 2001; Shiferaw and Karma 2006). These dynamic complexities have serious implications for the analysis and treatment of hypertension, as the probabilities of misdiagnosis of state, dysfunction, and potential morbidity cannot with certainty be based on the linear or Gaussian statistics usually employed in epidemiological and related studies. A Bayesian analysis of decision probabilities is used to point up ambiguities in reported results. There is gradual recognition of this situation, but so far little established linkage between nonlinear dynamical modeling and clinical practice, except perhaps in some recent biomedical physics modeling.

Keywords

Nonlinear dynamics • Coupled attractors • Cardiology • Bayesian inference • Clinical misdiagnosis • Epidemiology

> Any mammal's heart is always subject to untimely stimuli along the pathways of the autonomic nervous system from the brain and its nervous input tracts. (Winfree 1987, p. 46)

The human heart is one of the best known examples of a biophysical system that in its dynamics is not linear, not stationary, operates at a multiplicity of scales simultaneously, and exhibits fluctuating variability that is not noise but self-stabilizing responses to the diversity of transient stimuli, both physical and psychological, that constitute its environment.

Winfree's extensive work on recurrent quasiperiodic dynamics, summarized in his 1987 book on the three-dimensional dynamics of electrochemical waves and cardiac arrhythmias, is interesting not only for its clinical relevance but for the parallels and differences it establishes with other problems and modeling in nonlinear dynamics using complex polynomials (Gregson 1995). The heart has been treated as driven by coupled oscillators, and this sort of dynamical structure does have properties of self-regulation and sensitivity to external pulsed inputs (Murray 2002; Steeb 2002) that are biologically advantageous but sometimes terminally vulnerable to acute trauma (Chang et al. 2000). The ubiquitousness of forced coupled attractor dynamics in a diversity of scientific disciplines has recently been reviewed because of its importance (Nadis 2003).

A critical feature in the modeling is the identification of singularities. If the system is forced by external inputs onto the region of a singularity, then the rhythms are lost and may be irrecoverable, thus leading to what is popularly called a heart attack and death. The models used are different from those in psychophysics because the circadian rhythms are a dominant feature, and the regular or irregular fast local heartbeat periodicities (with at least two modes) are carried on the slower circadian processes. This dominance of circadian rhythms in pulse rate (RR) is so marked that attempts have been made to exploit its slow variations as being psychiatrically diagnostic (Iverson et al. 2000; Krypotos et al. 2011).

This means that real time series of diastolic, systolic (SAP), and pulse rate (RR) in parallel have a complicated nonlinear nonstationary structure that cannot be modeled simply. Experimental evidence on mammalian heart action has shown that in some cases it is chaotic (Bassingthwaighte and coworkers have also modeled cardiac dynamics as fractal, on the basis of the frequency distribution of blood flows through the capillaries of the heart musculature (Bassingthwaighte et al. 1989; Herbert 1995), in the technical sense of the word, and not simply nonlinear (Ditto 1996).

As Winfree has shown, the phase-space portrait of the four-dimensional attractor that resembles heart action is such that it is fundamentally wrong to describe it as stability about a point attractor with random perturbations. Sufficient statistics to characterize trajectories, at most scales from such a complicated attractor, cannot be simply the mean and variance of outputs, though these are almost invariably used in the reports of epidemiological and even within-subject analyses that are numerous in the relevant literature. There are, almost inevitably, large individual differences in the dynamics of open-loop and closed-loop coupling between RR and SAP, apart from the slower circadian rhythms upon which more rapid fluctuations are superimposed (Malliani et al. 1991).

It is important to emphasize that the time scales of the dynamics involved may be critical in determining the favorable or unfavorable implications of instabilities in pulse phase and/or pressure amplitude. Ely (1995) refers to the Akron police force study and the detectable adverse effects of shift work schedules, which disrupt circadian rhythms at a slow time scale. At the same time, instabilities at the ECG level, at high frequency, appear to be a good predictor of resistance to cardiac arrest.

There are also possible variations due to the health, culture, age, and sex of the subject, and even in whose presence the SAP is measured; what is called, unfacetiously, "white-coat hypertension" exists. The whole topic of blood pressure averages and relatively fast variations within the individual over time and more slowly across age and social groups (Stolarz et al. 2003; Wong and Wolf 2003) has acquired a vast research literature, with continued disputes on what figures actually mean (Freitag *k* Vasan 2003). A standard of 140/90 systolic/diastolic blood pressure had been adopted in recommendations by the World Health Authority in the 1970s, as a marker for clinical intervention, but this figure is not realistic for many healthy populations in the Western world, apart from undiagnosed or untreated hypertensives. Porta et al. (2002, p. 241) comment, "In elderly healthy men at rest, the RR interval and SAP are highly correlated at the LF and HF." "Elderly" here meant from a sample with a mean of 57 $\pm$ 10 years. These data were drawn from a large database constructed by Borne et al. (1998) as a baseline for studying heart transplant recipients. "Links in both causal directions are found and some closed-loop interactions in the HF region." They give an example (p. 248) from an elderly healthy man under control conditions, in which the RR ranges over about 65 b/min to 84 b/min and the SAP ranges between 180 and 200 mmHg (This implies that an elderly healthy man with an average SAP of about 160 mmHg would be over four standard deviations from and below the reference data, with a consequent probability of having high blood pressure *defined relative to the SAP range* of less than 1 in 5,000). The contrast is with a postoperative heart transplant recipient, where pulse rate is higher but SAP is lower.

Operation at Various Dynamic Scales

It is by now a commonplace that psychophysiological systems have at least fast/slow dynamics and that the information carried by the fast and the slow components is different in meaning for the control and stability of the system and its responsiveness to its environment. Also, the fast and slow parts are coupled in a nonlinear fashion. To extract crucial dynamical information from time series records, it is often advantageous to use symbolic dynamics (Bunde et al. 2002, pp. 16–18; Gregson 2005, 2011), as traditional methods, all with intrinsic linear assumptions, such as Gaussian statistics, Fourier partitions, or 1/f distributions, will fail to identify low and high clinical risk situations, though examples of attempted mathematical modeling exist (Goldberger 1990; Sleight and Casades 1995). For example, two SAP (or ECG) time series with the same mean and s.d. can be utterly different in their dynamics and consequently in their clinical prognosis. Modeling alternans as a precursor to fibrillation can also be used with switching manifolds (Thul and Coombes 2010).

Ebeling et al. (2002) suggest that for ECG records that constitute the fast cardiac dynamics in our discussion, the four-level S_i partition into symbolic dynamics is appropriately

$$s_i = \begin{cases} 0 & \text{if } ti > (1 + a)\mu \\ 1 & \text{if } \mu < ti \leq (1 + a)\mu \\ 2 & \text{if } (1 - a)\mu < ti \leq \mu \\ 3 & \text{if } ti \leq (1 - a)\mu \end{cases}$$

where t_i are the RR intervals, μ is their mean, and $a = 0.1$. The normalized entropy of the s_i distribution is a basis for identifying persons with high cardiac risk; it is relatively low compared with healthy subjects. If the circadian rhythm is taken as a slow limit cycle, then with regular appropriately spaced multiple daily readings, the 4-state transition probability matrix based on the symbolic dynamics would be expected to show the characteristic off-diagonal form, with x indicating a dominant probability, that is, with anticlockwise or

$$\begin{bmatrix} - & & & x \\ x & - & & \\ & x & - & \\ & & x & - \end{bmatrix} \text{ or } \begin{bmatrix} - & x & & \\ & - & x & \\ & & - & x \\ x & & & - \end{bmatrix}$$

From a computational viewpoint, I find this sufficient set of only four levels surprising (Gregson and Leahan 2003), but it does not exclude partitioning to more than four, to maximize the entropy of a basal condition against which the typical degraded entropy of clinical cases may be compared, as indeed Ebeling et al. do.

The situation is such that not only is it misleading to draw any scientific or clinical conclusions from a single RR or SAP reading, but analysis of the dynamics

over reasonable time slices is still demanding of nonstandard statistical methods, often involving entropy measures and surrogate distributions as opposed to simple linear trends and residual variances (Pincus 1991, 2000; Guzzetti et al. 1996; Gregson and Pressing 2000; Ebeling et al. 2002; Wang et al. 2000; Gregson 2002; Voss et al. 1996; Wessel et al. 2000; Klonowski 2007).

> To quote Plamen et al. (2002, p. 219)
>
> Even under healthy basal conditions, physiological systems show erratic fluctuations resembling those found in dynamical systems driven far away from a single equilibrium state. Do such 'non-equilibrium' fluctuations simply reflect the fact that physiological systems are being constantly perturbed by external and intrinsic noise? Or do these fluctuations actually contain useful, 'hidden' information about the underlying non-equilibrium control mechanisms?

They show that physiological systems are inherently out-of-equilibrium systems; normal cardiac behavior exhibits complex variability lacking in subjects with heart failure. Short- and long-terra autocorrelations, indicative of fractal dynamics, vary significantly between high-risk and normal subjects. "The multifractality of heart beat time series also enables us to quantify the greater complexity of the healthy dynamics compared to pathological conditions. . .The power spectrum is not able to quantify the greater level of complexity of the healthy dynamics, reflected in the heterogeneity of the signal" (*op cit*, p. 247). It is worth noting that fractal measures are essentially multilevel self-similar entropy measures. Plamen et al. (2002, p. 278) conclude: "Distributions of experimental data that have fractal rather than Gaussian distributions or that are long-range correlated (and this holds for fast as well as slow scales) cannot be meaningfully characterized by their moments, such as the mean and variance." It is the mean and variance, and nothing else, that epidemiological studies usually attempt to report.

Relevance to 5-Hydroxytriptamine (5HT)

The repeated random resetting of the phase of the component rhythms is due to inputs that are not part of the intrinsic cardiac dynamics, but are essentially transient destabilizing. They are obviously part of the way that stress could act on the heart, and pathways from the brain to the heart appear to be involved (Byrne and Rosenman 1990). Stimuli creating acute anxiety usually input through the eyes or ears and not directly to the heart. Seeing or hearing of an unexpected horrific incident can it is widely believed induce cardiac arrest in some frail persons, who are usually protected so far as possible from getting such news. This precaution may be folklore; only chronic stress may be the critical factor. Winfree (1987, p. 101) writes: "spasm in a coronary artery temporarily makes the muscle more susceptible to arrhythmias, in part by eliciting neural traffic from the brain (Shepherd 1985; Skinner 1985)." That is, the neural brain-heart link is two-way and may form closed loops; positive feedback could induce tachycardia.

5HT has acquired a vast literature in semipopular medicine, being apparently involved with depression, cognition, anxiety, migraine, sleep, appetite (Williams 1998), and a diversity of brain activity that is associated with affective instabilities. The effects of 5HT on neurotransmission are not fully understood, in part because 5HT exists in at least four different molecular forms, and not all of these have been shown to be relevant to the action of cardiac baroreceptors. 5HT is perhaps better regarded as an indicator than a causal factor in some of these conditions. But it is worth noting that serotonin is a candidate neurotransmitter for baroreceptor neurons (Laguzzi et al. 1984). It should therefore be possible to link 5HT levels with at least circadian shifts in SAP and possibly lower-frequency instabilities extending over more than a day. The practical problems are those of continuous monitoring, but sustained elevation or depression of SAP levels could be coupled to average 5HT monitored at the same time. If this idea has any merit, it would imply a causal direction from 5HT to SAP, not feedback loops as they arise between RR and SAP.

Misdiagnosis and Inverse Probabilities

Suppose we label a set of cardiac dynamical conditions as $\{C\}$, and a set of blood pressure patterns as $\{B\}$. Most generally, we have then that

$$p\left(B_x \middle| C_y\right) \tag{1}$$

is the probability of one (B_x) of the set $\{B\}$ being a consequence of one (C_y) of the set $\{C\}$; x and y are just labels. Expressions like (1) are called likelihoods or conditional probabilities, and when they refer to real systems, then they are state *descriptions*. If we are given only B_x and asked to infer C_y, then this is a judgment about the probability

$$p\left(C_y | B_x\right) \tag{2}$$

and (2) is called an inverse probability or in clinical practice a diagnostic probability.

The pervasive and sometimes dangerous error is to assume that (1) and (2) are the same thing, both in logic and numerically. They may sometimes fortuitously (in trivial circumstances where both are equal to 1 or zero) be numerically the same, but they are not logically. In order correctly to get from (1) to (2), we have to consider at least one alternative, that is,

$$p(B_x | C_z) \tag{3}$$

where C_z is another condition alternative to and distinct in its causality from the C_y we thought of first. It is also necessary, from research data and the history of the case in hand, to have good estimates of (1) and (3). It is not sufficient to have only (1).

We are now in a position to get (2) that we want from Bayes' theorem, provided that we also have the base rates $p(C_y)$,$p(C_z)$, viz.,

$$P\left(C_y|B_x\right) = \frac{p\left(B_x|C_y\right)p\left(C_y\right)}{\left[p\left(B_x|C_y\right)p\left(C_y\right)+p(B_x|C_z)p(C_z)\right]} \tag{4}$$

To illustrate, put in some numbers. Let $B_x = 150$ mrnHg SAP, let $C_y =$ chronic high blood pressure, and let C_z – transient anxiety (I could have written transient depression here, with consequent low 5HT levels, which is expected in the elderly, and relevant evidence is accumulating about mood and SAP or cholesterol (Niaura 2002; Pollard and Schwartz 2003)). Then let $p\left(C_y\right) = .35, p(C_z) = 1 - p\left(C_y\right)$ as we are only considering two mutually exclusive and exhaustive alternatives, put [1] = 0.7, [3] = 0.9, and solve for [2]; we get

$$p\left(C_y|B_x\right) = \frac{.35 \times .7}{[.35 \times .7 + .65 \times .9]} = .295 \tag{5}$$

Clearly 0.295 is a minority diagnostic probability, as compared with (1) that was 0.7, a most likely diagnostic probability. It also now follows that the inverse probability

$$p(C_z \backslash B_x) = 1 - .295 = .705 \tag{6}$$

The situation gets worse (but is still computationally tractable) if in fact the values of (1) and (3) are not nice simple constants but distributions with variability across heterogenous patients or if we have to sample variability within a patient in order to get estimates and use whole time series of observations. Of course variability may be as much a danger sign in itself as an average of a stable process; this can be seen in intensive care conditions, and it is why pacemakers are installed in cardiac patients, to inhibit and stabilize the natural variability that follows from phase (i.e., pulse) resetting.

The importance of sequential information about baroreflex sensitivity has been explored by Parati et al. (2001), using very short high-frequency observations, based on the computer identification in the time domain of spontaneously occurring sequences of four or more consecutive beats, characterized by either a progressive rise in SAP and increase in RR or by a progressive decrease of SAP and shortening of RR. Such subsequences are obviously of low probability in stochastic random dynamics.

The interesting complication, that variability rather than average values may be the most informative diagnostic measure, implies that we have to replace $B_x|C_y$ a set $\{B_{x1}, B_{x2}, B_{x3}, \ldots\}|C_y$ and do something analogous for $B_x|C_x$. This means that unless you have reference tables from a relevant population of patients and conditions, with the appropriate base rates $p(C_y)$, $p(C_z)$, contingent upon age and sex, then you are making risky decisions and it is easy to get the reverse of what is the minimum-risk case, or the precise nature of the risk may be misunderstood.

In a decision theory approach it would be appropriate to extend (4) by adding in risk-cost factors to each terminal decision. If misdiagnosis entails either omitting or adding pharmaceutical intervention with consequent iatrogenic sequelae, then the analysis will be further skewed. So far I have not traced any adequate data on this problem, so it is not justified to begin to complicate the elementary algebra further here.

A single unreplicated high SAP value is taken by some medical workers to be indicative of risk, from the perspective of preventive medicine. However this can be a case of confusion worse confounded. The statistical problem is one of identifying and interpreting outliers, and this in turn is dependent on what the underlying time series dynamics actually are. If the series is stationary and basically Gaussian but with either single or clustered outliers (Ledford and Tawn 2003), then the inter-outlier-interval frequency distribution has a random or long-tail distribution. But if the series is a sample realization of a trajectory within an attractor basin, then it is bounded under the dynamic assumptions of Winfree (Pavićević and Šušić 2002), and apparent outliers may have a periodic inter-extreme distribution, due to the quasiperiodicity of the chaotic dynamics, as is well known from the characteristic spectral density of chaos, with a few isolated peaks on a wide range of secondary values. It is for this reason that the $p(B|C)$ terms and $p(C)$ terms in (4) cannot be single valued (though they may be entropy statistics based on subseries), as the diagnostic properties are dependent on higher-order time series properties and not on deviations from the first two moments, which is in any case may not exist outside primitive short-sample descriptors.

Epidemiological Survey Data

A survey of the social distribution of a single stable variable, such as the height of adults, is in sampling theory definable in terms of its sufficient statistics, and there is some coherent associated account of the sources and extent of errors of measurement. If, however, the process being studied is a dynamic time series within an individual, then seeking to find the distribution of the variability of its parameters over a population faces serious problems, because the sufficient statistics may not exist in terms of the first two moments, and our understanding of sources of error measurement is often, to say the least, opaque. The literature on SAP, RR, and pulse pressure (the difference between SAP and diastolic pressure) as based on average values over samples of patients can only be described as exasperatingly inconclusive (The variability in the dynamic cross-coupling of the two blood pressure values amplifies the variance of the pulse pressure and makes it uninterpretable within the assumptions of linear stationarity, so that tests of significance, on which studies rely, are incoherent), particularly on the question of what are the most valid predictors of cardiac failure (Strandberg and Pitkala 2003). There is another complication in that the social subgroups for whom the death risks are supposedly highest are those for whom the epidemiological data are the most sparse, except in the case of studying late-life diabetes, which has a complicated relation to

hypertension revealed by the spectral analysis of RR variability; again, the absence of variability is indicative of poor prognosis (Bellavere 1995). There are some meta-analyses (Malik and Camm 1995); in those studies, SAP variability may be treated as a consequence of its dynamic coupling with RR variability. That is, it is treated as a dependent variable, sometimes mediated by respiration rates, from simpler considerations of physiological action that is not modeled as intrinsically nonlinear.

The whole area of the epidemiology and treatment of hypertension is a subject of dispute, and alternative policies are advanced by US and European bodies. Included in the latest European review, by the Guidelines Committee of the ESH/ESC (2003), is some criticism of epidemiological surveys which are outside the scope of this chapter but are motivated in part by the facts that both longer life expectancies and more prevalent hypertension coexist in Europe as compared with the US surveys.

Following on the argument in the previous section, the problem of making sense of likelihoods is usually treated by rewriting Bayes' theorem in likelihood ratio form, which looks like this:

$$\Lambda(z,0) = \frac{p(C_z|B_x)}{p(C_0|B_x)} = \frac{p(B_x|C_z)p(C_z)}{p(B_x|C_0)p(C_0)} \tag{7}$$

and C_0 has been introduced to symbolize normal cardiac activity. The likelihood ratio Λ is then a measure of the odds that observing B_x is associated with hypertension and not normal, in the absence of any other collateral evidence. Strictly the conditional probabilities should be rewritten as

$$p(B_x > \beta | \sim \Sigma, C_z) \, and \, analogously \, for \, C_0 \tag{8}$$

where β is a decision level. Here we will use the WHO 140 mmHg for SAP, because there has been a change in clinical opinion that now focuses more on systolic than on diastolic pressures (Strandberg and Pitkala 2003) in attempting to avoid cardiovascular risk. Let the total symptomatology of $\{C\}$ be S; then (This now standard backslash notation is to be read that $S \backslash T$ = "the set S excluding the subset T") $\Sigma = S \backslash B_x$ and $\sim \Sigma$ means "none none of Σ."

The blood pressure study of 1987 in Australia (NIOHS 1987) gives some incomplete data that enables us tentatively to explore (8). Unfortunately we need tables of age x sex x symptoms of hypertension x SAP, but the tabulation is split between variables. Table 5.1.4 of that study, and recalculating using cumulative percentages, suggests that of all men in the survey (N = 3,309), 17.7 % are over the WHO 140 mmHg level on a single measurement at a medical examination. (We have no data here on variability of SAP within a subject, nor any confidence intervals on the raw percentages, and cohorts are confounded with time-slice samples. Most modern studies cited here still have no outcome morbidity or mortality sequelae tabulated.). The figure for 464 men in the 55–66 years of age range is 36.4 %, which is

$$p(B_x > \beta | \{C\}), \tag{9}$$

it is not (8). It is not proper to conclude that one-third of older men walking around should immediately fall dead in their tracks, though a follow up of the sample to find when and why they each died would have been most helpful. One could do that in the Scandinavian countries, because of the way that health records are kept there, though not apparently in Australia.

Table 6.2.5 gives frequencies and percentages on hypertensive medication, and in the 56–66 age group, 84, that is, 18 % or about one in five, are receiving some medication. Ignoring the probability of overmedication, by the WHO criterion, at least half are untreated and surviving at the time of the survey. They also thus have time to die of something else, and about two-thirds of all men will do that. There are no data for the over-66s, unlike the fuller data used by Porta et al. (2002) that was cited in the first section of this chapter. We know that the proportion of men with hypertension increases with age in some cultures (Wong and Wolf 2003), so the best estimates of (8) for over-70s would be higher in Australia, but the Porta et al. (2002) sample is still described (and hence untreated) as healthy.

The Wong and Wolf (2003) study is one of the few that separates cohort and time-slice effects, by having 5- and 10-year follow-ups (of the study, not of the same individuals, which preferably it would be; that way we get mortalities). So in the Yugoslav cohort, the senescence rate was 0.87 mmHg/year, and the secular trend over 10 years was 0.405 mmHg/year. The cohort ($N = 119$) that was in the age range 65–69 in 1972 has a mean SAP of 148.94, with an s.d. of 21.71 (this is rather disguised in the data tabulation by using s.e.s.). If the SAP is distributed across subjects approximately normally, then 17 % will have SAPs of over 171 mmHg. Obviously more than half are over 140 mmHg.

Grounds for Survival

We now come back to the questions of why about half of hypertensive men are untreated by orthodox medicine, and why they are survivors. One answer is that they don't feel ill or they patronize alternative medicines, but another is that they have a lifestyle that avoids stress, and so they minimize (mostly unknowingly) the probability of pulse resetting onto singularities, but are still at the upper end of a multimodal distribution of SAP readings. The shape of the frequency distribution of Λ in (7) is not the same thing as the frequency distribution of SAP.

Patel (1990, p. 441) notes "lowering mild hypertension is important because it has been shown that two-thirds of coronary heart disease and three-quarters of stroke mortality occurs in patients with mild hypertension" (These mortalities don't correspond to (10) below; they are of the form $p(B > \beta | D)$ and not $p(D | B > \beta)$).

The effects of such interventions as meditation on h.r.v. as inducing very complex dynamics are related here (Sarkar and Barat 2008). Three-quarters of all hypertensives are in the mild hypertension category, although the rate of complication in this group is low – approximately 1 % per year. Thus, even if we have

effective antihypertension drugs, a large proportion has to be medicated for the rest of their lives to prevent a small number of complications. Patel adds, "It is not surprising that the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (1984) has recommended that in all patients with mild hypertension, nonphar-macological treatment should be tried first and antihypertension medication added only when other treatment fails to produce satisfactory control of blood pressure."

We must stop to ask how does this 1 % that Patel cited relate to (7) and (8). It doesn't; it is yet another measure. In likelihood ratio terms it is

$$\Lambda(L,D) = \frac{p(L|B > \beta)}{P(D|B > \beta} = 0.99 \tag{10}$$

where $L = living$ and $D = dead$.

A tabulation of 29 studies, of which each had a control group (Byrne and Rosenman 1990, p.445–447), showed that relaxation and stress management without drugs had a significant effect in reducing systolic mean levels; in a more complex study of 134 patients (Patel et al. 1985), it was found that behavioral therapy reduced SAP by about 7.5 mmHg. If such therapy was combined with stopping drugs, then SAP did not rise; if drugs were stopped without behavior therapy having been used for 1 year, then SAP rose by 13.9 mmHg. It transpired that the actual training of the behavioral therapists was a critical factor, irrespective of what professional background they brought to the task. The complex relationships created by the dynamic coupling of RR to SAP as already noted by the undesirable effect of depression on RR variability (Yeragani et al. 2002) and by the evidence (Zyczkowska et al. 2003) that hypertension in the elderly is associated with lower risk of Alzheimer's syndrome weaken any facile generalizations about the need to reduce hypertension more than slightly.

Conclusion

To summarize, there are now at least three distinct domains of discourse that attempt to inform our understanding of cardiac dynamics, and it is often impossible to translate from one to another or to reconcile their findings. We have (i) simple measures, such as RR, that have been around since antiquity and extend into epidemiological tabulations without causal insights, (ii) we have brain-heart relations mapping between anxiety and physiology, and (iii) we have the nonlinear dynamics of complex systems. That one (iii) is the last to appear on the scientific scene, because it requires methods of both mathematics and data analysis that were not available before the 1980s.

The understanding of the complicated dynamics of the heart, and the relevance of that nonlinear picture to clinical diagnosis and treatment, postdates by some years the widespread use of indicators such as 140/90 popularized by the WHO. Work in the manner of Winfree's analyses and the tabulated epidemiological data

on RR and SAP are almost mutually exclusive. They are two approaches that do not interact, though logically they ought. If the critical variables in the dynamics are the rate and magnitude of phase resettings, which correlate with the variance of the RR, and these are not strongly correlated with the mean SAP and it is falsely assumed that a single observation of SAP on one subject has an expectation of the mean (which obviously does not if the SAP is distributed fractally multimodally), then the apparent irrelevance of the mean SAP (though it is confounded with age) to morbidity is explained. Errors in diagnosis are partly to be expected for cultural reasons: Baron (1994, p. 350) notes that though many medical students are taught to apply expected utility theory to decision making, few continue to use that approach after finishing training.

Because of the intricate and subtle nonlinear dynamics of cardiac action, what is at least needed are data on the variability (V_{cv}) of the coefficient of variation (*s.d./mean*) over time within the time series of single individuals and between individuals within cohorts of a limited age range. What is missing, on this argument, is

$$\Lambda(Cz, 0) = \frac{p(V_{cv}|C_z)p(C_z)}{p(V_{cv}|C_0)p(C_0)} \tag{11}$$

which is admittedly difficult and costly to collect, particularly as it is the elderly who are the supposedly ideal subjects for such a study. There are some studies that have used both time domain and frequency domain measures on RR and at the higher ECG frequencies, and some awareness that nonlinear dynamics complicate the picture and the interpretation of results (Sleight and Casadei 1995). Combining a diversity of measures, including time-frequency representation (TFR) and information entropy, provides more insights into premature deaths (Clariá et al. 2008). The terms in [10] have to be interpreted as integrals over time of one cohort; it is impossible to collect $p(B_x \backslash D)$ after death. A sample from within nursing homes would make $p(CQ)$ so small that the results would be suspect.

Previously, Julius (writing in Byrne and Rosenman 1990, p. xiii) commented on the gap between some biological psychiatric and psychopathological explanations of hypertension, another sort of conceptual gap that is hard to bridge. However, that gap can be bridged practically, in that there are treatment programs and research studies where both pharmacological and cognitive behavioral therapies are judiciously combined. Mixing nonlinear dynamics and epidemiological research is a much more difficult problem, because epidemiology can only collect a few observations on each subject and is culturally tied to a package of statistical analyses that are utterly sterile in the face of sampling time series generated by complicated dynamics (Herbert 1996).

The essential life-preserving dynamics of the heart are fractal, even intermittently chaotic, and are lost to the clinical observer if they are filtered through linear models, such as averaging or even worse taking only an extreme value. Dynamically, the heart is an open dissipative system. One can hardly do better than end, in this respect, with the well-known aphorism of the late and eminent statistician

John W. Tukey (The life and work of Turkey is celebrated in an issue of *The Annals of Statistics* in 200); "More lives have been lost looking at the raw periodogram than by any other action involving time series."

References

Baron, J. (1994). *Thinking and deciding* (2nd ed.). New York: Cambridge University Press.

Bassingthwaighte, J. B., King, R. B., & Roger, A. S. (1989). Fractal nature of regional myocardial blood flow heterogeneity. *Circulation Research, 65*, 578–590.

Bellavere, F. (1995). Heart rate variability in patients with diabetes and other noncardiological diseases. In M. Malik & A. J. Camm (Eds.), *Heart rate variability* (pp. 507–516). Armonk: Futura.

Bunde, A., Kropp, J., & Schellnhuber, H. J. (2002). *The science of disasters: Climate disruptions, heart attacks and market crashes*. Berlin: Springer.

Byrne, D. G., & Rosenman, R. H. (1990). *Anxiety and the heart*. Washington, DC: Hemisphere Press.

Chang, H.-S., Staras, K., & Gilbey, M. P. (2000). Multiple oscillators provide metastability in rhythm generation. *Journal of Neurosciences, 20*, 5135–5143.

Clariá, F., Vallverdú, M., Baronowski, R., Chojnowska, L., & Caminal, P. (2008). Heart rate variability analysis based on time-frequency representation and entropies in hypertrophic cardiomyopathy patients. *Physiological Measurement, 29*(3), 401–416.

Ditto, W. L. (1996). Applications of chaos in biology and medicine. In D. E. Herbert (Ed.), *Chaos and the changing nature of science and medicine: An introduction* (pp. 175–199). Woodbury: American Institute of Physics.

Ebeling, W., Molgedey, L., Kurths, J., & Schwarz, U. (2002). Entropy, complexity, predictability and data analysis of time series and letter sequences. In A. Bunde, J. Kropp, & H. J. Schellnhuber (Eds.), *The science of disasters: Climate disruptions, heart attacks and market crashes* (pp. 1–25). Berlin: Springer.

Ely, D. L. (1995). Organization of cardiovascular and neurohormonal responses to stress. In*: Ely D. L. (Ed.) Stress: Basic mechanism and clinical implications. Annals of the New York Academy of Sciences, vol. 771* (pp. 594–608). New York: New York Academy of Sciences.

Goldberger, A. L. (1990). Fractal electrodynamics of the heartbeat. In J. Jalife (Ed.), *Mathematical approaches to cardiac arrhythmias* (Annals of the New York Academy of Sciences, Vol. 591, pp. 402–409). New York: New York Academy of Sciences.

Gregson, R. A. M. (1995). *Cascades and fields in perceptual psychophysics*. Singapore: World Scientific.

Gregson, R. A. M. (2002). Scaling quasi-periodic psychological functions. *Behaviormetrika, 29*, 41–57.

Gregson, R. A. M. (2005). Identifying ill-behaved nonlinear processes without metrics: The use of symbolic dynamics. *Nonlinear Dynamics, Psychology, and Life Sciences, 9*, 479–503.

Gregson, R. A. M. (2009). Conceptual problems in cardiological prediction. *Nonlinear Dynamics, Psychology, and Life Sciences, 13*, 207–222.

Gregson, R. A. M. (2011). Frontiers of nonlinear methods. In S. J. Guastello & R. A. M. Gregson (Eds.), *Nonlinear dynamical systems analysis for the behavioral sciences using real data* (pp. 583–599). Clermont: Taylor and Francis. Chapter 25.

Gregson, R. A. M., & Leahan, K. (2003). Forcing function effects on nonlinear trajectories: Identifying very local brain dynamics. *Nonlinear Dynamics, Psychology, and Life Sciences, 7*, 139–159.

Gregson, R. A. M., & Pressing, J. L. (2000). Dynamic modelling. In J. T. Cacioppo, L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (2nd ed., pp. 924–948). New York: Cambridge University Press.

Guidelines Committee of the ESH/ESC. (2003). European society of hypertension – European society of cardiology guidelines for the management of arterial hypertension. *Journal of Hypertension, 21*, 1011–1053.

Guzzetti, S., Signorini, M. G., Cogliati, C., Mezzetti, S., Porta, A., Cerutti, S., & Maliiani, A. (1996). Non-linear dynamics and chaotic indices in heart rate variability of normal subjects and heart-transplanted patients. *Cardiovascular Research, 31*, 441–446.

Herbert, D. (Ed.). (1995). *Chaos and the changing nature of science and medicine, an introduction* (Conference proceedings, 376). Woodbury: American Institute of Physics.

Iverson, G. L., Stampfer, H. G. & Gaetz, M. (2000). Reliability of circadian heart pattern analysis in psychiatry. *Paper presented at the annual conference of the Canadian Psychiatric Association, Victoria, BC. October 4, 2000.*

Klonowski, W. (2007). From conformons to human brains: An informal overview of nonlinear dynamics and its applications in biomedicine. *Nonlinear Biomedical Physics, 1*, 5. doi:10.1186/1753-4631-1-5.

Krypotos, A.-M., Jahfari, S., van Ast, V. A., Kindt, M., & Forstmann, B. U. (2011). Individual differences in heart rate variability predict the degree of slowing during response inhibition and initiation in the presence of emotional stimuli. *Frontiers in Cognition*. doi:10.3389, fpsyg.2011.00287.

Laguzzi, R., Reis, D. J., & Talman, W. T. (1984). Modulation of cardiovascular and electrocortical activity through serotonergic mechanisms in the nucleus tractus solitarius of the rat. *Brain Research, 304*, 321–328.

Ledford, A. W., & Tawn, J. A. (2003). Diagnostics for dependence within time series extremes. *Journal of the Royal Statistical Society, Series B, 65*, 521–543.

Malik, M., & Camm, A. J. (1995). *Heart rate variability*. Armonk: Fu-tura.

Malliani, A., Pagani, M., Lombardi, F., & Cerutti, S. (1991). Cardiovascular neural regulation explored in the frequency domain. *Circulation, 84*, 482–492.

Mezentseva, L. V., Kashtanov, S. I., Vostrikov, V. A., Zvyagintsev, M. A., & Kosharskaya, I. L. (2002). Chaos theory analysis of electrocardiograms recorded from humans and animals with ventricular fibrillation. *Biophysics, 47*, 352–358.

Murray, J. D. (2002). *Mathematical biology* (Chapter 9: Perturbed and Coupled Oscillators and Black Holes 3rd ed.). New York: Springer.

Nadis, S. (2003). All together now. *Nature, 421*, 780–782.

National Institute of Occupational Health and Safety. (1987). *Blood pressure study: Handbook of tables*. Canberra: Australian Government Publishing Service.

Niaura, R. (2002). Hostility and prediction of heart disease. *Health Psychology, 21*, 588–593.

Parati, G., di Rienzo, M., & Mancia, G. (2001). Dynamic modulation of baroreflex sensitivity in health and disease. In M. W. Chapleau & F. M. Abboud (Eds.), *Neuro-cardiovascular regulation: From molecules to Man* (Annals of the New York Academy of Sciences, Vol. 940, pp. 469–487). New York: New York Academy of Sciences.

Patel, C. (1990). Psychological and behavioral treatment of hypertension. In D. G. Byrne & R. H. Rosenman (Eds.), *Anxiety and the heart* (pp. 441–469). Washington: Hemisphere Press.

Patel, C., Marmot, M. G., Terry, D. J., Carruthers, M., Hunt, & Patel, M. (1985). Trial of relaxation in reducing coronary risk: Four-year follow-up. *British Medical Journal, 282*, 2005–2008.

Pavićević, Ž., & Šušić, E. (2002). Application of the cyclic properties of dynamical systems to the study of the boundary limits of arbitrary functions. *Doklady Mathematics, 66*, 313–315.

Pearson, E. S. and Hartley, H. O. (Eds.) (1972). *Biometrika Tables for Statisticians, Vol. 1*. Cambridge: Cambridge University Press.

Pincus, S. M. (1991). Approximate entropy as a measure of system complexity. *Proceedings of the National Academy of Sciences of the USA, 88*, 2297–2301.

Pincus, S. M. (2000). Approximate entropy in cardiology. *Herzschliche Elek-trophysiologie, 11*, 139–150.

Plamen, C. I., Goldberger, A. L., & Stanley, H. E. (2002). Fractal and multi-fractal approaches in physiology. In A. Bunde, J. Kropp, & H. J. Schellnhuber (Eds.), *The science of disasters: Climate disruptions, heart attacks and market crashes* (pp. 219–257). Berlin: Springer.

Pollard, T. M., & Schwartz, J. E. (2003). Are changes in blood pressure and total cholesterol related to changes in mood? An 18-month study of men and women. *Health Psychology, 22*, 47–53.

Porta, A., Furlan, R., Rimoldi, Pagani, M., Malliani, A., & van de Borne, P. (2002). Quantifying the strength of the linear causal coupling in closed loop interacting cardiovascular variability signals. *Biological Cybernetics, 86*, 241–251.

Preitag, M. H., & Vasan, R. S. (2003). What is normal blood pressure? *Current Opinions in Nephrology and Hypertension, 12*, 285–292.

Rao, R. K. A., & Yeragani, V. K. (2001). Decreased chaos and increased non-linearity of heart rate time series in patients with panic disorder. *Autonomic Neuroscience: Basic and Clinical, 88*, 99–108.

Sarkar, A., & Barat, P. (2008). Effect of meditation on scaling behavior and complexity of human heart rate variability. *Fractals, 16*(3), 199–208.

Shepherd, J. T. (1985). The heart as a sensory organ. *Journal of the American College of Cardiology, 5*(6), 83B–87B.

Shiferaw, Y., & Karma, A. (2006). Turing instability mediated by voltage and calcium diffusion in paced cardiac cells. *Proceedings of the National Academy of Sciences of the USA, 103*, 5670–5675.

Skinner, J. E. (1985). Regulation of cardiac vulnerability by the cerebral defense system. *Journal of the American College of Cardiology, 5*(6), 88B–94B.

Sleight, P., & Casadei, B. (1995). Relationships between heart rate, respiration and blood pressure variabilities. In M. H. Malik & A. J. Camm (Eds.), *Heart rate variability* (pp. 311–325). Armonk: Futura.

Steeb, W.-H. (2002). *The nonlinear workbook* (Chapter 7: Controlling and Synchronization of Chaos 2nd ed.). Singapore: World Scientific.

Stolarz, K., Staessen, J. A., Kuznetsova, T., Tikhonoff, V., State, D., Babeanu, S., Casiglia, E., Fagard, R. H., Kawecka-Jaszcz, K., Nikitin, Y., & European Project on Genes in Hypertension (EPOGH) Investigators. (2003). *Journal of Hypertension, 21*, 525–535.

Strandberg, T. E., & Pitkala, K. (2003). What is the most important component of blood pressure: Systolic, diastolic or pulse pressure? *Current Opinion in Nephrology and Hypertension, 12*, 293–297.

Thul, R., & Coombes, S. (2010). Understanding cardiac alternans: A piecewise linear modeling framework. *Chaos, 20*(045102), 1–13.

van de Borne, P., Montano, N., Narkiewicz, K., Degaute, J. P., Oren, P., Pagani, M., & Somers, V. K. (1998). Sympathetic rhythmicity in cardiac transplant recipients. *Circulation, 99*, 1606–1610.

Voss, A., Kurths, J., Kleiner, H. J., Witt, A., Wessel, N., Saparin, P., Osterziel, K. J., Schurath, R., & Dietz, R. (1996). The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. *Cardiovascular Research, 31*, 419–433.

Wang, S. Y., Zhang, L. F., Wang, X. B., & Cheng, J. H. (2000). Age dependency and correlation of heart rate variability, blood pressure variability and baroreflex sensitivity. *Journal of Gravitational Physiology, 7*, 145–146.

Wessel, N., Voss, A., Malberg, H., Ziehmann, C., Voss, H. U., Schirdewan, A., Meyerfeldt, U., & Kurths, J. (2000). Nonlinear analysis of complex phenomena in cardiological data. *Herzschrittmachertherapie und Elektrophysiologie, 11*(3), 159–173.

Williams, S. P. (1998). The serotonin transporter: A primary target for antidepressant drugs. *Journal of Psychopharmacology, 12*(2), 15–121.

Winfree, A. T. (1987). *When time breaks down*. Princeton: Princeton University Press.
Wing, L. M. H., Reid, C. M., & Ryan, P. (2003). A comparison of outcome with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *New England Journal of Medicine, 348*, 583–592.
Wong, J., & Wolf, H. K. (2003). Secular trends and senescence of blood pressure in a Japanese and Yugoslavian cohort of the seven countries study. *Blood Pressure, 12*, 32–39.
Yeragani, V. K., Krishna Rao, K. A. R., Smitha, M. R., Pohl, R. B., Balon, R., & Srinivasan, K. (2002). Diminished chaos of heart rate time series in patients with major depression. *Biological Psychiatry, 51*, 733–744.
Zyczkowska, J., Klich-Raczka, A., Wizner, B., et al. (2003). Hypertension and cognitive impairment in centenarians. *Journal of Hypertension, 21*, S18. abstract 3B.3.

Part V

Psychological Management of Patients with Cardiovascular Disease

Psychosocial Interventions for Patients After a Cardiac Event

Alun C. Jackson, Barbara M. Murphy, Chantal F. Ski, and David R. Thompson

Contents

Abstract

A large body of evidence links depression and coronary artery disease and includes findings that patients who experience depression at the time of an acute cardiac event die sooner than their nondepressed counterparts. Although cardiac rehabilitation programs addressing medical, lifestyle, and psychosocial

A.C. Jackson (✉)
Heart Research Centre, Melbourne, VIC, Australia

Centre on Behavioural Health, University of Hong Kong, Pakfulam, Hong Kong
e-mail: alun.jackson@heartresearchcentre.org

B.M. Murphy
Heart Research Centre, Melbourne, VIC, Australia

Department of Psychology, University of Melbourne, Melbourne, VIC, Australia

Faculty of Health, University of Newcastle, NSW, Australia
e-mail: barbara.murphy@heartresearchcentre.org

C.F. Ski • D.R. Thompson
Centre for the Heart and Mind, Australian Catholic University, Melbourne, VIC, Australia
e-mail: chantal.ski@acu.edu.au; david.thompson@acu.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_47

issues have positive effects on behavioral change, significantly reduce the risk of having future cardiac events, and reduce mortality, depressed mood and social isolation can compromise the positive effects of these programs. Systematic reviews have shown the effectiveness of psychological interventions for cardiac patients; however, comparison of interventions is difficult due to variation in target population, severity of depression, "dose" and mode of delivery of the intervention delivered, variation in outcome measures used, varied follow-up periods, and lack of detail on intervention content. Brief interventions have been shown to be effective in reducing depression, as has Internet-delivered cognitive-behavioral therapy for adults with high CVD risk. Interventions comprising psychological and social support-enhancing components, when compared with usual care, are also effective in reducing depressive symptoms in cardiac patients. Although effect sizes reflect a small benefit of these psychosocial interventions, it appears that they improve social support and possibly mental health quality of life, but no firm conclusions can be drawn as to whether these interventions impact on cardiac mortality and morbidity. Notwithstanding methodological limitations and the modest effects achieved, psychological and psychosocial interventions are worth implementing, post-cardiac event, as unresolved depression is a major cause of death and disability in cardiac patients.

Keywords
Psychosocial intervention • Cardiac patients • Depression • Social isolation

Introduction

Over two decades of research has demonstrated the association between depression, whether characterized as mild or as major depressive disorder (MDD,) and coronary artery disease (CAD) (Whooley and Wong 2013). In addition to findings that depression is an independent risk factor for the development of CAD in healthy populations (Lett et al. 2004), the adverse effects of depression on patient outcomes have been well documented. Depressed patients have higher levels of biomarkers that promote atherosclerosis, reduced heart rate variability suggesting increased sympathetic activity, and increased C-reactive protein, an indicator of increased inflammatory response (Lichtman et al. 2008; Taylor 2010). Behaviorally, depressed patients report lower medication compliance (Gehi et al. 2005; Ziegelstein et al. 2000), higher rates of smoking (Kubzansky et al. 1998), more intake of dietary fat (Murphy et al. 2013), lower physical activity (Murphy et al. 2013), and higher rates of sedentary behavior (Brummett et al. 2003). Socioeconomic factors including social isolation, low income, low education, and manual occupations are also associated with both depression and mortality (Brummett et al. 2003; Case et al. 1992; Kaplan 1992).

There is growing evidence that cardiac patients who experience depression at the time of an acute cardiac event die sooner than their non-distressed counterparts (Barth et al. 2004; van Melle et al. 2004), with in-hospital depression shown to

predict 10-year mortality after both acute myocardial infarction (AMI) (Welin et al. 2000) and coronary artery bypass surgery (CABGS) (Connerney et al. 2010). It has been suggested that even mild depressive symptoms are associated with poorer mortality outcomes (Bush et al. 2001; Murphy et al. 2013). However, relatively few studies have investigated the prognostic importance of "mild" in-hospital depression in cardiac patients.

Emerging evidence suggests that in-hospital depressive symptoms resolve for many patients during early convalescence (Blumenthal et al. 2003; Murphy et al. 2008a, b) and that these patients are not at ongoing risk for poor outcomes (Blumenthal et al. 2003; Thombs and Ziegelstein 2010). This suggests that in-hospital depression might not be the best indicator of later mortality risk. A meta-analysis of 34 studies of mortality in coronary heart disease (CHD) patients reported larger effects when depression was assessed later rather than earlier, supporting this hypothesis (Nicholson et al. 2006). As most change in depressive symptoms occurs in the first 2 months after an acute event (Murphy et al. 2008a, b) and most outpatient cardiac rehabilitation programs are offered around 4–6 weeks post-cardiac event, the timing of this generic intervention fits well with the needs of those people with unresolved depressive symptoms that may be amenable to change within the generic cardiac rehabilitation programs or in adjunct psychosocial interventions.

The Impact on Depression of "Generic" Cardiac Rehabilitation

Well-structured multidisciplinary cardiac rehabilitation (CR) programs that address medical, lifestyle, and psychosocial issues have positive effects on behavioral change, significantly reduce the risk of having future cardiac events, and reduce mortality by approximately 25 % (Beauchamp et al. 2013; Briffa et al. 2009). These programs lead to improved clinical and behavioral outcomes, including fewer hospital readmissions, better adherence to pharmacotherapy, enhanced functional status, improved risk profile, less depression, and better quality of life (Briffa et al. 2009; Eshah and Bond 2009; Lewin and Doherty 2013). Focusing on the effect of "non-psychosocial specific" or "generic" cardiac rehabilitation on depression, Gellis and Kang-Yi (2012) conducted a meta-analysis of 18 randomized controlled trials (RCTs) of in-home or outpatient CR. Three of the studies concerned outpatient programs; another three involved a combination of outpatient and home-based intervention. Ten of the studies involved patients with a primary diagnosis of heart failure (HF) ($n = 1{,}086$), while eight recruited patients with coronary artery disease (CAD) ($n = 2{,}660$). Interventionists were multidisciplinary, delivering face-to-face, telehealth, and telephone services. Eleven studies reported overall positive effects (small to large effect sizes) on depression using the Patient Health Questionnaire (PHQ-9), Hamilton Rating Scale for Depression, or the Geriatric Depression Scale.

Analysis of depression outcomes using the Hospital Anxiety and Depression Scale (HADS-D) for a 12-week exercise-focused outpatient program in Switzerland confirmed these positive findings for patients with CAD ($n = 520$) but not with peripheral artery disease (PAD) ($n = 69$) (Stauber et al. 2013). The latter group

showed no improvement in depression but did show reduced anxiety. The low level of amelioration of depressed mood in the PAD patients was hypothesized to be the result of a higher rate of chronic rather than reactive depression and impaired functional capacity which impacted on these patients' ability to achieve the psychological benefits of improved and sustained physical exercise (Stauber et al. 2013).

Influence of Mood States on CR Uptake, Completion, and Lifestyle Modification

Among people eligible for CR, referral rates are generally low with fewer than one in three people referred actually attending in Australia (National Heart Foundation of Australia 2010) and around 40 % of heart attack patients and 28 % of angioplasty patients attending in England, Northern Ireland, and Wales (British Heart Foundation 2010). Those at highest risk of recurrent disease are least likely to participate in CR and of those who do attend, not all complete the full CR program (Bunker et al. 1999; Johnson et al. 2004; Redfern et al. 2007; Scott et al. 2003). A systematic review of 32 studies identified 374 patient-reported factors associated with uptake and completion of cardiovascular lifestyle behavior change programs (Murray et al. 2012). Of the factors identified as inhibiting uptake of CR, depression and stress were both independent predictors. Anxiety was not found to be predictive of non-attendance with one study finding that anxiety may facilitate attendance (Grace et al. 2002).

Even if people attend CR, sustained behavioral change and lifestyle modification are not assured (Davies et al. 2010; Gupta et al. 2007; Murphy et al. 2006). Psychosocial factors such as depressed mood (Ziegelstein et al. 2000) and social isolation (Davies et al. 2010) exacerbate nonadherence to medication regimes and lifestyle advice, as do cognitive barriers such as negative thoughts and beliefs (Martins and McNeil 2009). Many of the same factors that deter people from commencing CR also contribute to non-completion of the programs. While anxiety may facilitate completion in the same way that it facilitates uptake, depressive symptoms, being on antidepressant medication and greater neuroticism, all predict greater attrition, as does social isolation and not being in the workforce which may be an indicator of both social isolation and limited income (Murray et al. 2012). Whooley (2006) and Whooley and Wong (2013) suggests that in cardiac patients with mild to moderate depression, psychotherapy together with self-management is the most appropriate first-line treatment. However, this treatment is dependent both on its timely availability and the recognition of the depression or compromised mood state.

As numerous studies have found, many people do not disclose their compromised mood state (Jorm et al. 2004; Kessler et al. 2001), especially if they perceive it to be serious. This emphasizes the importance of screening for depression in CR as recommended by the Heart Foundation of Australia (Colquhoun et al. 2013), following the 2008 recommendations of the American Heart

Association (Lichtman et al. 2008). The Australian guidelines state that "routine screening for depression is indicated at first presentation and again at the next follow-up appointment. A follow-up screen should occur 2–3 months after the event," (44) in recognition of the higher risk of secondary events in those with unresolved depression (Nicholson et al. 2006). Having identified depression in cardiac patients post-event, treatment may comprise pharmacological or psychotherapeutic interventions administered singly or in combination over shorter or longer periods. Psychotherapeutic interventions may be offered through a variety of modes of delivery (face-to-face individual or group, telephone, Internet) and may involve a variety of manualized or non-manualized therapeutic approaches offered alone or in combination with self-management. The following sections review a number of these psychotherapeutic interventions.

Psychological Interventions

A number of systematic reviews, with or without meta-analyses, of psychological interventions for CHD patients are now available (Dickens et al. 2013; Mavrides and Nemeroff 2013; Whalley et al. 2011). These are briefly summarized below; however, in so doing we are mindful of Jelinek et al.'s (2011) caveats on interpretation of such aggregated data. These are that interventions are often not described fully enough to definitively compare effects between intervention and control groups and that meta-analyses represent a form of retrospective subgroup analysis and are hypothesis-generating rather than definitive tests of a priori hypotheses.

Whalley et al. (2011) aimed to estimate the effects of psychological interventions on mortality and psychological symptoms in patients who had experienced a myocardial infarction, a revascularization procedure or percutaneous transluminal coronary angioplasty (PTCA) and those with angina or angiographically defined cardiac heart disease. All psychological interventions delivered by health-care workers with specific training in psychological techniques were considered, and trials were only considered where the effect of the psychological intervention could be evaluated independently. Included studies had to compare psychological treatment with usual care or compare psychological treatment plus exercise with an exercise-only condition. Primary outcomes for the review included all-cause and cardiac-related mortality; nonfatal MI, revascularization (CABG and PCI); as well as anxiety, depression, stress, and type A behavior/hostility. Secondary outcomes included health-related quality of life (HRQoL). A total of 24 studies (51 publications) was included, reporting data from a total of 9,296 patients (74 % male). Eight of the 24 studies indicated that patients had clinically significant psychopathology at the pre-randomization stage. The mean number of hours spent in treatment was 26.1 (min 2.4, max 96, SD = 26.8). For the 22 studies providing sufficient information to enable categorization of treatment aims and components, the focus was reduction in stress (16 treatments), anxiety (15), depression (12), and type A behavior including anger and hostility (10) and improved disease adjustment (10).

Bearing in mind a fairly high risk of bias in the studies (unclear randomization procedure, non-blinded outcome assessment), the review found that psychological intervention resulted in small to moderate improvements in depression and anxiety. There was no consistent evidence, however, of a positive effect on HRQoL or other psychological outcomes, including perceived stress, type A behaviors, anger, and perceived exhaustion. Targeted type A behavior was positively associated with intervention effects for depression, while the inclusion of family in treatment, provision of risk information, and inclusion of client-led discussion and emotional support were negatively associated with depression outcomes. There was no strong evidence that psychological intervention, compared to usual care, reduced total deaths or risk of revascularization or nonfatal infarction in patients with CHD. However, there were significantly fewer deaths attributed to cardiac causes among treated patients. The authors suggest that (Whalley et al. 2011) the wide variation in the types of intervention used to treat cardiac patients included in the review reflects uncertainty in the theoretical and empirical literature linking emotion with cardiac outcomes and that subtyping – what interventions work best for whom – is premature.

Dickens et al. (2013) extended Whalley et al.'s (2011) review (with a 14 % overlap of included studies) to explore which psychological treatments were most effective for people with CHD. They reviewed 62 independent studies with outcome data for 64 independent treatment comparisons ($N = 17{,}397$). As with other reviews, there was a great deal of heterogeneity between studies: conditions included both acute and stable CHD; treatment sessions varied between 1 and 156 sessions with a mean of 14.4; in 29 studies, intervention was by a single person or unidisciplinary team and in 22 by a multidisciplinary team, and risk of bias varied, for example, only 20 studies used researchers blinded to the intervention to assess outcome. Again, bearing in mind the limitations of heterogeneity and risk of bias, it was found through random-effect multivariate meta-regression that psychological interventions improved depression, although the effect was small (SMD = 0.18, $p < 0.001$). Problem solving (SMD = 0.34), general education (SMD = 0.19), skills training (SMD = 0.25), cognitive-behavioral therapy (CBT; SMD = 0.23), and relaxation (SMD = 0.15) had small effects on CHD patients irrespective of their depression status. Among high-quality trials of depressed CHD patients, only CBT showed significant albeit small effects (SMD = 0.31). When entered into multivariable analysis, no individual treatment component, including increasing social support, significantly improved depression.

Mavrides and Nemeroff's (2013) review of depression treatment in cardiovascular disease (CVD) included trials of tricyclic antidepressants (TCAs), TCAs and bupropion (an atypical antidepressant and antismoking aid), and selective serotonin reuptake inhibitors (SSRIs). Five trials involving psychotherapeutic techniques and/or collaborative care were included. The review concluded that there was considerable evidence from RCTs that antidepressants, especially SSRIs, are safe in the treatment of major depression in patients with CVD and that acute coronary syndrome (ACS) patients with persistent depression treated with problem-solving therapy and pharmacotherapy show significantly reduced depression compared

with usual care patients in the Coronary Psychosocial Evaluation Studies (COPES) Trial (Davidson et al. 2010). Post-CABG patients were also shown to benefit from face-to-face CBT and supportive stress management as well as a telephone-delivered collaborative care intervention. Similar effects of both pharmacological interventions have been reported in heart failure patients (Woltz et al. 2012), although this review provided much weaker evidence for the effects of CBT on depression, with one study demonstrating sustained reduction in depression for patients receiving a combination of CBT, exercise, and attention control, but no reduction for patients receiving any of these in isolation.

It is clear from these systematic reviews of psychological interventions, with a variety of cardiac patients, that comparison of interventions is difficult due to the wide variation in target population; severity of depression being addressed; "dose" of the intervention delivered, by whom and in what modality; primary and secondary outcome measures used and the measurement tools employed; and follow-up periods. Of particular concern is lack of information on the actual components of interventions, through reference to a treatment manual, for example.

With respect to specific interventions, a major issue is that many of the studies report one-off interventions with little, if any, replication by other teams being reported, making findings more difficult to interpret. For example, Chair et al. (2012) conducted an RCT ($N = 146$) with CHD patients attending CR but who had been assessed as having poor motivation, by low readiness to change scores or having dropped out of CR previously. Patients ($n = 73$) in the control group received usual care (23 sessions of supervised exercise, behavioral education, and diet education), while those in the treatment group ($n = 73$) received usual care plus four sessions of motivational interviewing each lasting 30–45 min. No details of manualization are given, although motivational interviewing fidelity checking was undertaken. There was no significant difference between the two groups on clinical outcomes (e.g., body mass index (BMI), blood pressure, cholesterol), although patients in the treatment group had greater improvement in health-related quality of life (SF-36) scores in the "aspects of general health" (4.74, 95 % CI 0.04–9.44; $p = 0.048$) and "role limitation due to emotional problem" (8.80, 95 % CI 1.16–16.43; $p = 0.024$) areas. While both groups improved in depression, there was a greater increase in anxiety (HADS-A) in the treatment group than in the control group (0.96, 95 % CI 0.09–1.83; $p = 0.030$). The authors note that this unexpected result raises many questions: location of the study, belief systems of the patients, and appropriateness of the motivational interviewing content. More evidence, particularly from replication studies and preferably not excluding people with comorbid mental health issues, as in this study, is needed to better understand this phenomenon of increased anxiety.

Motivational interviewing was also assessed along with CBT in the *Beating Heart Problems* RCT (Murphy et al. 2013). This program was designed to support patients to develop behavioral and cognitive self-management skills. Patients ($N = 275$) consecutively admitted to two Melbourne hospitals after AMI (32 %) or for CABG (40 %) or PCI (28 %) were randomized to treatment (T; $n = 139$) or control (C; $n = 136$) groups. Treatment group patients were invited to participate in the

8-week group-based program. Patients underwent risk factor screening 6 weeks after hospital discharge (prior to randomization) and again 4 and 12 months later. At both follow-ups, treatment and control groups were compared on a 2-year risk of a recurrent cardiac event and key behavioral outcomes, using both intention to treat and "completers only" analyses. Patients ranged in age from 32 to 75 years (mean = 59.0; SD = 9.1). Most (86 %) were male. Compared with controls, the treatment group tended toward greater reduction in 2-year risk, at both the 4-month and 12-month follow-ups. Significant benefits in dietary fat intake and functional capacity were also evident. Overall, the *Beating Heart Problems* program showed modest but important benefit over usual care at four and, to a lesser extent, 12 months post-event.

Mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) effects on psychological and physical outcomes for people with vascular disease have been reviewed (Abbott et al. 2014). Small to moderate effects on stress and depression were found in a study of people with heart disease who had undergone coronary perfusion; although for baseline values, education, age, and comorbidity, the effects remained significant only for those <60 years of age.

These three examples show relatively modest results for "standard" face-to-face interventions for patients alone. A systematic review of evidence on the effectiveness of psychological interventions for patients with CHD and their partners (Abbott et al. 2014) found that in two of seven included studies, psychological interventions result in modest improvements in patients' depressive symptoms, anxiety, knowledge of disease and treatment, and satisfaction with care. In addition partners' anxiety, knowledge and satisfaction also improved in these two studies together with a nonsignificant trend for improvements in depressive symptoms. In contrast, Whalley et al.'s review (2011) found that the inclusion of family in treatment was negatively associated with depression outcomes. Given these modest results, and the recent evidence that alternative models of CR, such as brief, home-based, telephone-delivered, and individualized models, are as effective in reduction of CVD risk factors as hospital-based programs, are alternative models of psychological intervention with cardiac patients effective?

Brief Interventions

Minimal or brief interventions are those treatments involving less professional time and/or resources than are typical of traditional therapy (Heather 1986). In other areas of complex behavioral change, often with high levels of comorbidity, such as in pathological gambling, such interventions are defined as ranging from 10 min to four sessions (Petry et al. 2008). These interventions provide nonthreatening, cost-effective, and time-efficient alternatives to traditional psychological interventions, particularly to those with earlier onset and less severe behavioral and psychological problems. Typically, these interventions involve minimal therapist contact, including self-help workbooks with booster sessions, brief advice, face-to-face interventions with up to four sessions, brief interventions delivered via telephone and online

media, and interventions delivered through CDs, DVDs, and videoconferencing (Petry 2005).

Depression-focused interpersonal care (IPC) delivered by a psychiatric nurse with one-day training in IPC and consisting of at least one in-hospital face-to-face session and up to six subsequent telephone calls has been shown to decrease the use of health-care services in 6 months after discharge following MI, where there were no other long-term diseases present (Oranta et al. 2012). This was seen as a cost-effective intervention both in terms of public health system burden and minimal cost associated with interventionist training and delivery of the intervention. Another nurse-delivered brief intervention comprising a single, 30-min one-on-one cognitive therapy (CT) in-hospital session, followed by a 5–10-min booster phone call 1-week post-discharge, for heart failure patients, has been reported (Dekker et al. 2012). Importantly, the CT intervention is well described with six steps focusing on reducing negative emotions through thought-stopping and affirmations. Depression scores (BDI-II) reduced in both the treatment and usual care group at 3 months' follow-up but with a non-statistically significant trend for the CT group to have a faster decline in symptoms as well as a faster decline in negative thinking and improvement in health-related quality of life. Patients in the treatment group had longer cardiac event-free survival at 3 months than the usual care group (80 % vs. 40 %), with the control group being 3.5 times more likely to experience a cardiac event in the follow-up period.

The Mindful Heart RCT (Nyklicek et al. 2014), comparing a four-session mindfulness-based stress reduction group intervention for PCI patients with a self-help booklet containing the same information as the four-session intervention, found that the group intervention showed larger increases in psychological and social quality of life ($p < 0.05$, partial eta(2) = 0.04 and 0.05, respectively). However, for symptoms of anxiety and depression, and for perceived stress, this effect was evident only in patients <60 years ($p < 0.01$, partial eta(2) = 0.10 and 0.15, respectively). These effects were partially or fully mediated by increase in mindfulness. One difficulty with interpretation of the results, which the authors acknowledge, is that it is unclear as to whether the self-help booklet produced the observed changes in that group or whether this represented "natural" recovery. A nonintervention control group would have been necessary to discern this.

In addition to brief cognitive therapy and mindfulness-based stress reduction, short-term psychotherapy (the STEP-IN-AMI trial) (Roncella et al. 2013) and a brief psycho-educational intervention (Turner et al. 2013) have also been demonstrated to ameliorate depression and, in the former case, to increase perceived quality of life at 6- and 12-month follow-up. The STEP-IN-AMI trial aimed to provide a standardized short-term therapy (STP) intervention based on a synthesis of analytical psychology, psychoanalysis, and humanistic-existential methods for AMI patients. The STP intervention challenges the notion of "brief" as outlined at the beginning of this section, as it involved between 3 and 11 individual counseling sessions and five 2-h group sessions. Two points are important. First, this may not look like a "brief" intervention, but it is included here as it is "brief" compared with the usual administration of a psychodynamic intervention. Second, although the

administration of the intervention in the trial was "standardized" by having one psychotherapist leading the interventions, it is virtually impossible to standardize a person-centered psychodynamic intervention in real-world practice where the quality of the therapeutic relationship, arguably the most important aspect of this type of intervention, is variable (Orlinksy et al. 1994; Smith et al. 2004).

In the one-session individual intervention versus a six-session CBT group intervention (Turner et al. 2013), 57 community-dwelling cardiac patients (ACS, PCI, CABG, heart failure, atrial fibrillation, cardiomyopathy) scoring >13 on the Beck Depression Inventory II (BDI-II) received a single-session brief intervention. They were then block randomized to either six sessions of group CBT ($n = 25$) or no further intervention (BI; $n = 32$). All were reassessed at 2, 6, and 12 months. Differences between treatment groups in the primary (BDI-II) and secondary [rates of depression; anxiety symptoms, as measured by the HADS-A] outcomes were examined using generalized linear mixed models. Significant improvements were seen for the total group from baseline to 12 months on BDI-II and HADS-A scores. However, no differences were found between the CBT and BI conditions on change in BDI-II score, rates of major depressive episode, or HADS-A score. Post hoc analysis on the total group which found a 12-month symptom non-remission was associated with higher baseline BDI-II score ($p = 0.03$), more visits to health professionals 12 months prior to baseline ($p = 0.05$), and a greater likelihood of either drinking alcohol over recommended levels or smoking at baseline ($p = 0.01$). The fact that one individual session was as effective as the 6-week group, CBT intervention on reduction of anxiety and depression is important, although there are issues with interpretation. An individual session is being compared with a group intervention to which only 36 % of those allocated attended all six sessions.

The content of the individualized session, however, is worth noting: individual feedback on assessment results including patient's depression, anxiety, and alcohol use profiles; recommendations for treatment; written self-help material; information on referral sources; and personalized letters or phone calls to general practitioners (GPs), CR nurses, and specialists regarding the baseline and 2-month assessment. The first of these, individualized feedback, especially when placed in the context of peer norms (how does your behavior/depression/anxiety/exercise regimen compare with people of your age, illness severity, etc.?) and undertaken in the context of a motivational interview, has been shown to be effective in behavioral change with respect to a range of problematic behaviors such as alcohol misuse (Carey et al. 2007; Hustad et al. 2014), and it is not surprising that it has been shown to be effective in the context of CR-related behavioral change.

Alternative Modes of Psychological Service Delivery

The effectiveness of individualized brief interventions emphasizing autonomy and choice, but backed by relevant health-care providers and localized behavioral change supports, has also been demonstrated in a variety of alternative cardiac rehabilitation settings (Clark et al. 2013; Neubeck et al. 2009). These nonhospital-

based alternative settings include telehealth interventions that were either multifactorial individualized interventions, exercise-focused interventions, or recovery-focused interventions following MI or CABG surgery; Internet-based risk factor modification interventions; community- or home-based CR; rural, remote, and culturally relevant interventions; multimodal interventions; and complementary and alternative therapy interventions. Generalizing from these studies is difficult, however, as they reflect a high level of heterogeneity in conditions addressed, time spent with patients, person delivering the intervention, and whether they were alternatives or adjuncts to "standard" CR. There are few reports of psychologically focused interventions in these reviews, with interventions more likely to focus on risk factor behavioral change and post-event adjustment. Of the few reporting a psychological or psychosocial focus, one showed no benefits in psychosocial adjustment following nurse-delivered telephone counseling (Gallagher et al. 2003), while the other showed no difference in depression or perceived social support in a peer-delivered telephone intervention for male CABG patients at 6- and 12-week follow-up. However, at 12-week post-discharge, the control group had significantly greater utilization of health services (family physician visits, emergency room visits) than the telephone intervention group ($p = 0.02$, $p = 0.04$, respectively) (Colella 2009). This impact on health service use is similar to that reported by Oranta et al. (2012) in their Finnish interpersonal counseling study. A further telehealth study (Cartwright et al. 2013) found no main effect on health-related quality of life, depression, or anxiety in heart failure patients, while in contrast, the "ProActive Heart" telephone coaching study found statistically significant reductions in anxiety and a trend to reduction of depression in MI patients (O'Neil et al. 2014). The reported effects on PHQ-9 measured depression were higher, however, in the tele-HEART intervention with an older group (mean age = 79 years, with 22.5 % over 85) of heart failure patients (Gellis et al. 2012).

One positive arising from alternative modes of delivery of psychological interventions may be higher rates of take-up and retention of patients receiving web-based interventions (70–95 %) compared with face-to-face interventions (30 %) (Paul et al. 2013). Greater adherence and adoption of beneficial physical activity as well as small but robust improvements in depression have also been reported for the use of Internet-delivered CBT for adults with high CVD risk but low to moderate depression (Glozier et al. 2013). The InterHerz trial (Messerli-Burgy et al. 2012) will test whether such depression and stress can be ameliorated by a web-based interactive intervention (Deprexis) that is responsive to patients as they complete modules which are not manualized but broadly consistent with a CBT perspective.

Psychosocial Interventions

Many of the studies cited so far comprise primarily psychological interventions. There has, however, been a number of evaluations of interventions comprising both psychological and social support-enhancing components or psychosocial

interventions (Thompson and Ski 2013), for people with CHD and depression (Berkman et al. 2003; McLaughlin et al. 2005). The results of these studies suggest that psychosocial interventions are effective at reducing depressive symptoms.

This section reviews a number of RCTs to assess the effectiveness of psychosocial interventions, compared to usual care, for people with CHD and depression. Four studies are two-group, parallel designs which compared a psychosocial intervention with usual care (Barth et al. 2005; Berkman et al. 2003; McLaughlin et al. 2005; Salminen et al. 2005). One study is a 2 × 2 factorial design which evaluated a psychosocial intervention compared with usual care and a selective serotonin reuptake inhibitor antidepressant with placebo (Lesperance et al. 2007). Sample sizes range from 59 to 856 (for patients with depression). Mean ages range from 56 to 75 years, and percentage of male ranges from 48 % to 82 %. The studies were undertaken in a range of hospital, academic, and community settings.

The studies enrolled participants with a variety of CHD diagnoses and levels of depression. With regard to depression, one study enrolled patients with unipolar affective disorder (major depression, dysthymia, or depressive adjustment disorder) (Barth et al. 2005), and one study included participants with major depression (Lesperance et al. 2007); these diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. One study included participants with mild or moderate depressive symptoms based on the HADS. The ENRICHD study included participants with major depression, minor depression with a history of major depression, or dysthymia (based on DSM criteria) or with low perceived social support (LPSS); however, only participants with depression and LPSS received psychological and social components (Berkman et al. 2003). Another study (Salminen et al. 2005) included patients without depression but undertook subgroup analysis on patients with moderate or severe depressive symptoms, based on the Zung Self-Rating Depression Scale (ZSDS).

As with the psychological interventions reviewed earlier, the interventions varied in their therapeutic elements, frequency, length, and mode of intervention. Two interventions involved CBT (Barth et al. 2005; McLaughlin et al. 2005), two studies incorporated counseling (McLaughlin et al. 2005; Salminen et al. 2005), and one study utilized interpersonal psychotherapy (Lesperance et al. 2007). Social isolation was addressed by four interventions (Berkman et al. 2003; Lesperance et al. 2007; McLaughlin et al. 2005; Salminen et al. 2005) and one program aimed to motivate patients to seek external services for enduring depressive illness (Barth et al. 2005). The interventions were delivered by a variety of health professionals (psychotherapist (Barth et al. 2005); clinical or counseling psychologists, clinical psychiatrists, clinical social worker, or psychiatric nurse (Berkman et al. 2003); experienced doctoral or master's level therapist (Lesperance et al. 2007); doctoral-level psychiatrist/clinical psychologist/intern (McLaughlin et al. 2005); and nurse plus physiotherapist for exercise (Salminen et al. 2005)) in group and individual settings and in-person and by telephone. All the included studies compared the intervention with usual clinical management.

The five studies reported on a variety of outcomes. All studies reported on the primary outcome of depressive symptoms and used a range of assessment tools

including the BDI (Barth et al. 2005; Blumenthal et al. 2003; Lesperance et al. 2007), the HADS (Barth et al. 2005; McLaughlin et al. 2005), the Hamilton Rating Scale for Depression (HAM-D) (Berkman et al. 2003; Lesperance et al. 2007), and the ZSDS (Salminen et al. 2005). The studies reported a variety of secondary outcomes including mortality (all-cause and cardiovascular) and revascularization (Berkman et al. 2003), recurrent MI (Berkman et al. 2003; Lesperance et al. 2007), anxiety (Barth et al. 2005; McLaughlin et al. 2005), social support (Berkman et al. 2003; Lesperance et al. 2007), quality of life (Berkman et al. 2003), and mental functioning (Mendes de Leon et al. 2006).

These studies suggest that psychosocial interventions, incorporating a focus on affect and social support, compared with usual care, appear to be effective in reducing depressive symptoms in patients with CHD and depression. The magnitude of the effect size reflects a small benefit of the intervention. In addition, it appears that psychosocial interventions improve social support and possibly mental health quality of life.

This small benefit seen in depressive symptoms is consistent with the systematic reviews previously discussed which examined psychological (rather than psychosocial) interventions in CHD patients (Dickens et al. 2013; Whalley et al. 2011). The studies reported in this section focused on psychosocial interventions only in patients with CHD and depression, and it should be noted that this population may be more resistant to treatment than a population with a range of depressive symptoms – including those without symptoms. As with the psychological interventions, these studies show that short-term interventions (3 months or less) may be more effective than long-term interventions (more than 3 months). This result could be due to a number of factors other than the intervention length. For example, studies with short-term intervention also had short-term follow-up, and it is likely that the effect of the intervention reduces over time.

The finding that psychosocial interventions improve social support and mental health quality of life in addition to depressive symptom is not surprising given the link between them (Rozanski et al. 2005). The outcomes of mortality, recurrent MI, and revascularization were only assessed by one or two of the five studies noted here, and no firm conclusions can be drawn as to whether psychosocial interventions impact on these outcomes. Other systematic reviews have addressed these outcomes, and there appears to be some evidence of a reduction in cardiac mortality (Whalley et al. 2011), but none in total mortality or cardiac revascularizations or nonfatal MI (Baumeister et al. 2011; Thombs et al. 2008; Whalley et al. 2011).

Although the evidence indicates that psychosocial interventions appear to reduce depressive symptoms in people with CHD and depression, there are some caveats. There are a number of components of any psychosocial intervention or indeed any complex intervention, such as staff delivering it, mode of delivery, setting, timing, frequency, and duration. Therefore, psychosocial interventions are not a standardized package and cannot be replicated exactly, even in cases where there is manualized treatment. Each psychosocial intervention is somewhat unique to the interventionist and patient and likely to have a different effect on each individual who receives it. However, despite the expected heterogeneity of the interventions,

the effect size for depressive symptoms was similar for each study suggesting that, despite nonstandardized interventions being compared, they were of similar effectiveness.

These studies are of patients who had CHD and depression. The severity of depression varies in the studies (from major depression to mild depressive symptoms), but the effect size of the studies is statistically homogeneous. This suggests that all patients with CHD and depression are able to benefit from the intervention regardless of the severity of depression. It should be acknowledged, however, that the ENRICHD trial (Berkman et al. 2003) contributed 63 % of all of the participants included in the studies outlined here (856/1,358) and was responsible for 56 % and 70 % of the weight of the reported results for the depressive symptoms and social support outcomes, respectively. Thus, the ENRICHD trial is driving or is solely responsible for most of the results reported in this brief review of psychosocial interventions.

A recent meta-analysis of the effect of psychosocial interventions on patients with chronic heart failure found a significant overall improvement in quality of life (Samartzis et al. 2013). However, psychosocial intervention was defined rather loosely as a "structured nonpharmacologic intervention. . .focused on improving psychologic and/or social aspects. . ." (p. 126). It did not necessarily include a social component.

Conclusion

In summary, psychological and psychosocial interventions result in modest reductions in depressive symptoms and improvements in social support in patients with CHD and depression, although no firm conclusions can be drawn as to whether these interventions impact on outcomes such as cardiac mortality and morbidity. There are many issues, however, in generalizing from the studies reviewed, namely: multiple cardiac conditions in the patients with varying levels of severity; multiple interventions, most of which are not manualized for ease of replication; measurement of different endpoints using a variety of scales and assessments, in the case of the psychological constructs in particular; variation in follow-up times; variation in psychological and physical comorbidity present; age range surveyed; varying extent to which the discrete components of multimodal interventions are specified and the associated problem of attribution of effect; variation in short-term or long-term interventions; and variations in mode of delivery.

Notwithstanding these methodological limitations and the modest effects achieved, psychological and psychosocial interventions are worth implementing, post-cardiac event. As unresolved depression is a major cause of death and disability in cardiac patients, all initiatives that impact positively on patient's mental health and quality of life are worthy of further attention.

References

Abbott, R. A., Whear, R., Rodgers, L. R., Bethel, A., Thompson Coon, J., Kuyken, W., . . . Dickens, C. (2014). Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. *Journal of Psychosomatic Research, 76*(5), 341–351. doi: 10.1016/j.jpsychores.2014.02.012.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine, 66*(6), 802–813. doi:10.1097/01.psy.0000146332.53619.b2.

Barth, J., Paul, J., Harter, M., & Bengel, J. (2005). Inpatient psychotherapeutic treatment for cardiac patients with depression in Germany – Short term results. *Psychosocial Medicine, 2*, Doc04.

Baumeister, H., Hutter, N., & Bengel, J. (2011). Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database of Systematic Reviews, 9*, CD008012. doi:10.1002/14651858.CD008012.pub3.

Beauchamp, A., Worcester, M., Ng, A., Murphy, B., Tatoulis, J., Grigg, L., . . . Goble, A. (2013). Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up. *Heart, 99*(9), 620–625. doi: 10.1136/heartjnl-2012-303022.

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catellier, D., Cowan, M. J., . . . Enhancing Recovery in Coronary Heart Disease Patients Investigators. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. *JAMA, 289*(23), 3106–3116. doi: 10.1001/jama.289.23.3106.

Blumenthal, J. A., Lett, H. S., Babyak, M. A., White, W., Smith, P. K., Mark, D. B., . . . Investigators, N. (2003). Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet, 362*(9384), 604–609. doi: 10.1016/S0140-6736(03)14190-6.

Briffa, T. G., Kinsman, L., Maiorana, A. J., Zecchin, R., Redfern, J., Davidson, P. M., . . . Denniss, A. R. (2009). An integrated and coordinated approach to preventing recurrent coronary heart disease events in Australia. *Medical Journal of Australia, 190*(12), 683–686.

British Heart Foundation. (2010). The National Audit of Cardiac Rehabilitation: Annual statistical report 2010. British Heart Foundation, 2010. www.bhf.org.uk/publications/view-publication.aspx?ps=1001019. Accessed 24th Jul 2014.

Brummett, B. H., Babyak, M. A., Siegler, I. C., Mark, D. B., Williams, R. B., & Barefoot, J. C. (2003a). Effect of smoking and sedentary behavior on the association between depressive symptoms and mortality from coronary heart disease. *American Journal of Cardiology, 92*(5), 529–532.

Brummett, B. H., Barefoot, J. C., Vitaliano, P. P., & Siegler, I. C. (2003b). Associations among social support, income, and symptoms of depression in an educated sample: The UNC Alumni Heart Study. *International Journal of Behavioral Medicine, 10*(3), 239–250.

Bunker, S., McBurney, H., Cox, H., & Jelinek, M. (1999). Identifying participation rates at outpatient cardiac rehabilitation programs in Victoria, Australia. *Journal of Cardiopulmonary Rehabilitation, 19*(6), 334–338.

Bush, D. E., Ziegelstein, R. C., Tayback, M., Richter, D., Stevens, S., Zahalsky, H., & Fauerbach, J. A. (2001). Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *American Journal of Cardiology, 88*(4), 337–341.

Carey, K. B., Scott-Sheldon, L. A., Carey, M. P., & DeMartini, K. S. (2007). Individual-level interventions to reduce college student drinking: A meta-analytic review. *Addictive Behaviors, 32*(11), 2469–2494. doi:10.1016/j.addbeh.2007.05.004.

Cartwright, M., Hirani, S. P., Rixon, L., Beynon, M., Doll, H., Bower, P., . . . Whole Systems Demonstrator Evaluation, T. (2013). Effect of telehealth on quality of life and psychological outcomes over 12 months (Whole Systems Demonstrator telehealth questionnaire study):

Nested study of patient reported outcomes in a pragmatic, cluster randomised controlled trial. *BMJ, 346*, f653. doi: 10.1136/bmj.f653.

Case, R. B., Moss, A. J., Case, N., McDermott, M., & Eberly, S. (1992). Living alone after myocardial infarction. Impact on prognosis. *JAMA, 267*(4), 515–519.

Chair, S.Y., Chan, S. W-C., Thompson, D.R., Leung, K-P. Ng, S. K-C., Choi, K.C. (2012). Short-term effect of motivational interviewing on clinical and psychological outcomes and health-related quality of life in cardiac rehabilitation patients with poor motivation in Hong Kong: A randomized controlled trial. *European Journal of Preventive Cardiology, 19*(6), 1383–1392. doi:10.1177/1741826711425428

Clark, R. A., Conway, A., Poulsen, V., Keech, W., Tirimacco, R., & Tideman, P. (2013). Alternative models of cardiac rehabilitation: A systematic review. *European Journal of Preventive Cardiology*. doi:10.1177/2047487313501093.

Colella, T. J. F. (2009). *The effect of a professionally-guided telephone peer support intervention on early recovery outcomes in men following coronary artery bypass graft surgery*. Alberta: University of Calgary. Accessed 3rd Aug 2014 http://www.collectionscanada.gc.ca/obj/thesescanada/vol2/002/NR49601.PDF.

Colquhoun, D. M., Bunker, S. J., Clarke, D. M., Glozier, N., Hare, D. L., Hickie, I. B., . . . Branagan, M. G. (2013). Screening, referral and treatment for depression in patients with coronary heart disease. *Medical Journal of Australia, 198*(9), 483–484.

Connerney, I., Sloan, R. P., Shapiro, P. A., Bagiella, E., & Seckman, C. (2010). Depression is associated with increased mortality 10 years after coronary artery bypass surgery. *Psychosomatic Medicine, 72*(9), 874–881. doi:10.1097/PSY.0b013e3181f65fc1.

Davidson, K. W., Rieckmann, N., Clemow, L., Schwartz, J. E., Shimbo, D., Medina, V., . . . Burg, M. M. (2010). Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: Coronary psychosocial evaluation studies randomized controlled trial. *Archives of Internal Medicine, 170*(7), 600–608. doi: 10.1001/archinternmed.2010.29.

Davies, P., Taylor, F., Beswick, A., Wise, F., Moxham, T., Rees, K., & Ebrahim, S. (2010). Promoting patient uptake and adherence in cardiac rehabilitation. *Cochrane Database of Systematic Reviews, 7*, CD007131. doi:10.1002/14651858.CD007131.pub2.

Mendes de Leon, C. F., Czajkowski, S. M., Freedland, K. E., Bang, H., Powell, L. H., Wu, C., . . . investigators, E. (2006). The effect of a psychosocial intervention and quality of life after acute myocardial infarction: The Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial. *Journal of Cardiopulmonary Rehabilitation, 26*(1), 9–13; quiz 14–15.

Dekker, R. L., Moser, D. K., Peden, A. R., & Lennie, T. A. (2012). Cognitive therapy improves three-month outcomes in hospitalized patients with heart failure. *Journal of Cardiac Failure, 18*(1), 10–20. doi:10.1016/j.cardfail.2011.09.008.

Dickens, C., Cherrington, A., Adeyemi, I., Roughley, K., Bower, P., Garrett, C., . . . Coventry, P. (2013). Characteristics of psychological interventions that improve depression in people with coronary heart disease: A systematic review and meta-regression. *Psychosomatic Medicine, 75*(2), 211–221. doi: 10.1097/PSY.0b013e31827ac009.

Eshah, N. F., & Bond, A. E. (2009). Cardiac rehabilitation programme for coronary heart disease patients: An integrative literature review. *International Journal of Nursing Practice, 15*(3), 131–139. doi:10.1111/j.1440-172X.2009.01738.x.

Gallagher, R., McKinley, S., & Dracup, K. (2003). Effects of a telephone counseling intervention on psychosocial adjustment in women following a cardiac event. *Heart and Lung, 32*(2), 79–87. doi:10.1067/mhl.2003.19.

Gehi, A., Haas, D., Pipkin, S., & Whooley, M. A. (2005). Depression and medication adherence in outpatients with coronary heart disease: Findings from the Heart and Soul Study. *Archives of Internal Medicine, 165*(21), 2508–2513. doi:10.1001/archinte.165.21.2508.

Gellis, Z. D., & Kang-Yi, C. (2012). Meta-analysis of the effect of cardiac rehabilitation interventions on depression outcomes in adults 64 years of age and older. *American Journal of Cardiology, 110*(9), 1219–1224. doi:10.1016/j.amjcard.2012.06.021.

Gellis, Z. D., Kenaley, B., McGinty, J., Bardelli, E., Davitt, J., & Ten Have, T. (2012). Outcomes of a telehealth intervention for homebound older adults with heart or chronic respiratory failure: A randomized controlled trial. *Gerontologist, 52*(4), 541–552. doi:10.1093/geront/gnr134.

Glozier, N., Christensen, H., Naismith, S., Cockayne, N., Donkin, L., Neal, B., . . . Hickie, I. (2013). Internet-delivered cognitive behavioural therapy for adults with mild to moderate depression and high cardiovascular disease risks: A randomised attention-controlled trial. *PLoS One, 8*(3), e59139. doi: 10.1371/journal.pone.0059139.

Grace, S. L., Abbey, S. E., Shnek, Z. M., Irvine, J., Franche, R. L., & Stewart, D. E. (2002). Cardiac rehabilitation II: Referral and participation. *General Hospital Psychiatry, 24*(3), 127–134.

Gupta, R., Sanderson, B. K., & Bittner, V. (2007). Outcomes at one-year follow-up of women and men with coronary artery disease discharged from cardiac rehabilitation: What benefits are maintained? *Journal of Cardiopulmonary Rehabilitation and Prevention, 27*(1), 11–18. quiz 19-20.

Heather, N. (1986). Minimal treatment interventions for problem drinkers. In G. Edwards & D. Gill (Eds.), *Current issues in clinical psychology* (pp. 120–156). London: Plenum.

Hustad, J. T., Mastroleo, N. R., Kong, L., Urwin, R., Zeman, S., Lasalle, L., & Borsari, B. (2014). The comparative effectiveness of individual and group brief motivational interventions for mandated college students. *Psychology of Addictive Behaviors, 28*(1), 74–84. doi:10.1037/a0034899.

Jelinek, M., Clark, A. M., Oldridge, N. B., Briffa, T. G., & Thompson, D. R. (2011). Reconciling systematic reviews of exercise-based cardiac rehabilitation and secondary prevention programmes for coronary heart disease. *European Journal of Cardiovascular Prevention and Rehabilitation, 18*(2), 147–149. doi:10.1177/1741826710389388.

Johnson, N., Fisher, J., Nagle, A., Inder, K., & Wiggers, J. (2004). Factors associated with referral to outpatient cardiac rehabilitation services. *Journal of Cardiopulmonary Rehabilitation, 24*(3), 165–170.

Jorm, A. F., Griffiths, K. M., Christensen, H., Parslow, R. A., & Rogers, B. (2004). Actions taken to cope with depression at different levels of severity: A community survey. *Psychological Medicine, 34*(2), 293–299.

Kaplan, G. A. (1992). Health and aging in the Alameda County Study. In K. W. Scheie (Ed.), *Aging, health behaviours and health outcomes* (pp. 69–88). Hillsdale: Lawrence Erlbaum Associates.

Kessler, R. C., Berglund, P. A., Bruce, M. L., Koch, J. R., Laska, E. M., Leaf, P. J., . . . Wang, P. S. (2001). The prevalence and correlates of untreated serious mental illness. *Health Services Research, 36*(6 Pt. 1), 987–1007.

Kubzansky, L. D., Kawachi, I., Weiss, S. T., & Sparrow, D. (1998). Anxiety and coronary heart disease: A synthesis of epidemiological, psychological, and experimental evidence. *Annals of Behavioral Medicine, 20*(2), 47–58.

Lesperance, F., Frasure-Smith, N., Koszycki, D., Laliberte, M. A., van Zyl, L. T., Baker, B., . . . Investigators, C. (2007). Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA, 297*(4), 367–379. doi:10.1001/jama.297.4.367.

Lett, H. S., Blumenthal, J. A., Babyak, M. A., Sherwood, A., Strauman, T., Robins, C., & Newman, M. F. (2004). Depression as a risk factor for coronary artery disease: Evidence, mechanisms, and treatment. *Psychosomatic Medicine, 66*(3), 305–315.

Lewin, R., & Doherty, P. (2013). Cardiac rehabilitation and mortality reduction after myocardial infarction: The emperor's new clothes? Evidence in favour of cardiac rehabilitation. *Heart, 99*(13), 909–911. doi:10.1136/heartjnl-2013-303704.

Lichtman, J. H., Bigger, J. T., Jr., Blumenthal, J. A., Frasure-Smith, N., Kaufmann, P. G., Lesperance, F., . . . American Psychiatric, A. (2008). Depression and coronary heart disease:

Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. *Circulation, 118*(17), 1768–1775. doi: 10.1161/CIRCULATIONAHA.108.190769.

Martins, R. K., & McNeil, D. W. (2009). Review of motivational interviewing in promoting health behaviors. *Clinical Psychology Review, 29*(4), 283–293. doi:10.1016/j.cpr.2009.02.001.

Mavrides, N., & Nemeroff, C. (2013). Treatment of depression in cardiovascular disease. *Depression and Anxiety, 30*(4), 328–341. doi:10.1002/da.22051.

McLaughlin, T. J., Aupont, O., Bambauer, K. Z., Stone, P., Mullan, M. G., Colagiovanni, J., . . . Locke, S. E. (2005). Improving psychologic adjustment to chronic illness in cardiac patients. The role of depression and anxiety. *Journal of General Internal Medicine, 20*(12), 1084–1090. doi: 10.1111/j.1525-1497.2005.00256.x.

Messerli-Burgy, N., Barth, J., & Berger, T. (2012). The InterHerz project – A web-based psychological treatment for cardiac patients with depression: Study protocol of a randomized controlled trial. *Trials, 13*, 245. doi:10.1186/1745-6215-13-245.

Murphy, B. M., Worcester, M. U., Elliott, P. C., Le Grande, M. R., Higgins, R. O., & Goble, A. J. (2006). Change in women's dietary fat intake following an acute cardiac event: Extent, predictors and comparison with non-cardiac Australian women and older adults. *European Journal of Cardiovascular Nursing, 5*(3), 206–213. doi:10.1016/j.ejcnurse.2006.01.002.

Murphy, B. M., Elliott, P. C., Higgins, R. O., Le Grande, M. R., Worcester, M. U., Goble, A. J., & Tatoulis, J. (2008a). Anxiety and depression after coronary artery bypass graft surgery: Most get better, some get worse. *European Journal of Cardiovascular Prevention and Rehabilitation, 15*(4), 434–440. doi:10.1097/HJR.0b013e3282fbc945.

Murphy, B. M., Elliott, P. C., Worcester, M. U., Higgins, R. O., Le Grande, M. R., Roberts, S. B., & Goble, A. J. (2008b). Trajectories and predictors of anxiety and depression in women during the 12 months following an acute cardiac event. *British Journal of Health Psychology, 13* (Pt 1), 135–153. doi:10.1348/135910707X173312.

Murphy, B. M., Le Grande, M. R., Navaratnam, H. S., Higgins, R. O., Elliott, P. C., Turner, A., . . . Goble, A. J. (2013). Are poor health behaviours in anxious and depressed cardiac patients explained by sociodemographic factors? *European Journal of Preventive Cardiology, 20*(6), 995–1003. doi: 10.1177/2047487312449593.

Murphy, B. M., Rogerson, M., Worcester, M., Elliott, P., Higgins, R., Le Grande, M., . . . Goble, A. (2013). Predicting mortality 12 years after an acute cardiac event: Comparison between inhospital and 2-month assessment of depressive symptoms in women. *Journal of Cardiopulmonary Rehabilitation and Prevention, 33*(3), 160–167. doi: 10.1097/HCR.0b013e318283927f.

Murphy, B. M., Worcester, M. U., Higgins, R. O., Elliott, P. C., Le Grande, M. R., Mitchell, F., . . . Goble, A. J. (2013). Reduction in 2-year recurrent risk score and improved behavioral outcomes after participation in the "Beating Heart Problems" self-management program: Results of a randomized controlled trial. *Journal of Cardiopulmonary Rehabilitation and Prevention, 33*(4), 220–228. doi: 10.1097/HCR.0b013e31828c7812.

Murray, J., Craigs, C. L., Hill, K. M., Honey, S., & House, A. (2012). A systematic review of patient reported factors associated with uptake and completion of cardiovascular lifestyle behaviour change. *BMC Cardiovascular Disorders, 12*, 120. doi:10.1186/1471-2261-12-120.

National Heart Foundation of Australia. (2010). *Secondary prevention of cardiovascular disease*. Melbourne: Author.

Neubeck, L., Redfern, J., Fernandez, R., Briffa, T., Bauman, A., & Freedman, S. B. (2009). Telehealth interventions for the secondary prevention of coronary heart disease: A systematic review. *European Journal of Cardiovascular Prevention and Rehabilitation, 16*(3), 281–289. doi:10.1097/HJR.0b013e32832a4e7a.

Nicholson, A., Kuper, H., & Hemingway, H. (2006). Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *European Heart Journal, 27*(23), 2763–2774. doi:10.1093/eurheartj/ehl338.

Nyklicek, I., Dijksman, S. C., Lenders, P. J., Fonteijn, W. A., & Koolen, J. J. (2014). A brief mindfulness based intervention for increase in emotional well-being and quality of life in percutaneous coronary intervention (PCI) patients: The MindfulHeart randomized controlled trial. *Journal of Behavioral Medicine, 37*(1), 135–144. doi:10.1007/s10865-012-9475-4.

O'Neil, A., Hawkes, A. L., Atherton, J. J., Patrao, T. A., Sanderson, K., Wolfe, R., . . . Oldenburg, B. (2014). Telephone-delivered health coaching improves anxiety outcomes after myocardial infarction: The 'ProActive Heart' trial. *European Journal of Preventive Cardiology, 21*(1), 30–38. doi: 10.1177/2047487312460515.

Oranta, O., Luutonen, S., Salokangas, R. K., Vahlberg, T., & Leino-Kilpi, H. (2012). Depression-focused interpersonal counseling and the use of healthcare services after myocardial infarction. *Perspectives in Psychiatric Care, 48*(1), 47–55. doi:10.1111/j.1744-6163.2011.00305.x.

Orlinksy, D. E., Grawe, K., & Parks, B. K. (1994). Process and outcome in psychotherapy – noch einmal'. In A. E. Bergin & S. L. Garfield (Eds.), *Handbook of psychotherapy and behavior change* (4th ed., pp. 270–376). New York: Wiley.

Paul, C. L., Carey, M. L., Sanson-Fisher, R. W., Houlcroft, L. E., & Turon, H. E. (2013). The impact of web-based approaches on psychosocial health in chronic physical and mental health conditions. *Health Education Research, 28*(3), 450–471. doi:10.1093/her/cyt053.

Petry, N. M. (2005). *Pathological gambling: Etiology, comorbidity, and treatment*. Washington, DC: American Psychological Association.

Petry, N. M., Weinstock, J., Ledgerwood, D. M., & Morasco, B. (2008). A randomized trial of brief interventions for problem and pathological gamblers. *Journal of Consulting and Clinical Psychology, 76*(2), 318–328. doi:10.1037/0022-006X.76.2.318.

Redfern, J., Ellis, E. R., Briffa, T., & Freedman, S. B. (2007). High risk-factor level and low risk-factor knowledge in patients not accessing cardiac rehabilitation after acute coronary syndrome. *The Medical Journal of Australia, 186*(1), 21–25.

Roncella, A., Pristipino, C., Cianfrocca, C., Scorza, S., Pasceri, V., Pelliccia, F., . . . Speciale, G. (2013). One-year results of the randomized, controlled, short-term psychotherapy in acute myocardial infarction (STEP-IN-AMI) trial. *International Journal of Cardiology, 170*(2), 132–139. doi: 10.1016/j.ijcard.2013.08.094.

Rozanski, A., Blumenthal, J. A., Davidson, K. W., Saab, P. G., & Kubzansky, L. (2005). The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology. *Journal of the American College of Cardiology, 45*(5), 637–651. doi:10.1016/j.jacc.2004.12.005.

Salminen, M., Isoaho, R., Vahlberg, T., Ojanlatva, A., & Kivela, S. L. (2005). Effects of a health advocacy, counselling, and activation programme on depressive symptoms in older coronary heart disease patients. *International Journal of Geriatric Psychiatry, 20*(6), 552–558. doi:10.1002/gps.1323.

Samartzis, L., Dimopoulos, S., Tziongourou, M., & Nanas, S. (2013). Effect of psychosocial interventions on quality of life in patients with chronic heart failure: A meta-analysis of randomized controlled trials. *Journal of Cardiac Failure, 19*(2), 125–134. doi:10.1016/j.cardfail.2012.12.004.

Scott, I. A., Lindsay, K. A., & Harden, H. E. (2003). Utilisation of outpatient cardiac rehabilitation in Queensland. *The Medical Journal of Australia, 179*(7), 341–345.

Smith, S., Thomas, S. A., & Jackson, A. C. (2004). An exploration of the therapeutic relationship and counselling outcomes in a problem gambling counselling service. *Journal of Social Work Practice, 8*(1), 99–112.

Stauber, S., Guera, V., Barth, J., Schmid, J. P., Saner, H., Znoj, H., . . . von Kanel, R. (2013). Psychosocial outcome in cardiovascular rehabilitation of peripheral artery disease and

coronary artery disease patients. *Vascular Medicine, 18*(5), 257–262. doi: 10.1177/1358863X13505861.

Taylor, C. B. (2010). Depression, heart rate related variables and cardiovascular disease. *International Journal of Psychophysiology, 78*(1), 80–88. doi:10.1016/j.ijpsycho.2010.04.006.

Thombs, B. D., & Ziegelstein, R. C. (2010). Screening in cardiovascular care. In A. J. Mitchell & J. C. Coyne (Eds.), *Screening for depression in clinical practice: An evidence-based guide*. New York: Oxford University Press.

Thombs, B. D., de Jonge, P., Coyne, J. C., Whooley, M. A., Frasure-Smith, N., Mitchell, A. J., . . . Ziegelstein, R. C. (2008). Depression screening and patient outcomes in cardiovascular care: A systematic review. *JAMA, 300*(18), 2161–2171. doi: 10.1001/jama.2008.667.

Thompson, D. R., & Ski, C. F. (2013). Psychosocial interventions in cardiovascular disease – What are they? *European Journal of Preventive Cardiology, 20*(6), 916–917. doi:10.1177/2047487313494031.

Turner, A., Hambridge, J., Baker, A., Bowman, J., & McElduff, P. (2013). Randomised controlled trial of group cognitive behaviour therapy versus brief intervention for depression in cardiac patients. *The Australian and New Zealand Journal of Psychiatry, 47*(3), 235–243. doi:10.1177/0004867412460592.

van Melle, J. P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G., Ormel, J., van Veldhuisen, D. J., . . . van den Berg, M. P. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosomatic Medicine, 66*(6), 814–822. doi: 10.1097/01.psy.0000146294.82810.9c.

Welin, C., Lappas, G., & Wilhelmsen, L. (2000). Independent importance of psychosocial factors for prognosis after myocardial infarction. *Journal of Internal Medicine, 247*(6), 629–639.

Whalley, B., Rees, K., Davies, P., Bennett, P., Ebrahim, S., Liu, Z., . . . Taylor, R. S. (2011). Psychological interventions for coronary heart disease. *Cochrane Database Systematic Reviews*, *8*, CD002902. doi: 10.1002/14651858.CD002902.pub3.

Whooley, M. A. (2006). Depression and cardiovascular disease: Healing the broken-hearted. *JAMA, 295*(24), 2874–2881. doi:10.1001/jama.295.24.2874.

Whooley, M. A., & Wong, J. M. (2013). Depression and cardiovascular disorders. *Annual Review of Clinical Psychology, 9*, 327–354. doi:10.1146/annurev-clinpsy-050212-185526.

Woltz, P. C., Chapa, D. W., Friedmann, E., Son, H., Akintade, B., & Thomas, S. A. (2012). Effects of interventions on depression in heart failure: A systematic review. *Heart and Lung, 41*(5), 469–483. doi:10.1016/j.hrtlng.2012.06.002.

Ziegelstein, R. C., Fauerbach, J. A., Stevens, S. S., Romanelli, J., Richter, D. P., & Bush, D. E. (2000). Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Archives of Internal Medicine, 160*(12), 1818–1823.

Treatment of Anxiety Within the Practice of Cardiology

Aanchal Sood, Marlies E. Alvarenga, and James A. Blumenthal

Contents

A. Sood (✉)
Voice Psychologists and Allied Professionals, Melbourne, VIC, Australia
e-mail: soodaanchal@gmail.com

M.E. Alvarenga
MonashHEART, Monash Cardiovascular Research Centre, Monash Health and Department of Medicine (SCS at Monash), Monash University, Melbourne, VIC, Australia
e-mail: marlies.alvarenga@monash.edu

J.A. Blumenthal
Department of Psychiatry and Behavioral Medicine, Duke University School of Medicine, Durham, NC, USA
e-mail: James.Blumenthal@duke.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_48

Abstract

This chapter will provide a definition of anxiety and describe methods for assessing it within cardiac practice. Next the epidemiology of anxiety disorders and prevalence of anxiety disorders in cardiovascular disease will be reviewed followed by literature on anxiety and cardiovascular disease. Subsequently, different treatment options including pharmacotherapy and different psychological approaches will be evaluated. Other treatment measures discussed in this chapter include breathing retraining, relaxation, and exercise therapy. The chapter concludes with recommendations for treatment of anxiety in heart disease along with future directions for research.

Keywords

Anxiety disorders • Breathing • Cognitive behavior therapy • Epidemiology • Exercise therapy • Hypnotherapy • In cardiovascular disease • Perceived locus of control • Pharmacotherapy • Psychoeducation • Relaxation therapy • Cardiovascular disease • In anxiety disorders • Cognitive behavior therapy (CBT) • Generalized anxiety disorder (GAD) • Noncardiac chest pain • Panic disorder • Post-traumatic stress disorder (PTSD) • Selective serotonin reuptake inhibitors (SSRIs) • Tricyclic antidepressants (TCAs)

Introduction

There is increasing recognition that the experience of worry and fear can lead to a troubled mind as well as a troubled heart. During the experience of anxiety and panic, the body's natural emergency response to perceived threat appears to not simply mimic the cardiac symptoms (i.e., palpitations, shortness of breath) but in itself contributes to the development and maintenance of heart disease. Watkins et al. (2013) found that people with comorbid anxiety disorders and heart disease had twice the risk of dying from any cause and that the presence of anxiety and depression in heart patients puts these patients at three times the risk of mortality. Therefore, treatment of anxiety in cardiac patients is both an important and imperative aspect of cardiac clinical practice.

Definition and Measurement of Anxiety

A negative affective state caused by an individual's perception of threat or pronounced anticipation of future, characterized by a perceived inability to control worry, is often explained as anxiety (Barlow 1998). Anxious feelings are considered as a normative experience to stressful/novel situations until its magnitude reaches a point contributing to dysfunctional responses and negative consequences, which may then be characterized as a disorder (Barlow 1998; Frijda 1986). Thus, normal and pathological anxiety symptomatology can largely be similar except in

the intensity, duration, and frequency of symptoms. The Diagnostic and Statistical Manual of mental disorders, Fifth Edition (DSM 5), is the most commonly used diagnostic instruments by allied health professionals to diagnose anxiety. In order to warrant a diagnosis of anxiety or trauma–stress-related disorder, the DSM 5 criteria must be met. According to the DSM 5 (2013):

- Generalized anxiety disorder (GAD) is characterized by excessive worrying and anxiety occurring for most days for at least 6 months, and the individual experiences difficulty to control the worry. The anxiety and worry are associated with three or more of the following symptoms: restlessness, fatigue, irritability, and muscle tension, mind racing, difficulty concentrating, and sleep disturbance. The anxiety and worry or physical symptoms cause clinically significant distress and cannot be better explained by another medical disorder or physiological effects of substance use.
- Panic disorder is characterized by recurrent unexpected panic attacks and reaches peak within minutes, and during which time four or more of the following symptoms are present: palpitations; accelerated heart rate; sweating; trembling; sensations of shortness of breath; feelings of choking; chest pain; nausea or abdominal pains; feeling dizzy or light-headed or faint; chills or heat sensations; paresthesias, derealization, or depersonalization; fear of losing control; and/or fear of dying. In addition to the existence of four or more of these symptoms, at least one of the attacks must be followed by 1 month or more of one or both: persistent worrying or concern about having additional panic attacks and their consequences and/or a significant maladaptive change in behavior related to panic attacks (e.g., behaviors designed to avoid panic attacks). The disturbance or physical symptoms cannot be better explained by another medical disorder or attributable to physiological effects of substance use.
- Post-traumatic stress disorder (PTSD) is diagnosed when an individual is exposed to actual or threatened death, event, or sexual violence in one or more of the following ways: directly experiencing the traumatic event, witnessing the event, learning that the traumatic experience occurred to a close family member or friend, or experiencing repeated or extreme exposure to aversive details of the traumatic event. Presence of one or more of the intrusive symptoms – recurrent involuntary and intrusive distressing memories of the traumatic event, recurrent distressing dreams in which the content is related to the traumatic event, dissociative reactions (e.g., flashbacks), intense or prolonged psychological distress at exposure to cues that resemble or symbolize the traumatic event, and marked physiological reactions to internal or external cues. In addition, persistent avoidance of stimuli associated with traumatic event and negative alterations in cognitions and mood begin to worsen after the traumatic event occurred. Also marked alterations in arousal and reactivity associated with the traumatic event are evidenced by two or more of the following symptoms: irritable mood, anger outbursts, reckless self-destructive behavior, hypervigilance, exaggerated startle response, problems with concentration, and/or sleep disturbance. All of the above are present for more than a month,

cause clinically significant distress, and cannot be better explained by another medical disorder or physiological effects of substance use.

Epidemiology of Anxiety Disorders

Anxiety disorders are the most commonly diagnosed forms of mental illness in the Western world and in the USA are responsible for one-third of the total expenditures of the federal government for mental illness. Approximately half of those costs are due to the repeated use of health-care services since people with anxiety disorders often solicit medical evaluation for symptoms that resemble physical illnesses. Nationally representative surveys indicate that as many as 30 % of patients will suffer from some kind of anxiety disorder during their lifetimes, a figure that has increased significantly over the past two decades.

In the USA, one in four in the general population will meet criteria for an anxiety disorder with a 1-year prevalence rate of 17.7 % (Kessler et al. 1994). Women are more likely to have an anxiety disorder than men (30.5 % vs 19.2 % lifetime prevalence), with lower socioeconomic status manifesting a higher prevalence (Kessler et al. 1994). Although the actual prevalence of anxiety disorders among cardiac patients is not known, Tully and Cosh (2013) reported an 11–14 % prevalence of generalized anxiety disorder (GAD) across 12 studies ($N = 3485$) and a pooled lifetime prevalence of 26 %. Frasure-Smith and Lesperance(2008) noted that 5.3 % of a sample of 804 patients with stable CHD had GAD and 41.4 % had elevated anxiety symptoms measured by the Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Noncardiac chest pain is diagnosed in approximately 50 % of patients who present to the ED, with 30 % of these found to have panic disorder with normal angiograms at follow-up (Fleet et al. 1998). Thus, the typical cardiologist will likely encounter a patient suffering from anxiety symptoms masquerading as cardiac disease.

Anxiety in Cardiovascular Disease

A substantial literature supports clinically important associations between psychiatric illness and chronic medical conditions. Patients with severe mental disorders have about twice the prevalence of the classic risk factors for coronary heart disease (CHD) (Birkenaes et al. 2006). Belief that emotions contribute to heart disease has a long history. If survivors of cardiovascular disease (CVD) are asked about contributing factors, 70 % tend to believe stress as one of the major contributing factor (Gudmundsdottir et al. 2001). CVD is considered as a leading cause of morbidity and mortality in the world (Lloyd-Jones et al. 2010). Growing evidence suggests a high correlation between the heart and emotion. A psychobiological model proposed that negative emotions contribute to altered physiological responses in some individuals and that these responses are harmful to the cardiovascular system. Strike and Steptoe (2005) found that emotions and stress are significant

precipitating factors for acute coronary syndromes. Several studies have demonstrated a predisposition to CHD due to interaction between conventional risk factors and psychological factors. Research has found that negative affective states contribute to an increased propensity to CVD (Kubzansky and Kawachi 2000; Kubzansky et al. 1997). Anxiety is not only considered as one of the most prevalent psychiatric diagnoses but also among the most common complaint in patients with CVD (Harter et al. 2003; Lavoie et al. 2004; Bayazi and Rastegari 2005). In addition, anxiety is seen most among individuals with CHD. Research suggests that 70–80 % of individuals suffering from an acute cardiac event tended to experience anxiety (Kubzansky et al. 1998). Although anxiety related to living with a debilitating condition is common among patients, chronic persistence is found among 20–25 % patients (Kubzansky and Kawachi 2000). Fear of sudden death, the lack of self-sufficiency, deficiency on sexuality, and the change of roles on family relationships or fear of losing their status and the fear of having a new infarction risk can all cause anxiety in patients. In addition, prevalence of anxiety is a poor predictor of short- and long-term success of treatment and hinders psychosocial adaptation and functionality by interfering in patient's ability to self-care (Kubzansky et al. 1998). Studies have demonstrated a link between CHD and anxiety disorders and between anxiety disorders and hypertension (Davies et al. 1999). In a study, Havik and Maeland (1990) found that patients suffering from comorbid CHD and anxiety displayed a slow progression into the work force and more often ceased employment than non-anxious patients with CHD. Anxiety can also increase the risk of subsequent CHD events and CHD mortality (Denollet and Brutsaert 1998).

Bankier et al. (2008) showed significant associations between generalized anxiety and CHD. It has further been investigated that despite prevalence of cultural diversity in how emotions can impact different individuals (Kirmayer 2001; Draguns and Tanaka-Matsumi 2003), patients suffering from acute myocardial infarction (AMI) displayed no difference in expression of anxiety (Moser and Jong 2005).

Elevated anxiety symptoms have been shown to be associated with a twofold increased risk of mortality in CABG patients (Tully et al. 2008; Szekely et al. 2007) and in outpatients with CHD (Rothenbacher et al. 2007; Strik et al. 2003). Furthermore, Frasure-Smith and Lesperance (2008) reported that CHD patients with GAD assessed 2 months following hospital discharge showed a 2.3-fold increased risk of adverse cardiac events, and Strik et al. (2003) reported a 2.8-fold increased risk of adverse events in acute post-MI patients in which anxiety was measured 1 month following hospital discharge. Similarly, a twofold increased risk of adverse events was observed in 76 stable CHD patients and in patients with elevated anxiety during annual clinic visits.

Considering that individuals with a diagnosis or incident of cardiac disease are unexpectedly confronted with a risk of mortality followed by worrisome thoughts about social, personal, and occupational lives, anxiety tends to be considered as normative. Research has found associations between psychiatric diagnosis, particularly depression, anxiety, and psychological difficulty to adjust to the diagnosis and condition implications; however, it fails to provide potential explanations of poor cardiovascular outcome in patients with depression and

anxiety. Furthermore, several studies have shown links between anxiety disorders and subsequent cardiovascular disease, sudden death, or increase risk of mortality (Kawachi et al. 1994a; Watkins et al. 2013). The patients are often confronted with numerous physical and mental stressors in coronary care units (Still 2002), and anxiety predominantly poses a serious problem for patients in care units where it can affect motivation and adherence to treatment and cause marked distress (Maghsudlu 2001). Hence, treatment of anxiety in CVD is of paramount importance. While treatment of depression in CVD has received significant attention, surprisingly, treatment of anxiety in cardiac patients has been less investigated. Thus, there is limited research on treatment options and implications of treatment in anxious patients with CVD.

Assessment

Many epidemiological studies have highlighted that chronic anxiety might constitute a risk for developing heart disease. Therefore, there is a need for specialist medical associations like the Royal Australian College of Cardiologists, the British Cardiovascular Society, and the American College of Cardiology, among others, to adopt national standards regarding the screening of psychosocial risk factors, such as anxiety. Psychological questionnaires have demonstrated high validity and reliability in assessing anxiety and comorbid depression and/or distress. The Beck Depression Inventory (BDI-II; Beck), the Patient Health Questionnaire-9 (PHQ), and the Zung Self-Rating Anxiety Scale or Hamilton Anxiety Scale (HAM-A) are psychometric tests which can accurately identify the presence of anxiety and depression and which ought to be administered to all cardiac patients as part of standard clinical practice. However, it might be that the time it takes to administer psychological testing has discouraged the practice of screening by cardiologists. In 2003, the National Heart Foundation of Australia put forth a position paper suggesting the use of an abbreviated version of the PHQ-9, the PHQ-2, as a way of screening for the possibility of depression in cardiac patients (Colquhoun et al. 2013). The position paper is yet to form part of clinical guidelines of the Australian College of Cardiologists.

Murphy et al. (in print) have proposed a system which "red flags" cardiac patients likely to suffer from depression and not just a normal reaction to a life-threatening event, such as a heart attack. Such system is yet to be developed for flagging patients at high risk of an anxiety disorder, such as panic disorder or post-traumatic stress. Janeway (2008) developed a treatment algorithm for anxiety in heart disease based on screening cardiac patients with the STOP-D, a screening tool for psychological distress designed specifically for cardiac patients (Young et al. 2007). This is a brief five-item self-report measure which is highly correlated with other measures of depression, anxiety, anger, and poor social support. Janeway (2008) points out that the advantage of this scale over others is its ease of administration and scoring, as well as the fact that it is freely available online to be used by cardiac nurses and cardiologists.

Janeway's Treatment Algorithm

The proposed treatment algorithm (Janeway 2008) uses the STOP-D scale as an initial screening tool (Young et al. 2007). If anxiety symptoms score equal or more than 4 points in the 8-point scale, a recommendation is made to monitor and reassess after 2–4 weeks. If anxiety persists at the same high levels at reassessment, cardiologists are asked to assess impact of mental state on treatment compliance and ability to maintain a healthy lifestyle. At this point a referral to a mental health professional is recommended. Patient ought to be reviewed again 2, 4, and 6 weeks later. If there is improvement, continue to monitor patient over the next 1–2 months. If the patient relapses or continues to worsen, a referral ought to be made to a mental health professional. The author flags noncompliance with medication, alcohol use/substance abuse, severe depression, mania, suicidality/homicidal ideation, severe stress, and a history of sexual and physical abuse as factors which ought to routinely form the basis of a referral to a mental health professional.

Treatment Options

Pharmacotherapy

Recognition of a biological basis for anxiety and depression lends support to treatment approaches which focuses on altering and "correcting" brain biochemistry. In particular, medical professionals find it reassuring to treat the body using a pharmacological paradigm. The right choice of medication for anxiety in cardiac disease is an issue of high importance as it can significantly impact the clinical outcome of these patients. A study indicated that deficiencies in the central neurotransmitter (serotonin) may not only contribute to development of psychiatric conditions, but it may also be implicated in the development and maintenance of hypertension and cardiovascular risk (Vikenes et al. 1999). Considering the link between cardiovascular risk and serotonin deficiencies, it is likely that targeting the same neurotransmitter may yield positive treatment outcomes for both anxiety and CVD.

Lehnert et al. (1987) found that increased serotonin in cerebrospinal fluid contributed to increased ventricular fibrillation and reduction in efferent sympathetic activity from the heart. Furthermore, selective serotonin reuptake inhibitors (SSRIs) tend to assist with heart rate variability, which is a marker of cardiovascular reactivity and often reduced in anxiety disorders (Yeragani et al. 1990). The high affinity of most SSRIs for the serotonin transporter contributing to reduced storage of serotonin in platelets has further been recommended as a potential rationale for cardioprotective action of SSRIs (Sauer et al. 2003). The SSRI paroxetine was found to contribute to remission of depressive symptoms in most patients with ischemic heart disease and was associated with less cardiovascular side effects (Roose et al. 1998). Considering that the same neurotransmitter is believed to have an association with depression and anxiety, the same medication may be ameliorating. However, the study has not been replicated with patients with anxiety and CVD.

Antidepressants are recommended as first line when pharmacotherapy is required for anxiety disorders. Selective serotonin reuptake inhibitors are effective in all anxiety disorders and selective and noradrenaline reuptake inhibitors in most anxiety disorders. They are the drugs of first choice, with the exception of obsessive compulsive disorder, and there is little evidence of a dose–response relationship with antidepressants and many patients will respond to standard doses (Lampe 2013).

Tousoulis et al. (2010) found that the use of SSRIs is likely to have a beneficial effect on clinical outcome of heart failure. Furthermore, Strik et al. (2000) found in a placebo-controlled trial that fluoxetine reduced symptoms of depression in patients with MI. One of the largest studies in the area of efficacy of SSRIs in CVD was conducted by Glassman et al. (2002) named as SADHART (sertraline antidepressant heart attack randomized trial). The participants in the study were patients with AMI and a diagnosis of depression. The patients were assigned to sertraline (50–200 mg/day) or placebo for 24 weeks. Sertraline was found to be as safe as placebo but was more effective in treating symptoms of severe depression and significant greater improvement in patient-rated global impression scores. However, efficacy of the same medication in patients with anxiety and AMI has not been replicated.

Davies et al. (2004) in their review indicated that a study found venlafaxine, a serotonin and noradrenaline reuptake inhibitor (SNRI), safe in patients with CHD. However, high doses of the medication can cause increase in blood pressure. Hence, caution was recommended due to dose-dependent nature of the medication. Another study examined the efficacy and safety of the combined use Vazonat and Adaptol (an anxiolytic) in patients with CHD and anxiety disorders. The results indicated that the combined use led to significant reduction in severity of anxiety symptoms, clinical improvement, and increased myocardial contractility. In addition, improvement in general health and mood was also found. Alvarez et al. (2003) in their literature review indicated that tricyclic antidepressants (TCAs) could be considered as a safe treatment for depression in patients with ischemic heart disease, heart failure, or previous MI. However, long-term treatment with TCAs can have adverse side effects, such as orthostatic hypotension.

Treatment of anxiety with psychopharmacology alone is challenging even in noncardiac psychiatric populations. Anxiolytic doses are usually higher than doses required to treat unipolar depression, perhaps as anxiety is generally slower to respond to treatment than depression (Lampe 2013); therefore, clinicians ought to be mindful of rapid dose escalation. Treatment outcomes are likely to be enhanced if anxious patients with cardiovascular disease receive psychological therapy in addition to pharmacotherapy.

Psychoeducation

As the old adage goes, understanding a problem is half its solution. Indeed, for cardiac patients possessing knowledge and understanding of their condition can assist with improved management and adherence to treatment.

For many patients, a natural reaction to a heart attack can be similar to what is observed in post-traumatic stress disorder. An individual is likely to be shocked by a near-death experience and is likely to feel hesitant to do usual tasks. An individual potentially may live the life-threatening event and avoid activities perceived as a risk (Braunwald et al. 2004). Furthermore, recurring anxious thoughts tends to impede ability to have a positive outlook of the future and is likely to negatively impact sleep. In addition, sticking to exercise regimens becomes harder with comorbid anxiety and CVD (Sardinha and Nardi 2012). Hence, normalization and psychoeducation become of paramount importance. The goal of psychoeducation is to provide patients with an explanatory model which includes anatomy, physiology, symptoms, and their relationship between anxiety and CVD. Drawing pictures which can help explain to the patient these relationships is also helpful.

It becomes integral for patients to have an understanding of biobehavioral pathways linking anxiety and adverse health outcomes. Biologically, anxiety has an adverse impact on the autonomic nervous system. Furthermore, with anxiety the lipid profile, the immune system, and the coagulation cascade get compromised. The mental stress associated with anxiety is known to have an association with excessive activation of sympathetic nervous system (Medich et al. 1991; Veith et al. 1994) and catecholamine release (Fehder 1999). This is found in both healthy individuals and people with poor health as evidenced by increased plasma norepinephrine and decreased heart rate (Yeung et al. 1991). Behaviorally, anxiety potentially reduces adherence to lifestyle. The reasons for poor adherence have not yet been clearly determined. However, patients with anxiety tend to have fewer coping mechanisms in response to stressful situations and are likely to use unhealthy ways to alleviate anxiety (Stewart et al. 2004). Feelings of not being in control, which is common in patients with anxiety and CVD (Moser and Dracup 1995), can cause feelings of powerlessness and poorer choices like unhealthy habits and lack adherence to cardiac rehabilitation. Gaining insight into the strong association between biological and behavioral pathways of anxiety and CVD is likely to promote sense of control and accountability in patients.

Other studies such as Recurrent Coronary Prevention Program (RCPP) were carried out to reduce Type A behaviors in patients with MI. It was found that there was 44 % reduction in Type A behavior (hostility, anger, depression) in patients with MI who received psychological intervention in addition to cardiac education compared to controls who received only cardiac education (Friedman et al. 1986). The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial found that behavioral treatment reduced depression and social isolation in patients with post MI. Other clinical trials found that when patients with myocardial ischemia and ventricular wall motion abnormalities were taught stress management and coping skills, there was a reduction in CHD recurrences (Blumenthal et al. 1997).

Cognitive Behavior Therapy

Cognitive behavior therapy (CBT) focuses on education, self-monitoring, skills training, cognitive restructuring, and relapse prevention. It highlights the

relationship between thoughts, feelings, and behaviors. Effectiveness of CBT in anxiety is known through research, and it remains as one of the best evidence-based therapeutic technique to treat symptoms of anxiety. Barlow et al. (1984) found positive impact of cognitive therapy on patients with clinical anxiety. Furthermore, cognitive restructuring, thought control, and relaxation have been found to have an ameliorating impact on coping with anxiety symptomatology (Durham and Turvey 1987).

Several studies have found CBT to be helpful in reducing anxiety and augmenting cardiac performance (Beck et al. 2004; Jacobs 2001). A study by Yousefy et al. (2006) randomly divided patients diagnosed with CHD into control and case groups. The case group completed CBT in eight 2-h structural sessions in addition to usual treatment for CHD. The results indicated that patients in the case group displayed evidence of improved quality of life and reduced anxiety ($P < 0.000$). The study further concluded that the physiological and neurobiological impacts of relaxation contributed to reduced muscle activity, delayed spinal reflexes, and subsequently reduced excitability of the brain cortex activity and autonomous nervous system. Yousefy et al. (2006) further indicated that vessel dilation and decreased blood pressure caused by the increased vasodilatory neurotransmitters resulted in improved cardiac outcome.

Cully et al. (2010) examined the effectiveness of tailored CBT for patients with chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) with comorbid symptoms of anxiety and depression. The traditional CBT techniques were expanded to in-person- or telephone-based sessions. It was identified that flexibility in traditional CBT delivery demonstrated ability to better deal with psychological challenges associated with complex cardiopulmonary patients. It is anticipated that after patients are struck with a life-threatening diagnosis and feelings of lack of control, it is likely that an individually tailored approach tends to offer a sense of control along with therapeutic benefits.

Studies have also found that CBT prevented recurrence of a heart attack (Gulliksson et al. 2011). Patients (362 people in Sweden) who had either a recent heart attack or blocked coronary arteries were either given standard medical treatment or standard medical treatment and 20 sessions of CBT over a 12-month period. Results revealed that the group that received CBT had a 45 % reduced rate of heart attacks and 41 % lower rate of other cardiac events. Furthermore, better adherence to therapy had a positive correlation with lower risk of subsequent cardiac events.

CBT techniques for treatment of anxiety in CVD can include providing psychoeducation on common signs and symptoms of anxiety followed by education on the CBT rationale. Assistance with identifying negative automatic thoughts and substituting them with rationale thoughts and constructive self-talk is likely to help patients in taking control over thoughts. Skills training can assist patients with responding rather than reacting to negative thoughts. Furthermore, relaxation can be a tool to become more alert to body signals and pay attention to behavioral and cognitive clues. Explaining the relationship between thoughts and emotions along with systematic desensitization can help patients better manage their anxiety levels.

Breathing Retraining and Relaxation

Dealing with a debilitating physical condition can impact on mental health in the form of stress. For some, it can feel much like recovering from a traumatic event. The individual diagnosed with a heart condition has experienced a life-threatening event that can cause them to respond with intense fear and helplessness. This fear can provoke a flight or fight response, also known as acute stress response, in the body. Rapid heartbeat, rapid breathing, and tense muscles are the most common physiological reactions. When a person senses something perceived as potentially threatening, a number of physiological changes take place in the body. The brain sends warning signals through the central nervous system. It impacts the autonomic nervous system (ANS) in our brain. The ANS control system can regulate heart rate, digestion, and respiratory rate. The reaction to a threat begins in the amygdala followed by activation of the pituitary gland. The adrenal glands also get activated simultaneously in a process of co-transmission, releasing epinephrine into the bloodstream. The release of chemical messengers increases blood pressure and blood sugar levels. High blood pressure is a major risk and perpetuating factor for heart disease. Hence, ways to respond to this physiological reaction warrant attention. One way is to invoke a relaxation response through various techniques, such as meditation, yoga, progressive muscle relaxation (PMR), guided imagery, small movements or posture change, and breathing instructions (sometimes aided by biofeedback). Typically an individual learns to observe moments of low and high tension in daily life, to practice during restful moments, and to manage periods of high tension in a different way. Dixhoorn and Duivenvoorden (1999) defined relaxation training as training an individual to allow and induce reduction in tension internally, without the use of external means.

Relaxation therapy has been found to be effective as an adjunct to regular medical care and standard cardiac rehabilitation. Linden et al. (1996) in a meta-analysis found that psychosocial intervention, such as stress management, relaxation, and CBT, positively assisted in reducing blood pressure, distress, and cholesterol levels in patients with coronary artery disease. Dixhoorn and White (2005) concluded in their systematic review that relaxation therapy can enhance recovery after cardiac ischemic event and intensive supervised relaxation is imperative for cardiac rehabilitation. Studies found that training in relaxation skills augmented the effects of psychoeducation (Amarosa-Tupler et al. 1989; Cowan et al. 2001; Nelson et al. 1994). Skills such as classical relaxation method and PMR can be taught to individuals through replicating symptoms of flight or fight response and/or anxiety during sessions and practicing them so that they can be applied when stressors arise. In PMR the aim is to reduce neuromuscular hypertension (McGuigan 1993). Similarly, Linden (1993) indicated that in autogenic training, the goal is to restore disturbed psychovegetative balance.

Winterfeid et al. (1993) found positive impact of autogenic relaxation training on blood pressure in patients with coronary heart disease. A high level of blood cholesterol level can contribute to atherosclerosis and an increased risk of heart disease. Furthermore, LDL cholesterol is considered as a major cause of CHD. Pal

et al. (2011) found that regular yoga interventions resulted in reduction in heart rate, body fat, total cholesterol levels, and LDL levels. Yoga practices were found to be beneficial for cardiac and hypertensive patients. Yoga practices also significantly improved blood pressure among people with hypertension (Blumenthal et al. 1989) and cardiovascular disease (Mahajan et al. 1999).

Anxiety in heart disease is sometimes manifested by the presence of panic attacks. These discreet periods of physiological discomfort accompanied by a sense of fear or loss of control are often difficult to recognize as their presentation tends to overlap with the clinical features of coronary heart disease (CHD) and cardiomyopathies (Tully et al. 2015) such as heart palpitations, shortness of breath, and chest pain. Panic attacks have been shown to be alleviated by breathing retraining (Lum 1983; Rapee 1985), mainly as hyperventilation appears to be a key element of the panic attack experience. Used alone, this technique appears to alleviate panic attacks but not necessarily extinguish the continued occurrence of panic. Thus, it should be used in addition to other treatments such as exposure therapy and cognitive restructure so to achieve long-term outcomes in anxious patients with CVD. Hence, relaxation training can be considered as a beneficial adjunct to existing treatment options. Research supports the utility of relaxation practices as it can enhance recovery process. Research particularly in respect to yoga practices was confined to Indian population, and future research could focus on replicating the same in other populations.

Hypnotherapy

Hypnosis or hypnotherapy aims to achieve a heightened state of awareness through the use of guided relaxation, intense concentration, and focused attention. A hypnotic state is believed to allow people to explore painful thoughts, feelings, and memories and enables people to perceive things differently, such as blocking an awareness of pain. Sunnen (2007) advised that self-regulation can have potential beneficial effects on cardiovascular health. Techniques, such as hypnosis/self-hypnosis and autogenic training, are likely to have positive outcomes in patients with stress and hypertension. Prolonged prevalence of stress invariably involves heart functions and can impact blood pressure. Furthermore, interpersonal communications, particularly if they are conflictual in nature, tend to impact the heart in the form of increased cardiac activity. It is recommended that cardiovascular harmony could be achieved by separating the emotional experience of negative emotions from their bodily experience (Sunnen 2007). A hypnotic state of mind and body is a special form of consciousness when awareness becomes more fluid. Using therapeutic means, this fluidity can flow into the body's neural networks and have a positive impact on organ systems. In the deepest stage of hypnosis, it is likely that through thoughts and feelings, the heart can be experienced as being reachable (Brown 1991).

Although hypnosis seems to yield some positive results, it remains a largely underutilized technique which can shorten postoperative hospital stays, promote the

physical recovery of patients from surgery, and aid in the psychological and emotional response of patients following surgery (Blankfield 2011). Indeed research indicates that self-hypnosis has the potential to reduce anxiety following coronary bypass surgery (Ashton et al. 1997). Hypnosis is also recommended as a successful adjunct to cope with heart disease (Doran 1991) and reducing symptoms of hypertension (Gay 2007). In a meta-analysis of surgical patients who had undergone hypnosis, it was found that 89 % of patients who had undergone hypnosis had better outcomes than 89 % of patients in control groups supporting the notion that hypnosis is an effective adjunctive procedure for a wide variety of surgical patients (Montogomery et al. 2002).

Values-Based Counseling and Perceived Locus of Control

Meaning-centered counseling is likely to provide a sense of purpose that is important for emotional well-being and assists an individual with crisis management. Reker (1997) found that personal meaning, social resources, optimistic attitude, positive self-talk, and physical health were predictors of depression in institutionalized elderly. Teaching skills for empowerment, strategies to effectively deal with the diagnosis, psychiatric symptomatology, and perceived control can reduce emotional stress in patients (Dracup et al. 2003). Research also suggests that medical well-being is associated with patient's belief about their ability to alter health-related behaviors (Oxman and Hull 1997). Furthermore, perceived control is associated with fewer symptoms of depression and anxiety in patients with heart disease (Moser and Dracup 1995). Hence, if psychological therapy with an aim to increase perceived control to respond to unpleasant situations is delivered as part of regular treatment of cardiac disease, it is likely to reduce risk of developing clinical symptoms of anxiety and/or depression. Psychoeducation about importance of perceived control and how it could potentially reduce feelings of vulnerability and helplessness could increase engagement. Furthermore, a positive sense of control can increase participation in engaging in activities that are likely to improve the outcome of a distressing situation.

Exercise Therapy

Undertaking rigorous physical activity is one of the greatest challenges in survivors of cardiac events. The fear associated with "exertion" leads to sedentary behaviors which place the patient at risk of future cardiac events. Epidemiological studies have long observed an inverse relationship between exercise and anxiety. Galper (2006) in a cross-sectional study found a strong relationship between mental health and physical activity. The study associated regular physical activity with better mental health and emotional well-being. Furthermore, a longitudinal study found that physical activity was associated with reduced risk of developing a mental health disorder. In a study of 8,098 adults, Goodwin (2003) reported that persons

who indicated that they exercise "regularly" were at reduced risk for being diagnosed with an anxiety disorder compared to their sedentary counterparts. Morgan et al. (2013) reviewed the evidence for the benefits of exercise for anxiety disorders and found that exercise tended to improve symptoms of anxiety.

The relationship between exercise and anxiety has been extensively examined over the last 15 years. Petruzzello et al. (1991) conducted three separate meta-analyses to quantitatively review the exercise–anxiety literature for state anxiety, trait anxiety, and psychophysiological correlates of anxiety. They found that exercise is indeed associated with reductions in anxiety, but only for aerobic forms of exercise. These effects were generally independent of both subject (i.e., age and health status) and descriptive characteristics. For state anxiety, exercise was associated with reduced anxiety, but had effects similar to other known anxiety-reducing treatments (e.g., relaxation). The trait anxiety meta-analysis revealed that random assignment was important for achieving larger effects when compared to the use of intact groups. Training programs also need to exceed 10 weeks before significant changes in trait anxiety occur. This time line is important to emphasize to patients who tend to show attrition after a couple of weeks of exercising due to lack of results.

Stonerock et al. (2015) conducted a critical review of the literature looking at 12 randomized controlled studies which examined exercise training in adults with either high levels of anxiety or an anxiety disorder. This group was chosen as it offers insight into the most acutely exercise phobic group of patients, such as patients with heart disease, who might perceive exercise as a threat to their well-being. They found that exercise provided benefits greater than placebo. However, most studies had significant methodological limitations, including small sample sizes, concurrent therapies, and inadequate assessment of adherence and fitness levels, which makes the findings inconclusive.

Williams et al. (2006) in a clinical review found evidence for positive health impacts of exercise through cardiac rehabilitation programs in patients with CHD, and hence it was recommended as a beneficial adjunct. Regular physical exercise was found to have beneficial effects through decreased sympathetic tone and increased parasympathetic tone (Adamu et al. 2006) and prevented CHD (Hu et al. 1999). The World Health Organization recommended that physical exercise must be sustained in the long term, be regular (at least 4–5 days per week), last for about 30 min, and be of mild to moderate intensity. Although research has yet not determined clear consensus of optimal duration, frequency, and type of exercises in prevention of coronary artery disease, the World Health Organization recommends that in order for exercise to have a positive impact, it needed to meet the aforementioned. Furthermore, patients with MI, who engage in regular exercise, are less likely to develop complications as a result of vigorous exercise (Mittleman et al. 1993). In addition, good evidence suggests that bouts of erratic exercise in middle age or those with a diagnosis of coronary artery disease increased the risk of MI and sudden cardiac death (Corrado et al. 2006).

Conclusions and Future Directions

In conclusion, it can be established that patients with cardiac disease with comorbid anxiety symptomatology are at increased risk of mortality, poor adherence to treatment, and risk of slow recovery. High prevalence of anxiety in CVD warrants that it clearly needs to be routinely assessed, possibly through psychological questionnaires and tests.

Patients with CVD are also at risk of developing complications with antidepressant treatment. When choosing medication in psychiatric morbidity with CVD, clinicians must consider the type and severity of heart disease and the type and severity of psychiatric condition and refer to clinical data evaluating efficacy and safety of a particular medication. Hence, careful examination of risk-to-benefit ratio must be conducted. It is important to note that although research indicates that depression and anxiety in CVD are equally prevalent and can be equally fatal, research in treatment of depression in CVD certainly outweighs research in treatment of anxiety in CVD. Furthermore, the link between anxiety and CVD is well established, and it becomes imperative to differentiate reaction to the experience of a serious physical condition (CVD) from clinical anxiety. Therefore, anxiety in CVD certainly warrants future research for better treatment options and recommendations in respect to efficacy and safety of different psychological and pharmacological treatments. Moreover, research has focused predominantly on the role of anxiety in heart disease, and no differentiation has been made between different types of anxiety disorders. Future research could also focus on identification and treatment options of different anxiety disorders in heart disease.

Considering the mixed outcomes of the side effect profile and potential drug interactions of SSRIs, larger and well-controlled trails are possibly needed to further evaluate efficacy and safety of pharmacological treatment. Furthermore, research has found significant positive outcomes with treatment with CBT, and it is likely that CBT can be considered as having a good efficacy in patients with CVD and depression and/or anxiety. However, research has focused more on treatment of depression symptomatology than anxiety symptomatology in CVD. Although few studies have shown cognitive restructuring to be beneficial, it is important to replicate these studies to evaluate and confirm efficacy. The literature in respect to nonpharmacological intervention treatment for anxiety in cardiac diagnosis is sparse. In addition, it is proposed that fears and apprehensions that patients with CVD experience are somewhat rationale in nature, and future research could potentially also focus on efficacy of other treatment options, such as Acceptance and Commitment Therapy (ACT) and rational emotive therapy. ACT focuses on fostering acceptance of unhelpful thoughts and emotions and aims to enhance committed action toward living a life toward chosen values. It is likely that ACT therapeutic technique could potentially teach clients to better deal with anxiety-related discomfort. In addition, although exercise is known to have a positive impact on anxiety and it can be a great way to help patient regain their physical confidence, there is lack of knowledge on how to best deal with anxiety-related

symptoms, which hinder patients to participate in exercise training. Future research could focus on effective strategies to engage patients in exercise training.

The existence of a relationship between anxiety and CVD has been established in the literature. However, more research is needed into tailored and individualized psychological treatment approaches required to provide evidence-supported treatment to patients with a diagnosis of CVD and clinical anxiety. Additionally, interventions tend to implement one-size-fits-all practice, and diverse individually tailored approaches are likely to address individual risk factors and motivation levels of patients with CVD. Cardiologists need to work alongside mental health professionals to enhance the quality of care and health outcomes in these patients. There needs to be less treatment fragmentation where patients might not see the connection between their anxious state and their heart disease. Of course, more mental health practitioners need to be trained in behavioral medicine to achieve this. Moreover, cardiologists need to be more aware that mental issues are part of their domain and pertinent to the treatment of heart disease. Future research could focus on developing ways in which the disciplines of cardiology and psychiatry/psychology can best work together to elucidate a better understanding of the human heart and the management of its emotions.

References

Adamu, B., Sani, M. U., & Abdu, A. (2006). Physical exercise and health: A review. *Nigerian Journal of Medicine, 15*(3), 190–196.

Alvarez, W., Pharm, D., Pickworth, K., & Pharm, D. (2003). Safety of antidepressants drugs in the patient with cardiac disease: A review of the literature. *Pharmacotherapy, 23*(6), 754–71.

Amarosa-Tupler, B., Tapp, J. T., & Carida, R. V. (1989). Stress management through relaxation and imagery in the treatment of angina pectoris. *Journal of Cardiopulmonary Rehabilitation, 9*, 348–355.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (fifth edition, text revision) (DSM 5)*. Washington, DC: APA.

Ashton, R., Whitworth, G., Seldomridge, J., et al. (1997). Self-hypnosis reduces anxiety following coronary bypass surgery: A prospective randomized trial. *Journal of Cardiovascular Surgery, 38*(1), 69–75.

Barlow, D. H. (1998). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. New York: Guilford Press.

Barlow, D. H., Hayes, S. C., & Nelson, R. (1984). *The scientist practitioner*. Oxford: Pergamon.

Bayazi, M. H., & Rastegari, Y. (2005). Relationship of type-2 behavioral pattern, hardiness and stress and coronary artery disease. *J Psycho Res, 1&2*, 40–58.

Beck, A. T., Emery, G., & Greenberg, R. L. (2004). *Anxiety disorder: The role of psychotherapy in effective treatment*. Washington, DC: American Psychological Association.

Birkenaes, A. B., Sogaard, A. J., & Engh, J. A. (2006). Sociodemographic characteristics and cardiovascular risk factors in patients with severe mental disorders compared to the general population. *Journal of Clinical Psychiatry, 67*(3), 425–433.

Blankfield, R. P. (2011). Suggestion, relaxation, and hypnosis as adjuncts in the care of surgery patients: A review of the literature. *American Journal of Clinical Hypnosis, 33*(3), 172–186.

Blumenthal, J. A., Emery, C. F., Madden, D. J., George, L. K., Coleman, R. E., Riddle, M. W., et al. (1989). Cardiovascular and behavioural effects of aerobic exercise training in healthy older men and women. *Journal of Gerontology, 44*, 147–157.

Blumenthal, J. A., Jiang, W., Babyak, M., et al. (1997). Stress management and exercise training in cardiac patients with myocardial ischemia. *Archives of Internal Medicine, 157*, 2213–2223.

Braunwald, E., Zips, P., Lippy, P., & Bonow, R. (2004). *Heart disease*. Elsevier Health Sciences (7th edn).

Brown, P. (1991). *The hypnotic brain*. New Haven: Yale University Press.

Colquhoun, D. M., Bunker, S. J., Clarker, D. M., Glozier, N., Hare, D. L., Hickie, I. B., Tatoulis, J., Thompson, D. R., Tofler, G. F., Wilson, A., & Branagan, M. G. (2013). Screening, referral and treatment for depression in patients with coronary heart disease. *Medical Journal of Australia, 198*(9), 483–484.

Corrado, D., Migliore, F., Basso, C., et al. (2006). Exercise and the risk of sudden cardiac death. *Herz, 31*(6), 553–558.

Cowan, M. J., Pike, K. C., & Budzynski, H. K. (2001). Psychosocial nursing therapy following sudden cardiac arrest: Impact on two-year survival. *Nursing Research, 50*, 68–76.

Cully, J. A., Stanley, M. A., Deswal, A, Hanania, N, A., Phillips, L. L., & Kunik, M. E. (2010). Cognitive- behavioral therapy for chronic cardiopulmonary conditions: Preliminary outcomes from an open trial. *Journal of Clinical Psychiatry, 12*(4): e1–e6.

Davies, S. J., Ghahramani, P., Jackson, P. R., Noble, T. W., Hardy, P. G., Hippisley-Cox, J., et al. (1999). Association of panic disorder and panic attacks with hypertension. *The American Journal of Medicine, 107*, 310–316.

Davies, S. J., Jackson, P. R., Potokar, J., & Nutt, J. N. (2004). Treatment of anxiety and depressive disorders in patients with cardiovascular disease. *BMJ, 328*, 939–943.

Denollet, J., & Brutsaert, D. L. (1998). Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. *Circulation, 97*, 167–173.

Dixhoorn, J. J., & Duivenvoorden, H. J. (1999). Effect of relaxation therapy on cardiac events after myocardial infarction: A 5 year follow-up study. *Journal of Cardiopulmonary Rehabilitation, 19*, 178–185.

Dixhoorn, J., & White, A. (2005). Relaxation therapy for rehabilitation and prevention in ischaemic heart disease: A systematic review and meta-analysis. *European Journal of Cardiovascular Prevention and Rehabilitation, 12*, 193–202.

Doran, G. (1991). Hypnosis as an adjunct to coping with heart disease. *Australian Journal of Clinical Hypnotherapy and Hypnosis, 12*(2), 1–5.

Dracup, K., Westlake, C., Erikson, V. S., Moser, D. K., Caldwell, M. L., & Hamilton, M. A. (2003). Perceived control reduces emotional stress in patients with heart failure. *Journal of Heart and Lung Transplantation, 22*, 90–93.

Draguns, J. G., & Tanaka-Matsumi, J. (2003). Assessment of psychopathology across and within cultures: Issues and findings. *Behaviour Research and Therapy, 41*, 755–776.

Durham, R. C., & Turvey, A. A. (1987). Cognitive therapy vs. behaviour therapy in the treatment of chronic general anxiety. *Behavior Research Therapy, 25*, 229–234.

Fehder, W. P. (1999). Alterations in immune response associated with anxiety in surgical patients. *CRNA, 10*, 124–129.

Fleet, R. F., Dipuis, G., Marchand, A., et al. (1998). Panic disorder in coronary artery disease patients with noncardiac chest pain. *Journal Psychosomatic Research, 44*, 81–90.

Frasure-Smith, N., & Lesperance, F. (2008). Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Archives of General Psychiatry, 65*(1), 62–71.

Friedman, M., Thoresen, C. E., Gill, J. J., et al. (1986). Alteration of type A behaviour and its effect on cardiac recurrences in post myocardial infarction patients: A summary of the recurrent coronary prevention project. *American Heart Journal, 112*, 653–655.

Frijda, N. H. (1986). *The emotions*. UK: Cambridge University Press.

Galper, D. I. (2006). Inverse association between physical inactivity and mental health in men and women. *Medicine & Science in Sports & Exercise, 38*, 173–178.

Gay, M. C. (2007). Effectiveness of hypnosis in reducing mild essential hypertension: A one-year follow up. *International Journal of Clinical and Experimental Hypnosis, 55*(1), 67–83.

Glassman, A. H., O'Connor, C. M., Califf, R. M., Swedberg, K., Schwartz, P., Bigger, J. T., Jr., et al. (2002). Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA, 288*, 701–709.

Global recommendations on physical activity for health. (2010) World Health Organisation. Switzerland.

Goodwin, R. D. (2003). Association between physical activity and mental disorders among adults in the United States. *Preventive Medicine, 36*, 698–703.

Gudmundsdottir, H., Johnston, M., Johnston, D. W., & Foulkes, J. (2001). Spontaneous, elicited and cued casual attributions in the year following a first myocardial infarction. *British Journal of Psychology, 108*, 237–248.

Gulliksson, M., Burell, G., Vessby, B., Lundin, L., Toss, H., & Svardsudd, K. (2011). Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care Project (SUPRIM). *Archives of Internal Medicine, 171*, 134–140.

Harter, M. C., Conway, K. P., & Merikangas, K. R. (2003). Associations between anxiety disorders and physical illness. *European Archives of Psychiatry and Clinical Neuroscience, 253*(6), 313–320.

Havik, O. E., & Maeland, J. G. (1990). Patterns of emotional reactions after a myocardial infarction. *Journal of Psychosomatic Research, 34*, 271–285.

Hu, F. B., Sigal, R. J., Rich-Edwards, J. W., et al. (1999). Walking compared with vigorous physical activity and risk of type 2 diabetes in women: A prospective study. *JAMA, 282*(15), 1433–1439.

Jacobs, G. D. (2001). *Clinical application of the relaxation response and mind-body in interventions*. Massachusetts: Harvard Medical School and Beth Israel Deaconess Medical Centre.

Janeway, D. (2008). An integrated approach to the diagnosis and treatment of anxiety within the practice of cardiology. *Cardiology in a Review, 17*(1), 36–43.

Kawachi, I., Sparrow, D., Vokonas, P. S., & Weiss, S. T. (1994a). Symptoms of anxiety and risk of coronary heart disease. The normative aging study. *Circulation, 90*(5), 2225–2229.

Kawachi, I., Colditz, G. A., Ascherio, A., et al. (1994b). Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation, 89*(5), 1992–1997.

Kessler, R. C., McGonagle, K. A., Zhao, S., et al. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United Sates: Results from the National Comorbidity Study. *Archives of General Psychiatry, 51*, 8–19.

Kirmayer, L. J. (2001). Cultural variations in the clinical presentation of depression and anxiety: Implications for diagnosis and treatment. *Journal of Clinical Psychiatry, 62*(13), 22–28.

Kubzansky, L. D., & Kawachi, I. (2000). Going to the heart of the matter: Do negative emotions cause coronary heart disease? *Journal of Psychosomatic Research, 48*, 323–337.

Kubzansky, L. D., Kawachi, I., Spiro, A., Weiss, S. T., Vokonas, P. S., & Sparrow, D. (1997). Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the normative aging study. *Circulation, 95*(4), 818–824.

Kubzansky, L. D., Kawachi, I., Weiss, S. T., & Sparrow, D. (1998). Anxiety and coronary heart disease: A synthesis of epidemiological, psychological, and experimental evidence. *Annals of Behavioral Medicine, 20*, 47–58.

Lampe, L. (2013). Drug treatment for anxiety. *Australian Prescriber, 36*, 186–189.

Lavoie, K. L., Fleet, R. P., Laurin, C., Arsenault, A., Miller, S. B., & Bacon, S. L. (2004). Heart rate variability in coronary artery disease patients with and without panic disorder. *Psychiatry Research, 128*(3), 289–299.

Lehnert, H., Lombardi, F., Raeder, E. A., Lorenzo, A. V., Verrier, R. L., Lown, B., et al. (1987). Increased release of brain serotonin reduces vulnerability to ventricular fibrillation in the cat. *Journal of Cardiovascular Pharmacology, 10*, 389–397.

Linden, W. (1993). The autogenic training method of JH Schultz. In P. M. Lehrer & R. L. Woolfolk (Eds.), *Principles and practice of stress management*. NY: Guilford Press.

Linden, W., Stossel, C., & Maurice, J. (1996). Psychosocial interventions for patients with coronary artery disease: A meta-analysis. *Archives of Internal Medicine, 156*, 745–752.

Lloyd-Jones, D. M., Hong, Y., Labarthe, D., et al. (2010). Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic impact goal through 2020 and beyond. *Circulation, 121*, 586–613.

Lum, L. C. (1983). Psychological considerations in treatment of hyperventilation syndromes. *Journal of Drug Research, 8*, 1867–1872.

Maghsudlu, S. (2001). *Rehabilitation of cardiac patients* (1st ed.). Tehran: Teymurzadeh Publications.

Mahajan, A. S., Reddy, K. S., & Sachdeva, U. (1999). Lipid profile of coronary risk subjects following yogic lifestyle intervention. *Indian Heart Journal, 51*, 37–40.

McGuigan, F. J. (1993). Progressive relaxation: Origins, principles and clinical applications. In P. M. Lehrer & R. L. Woolfolk (Eds.), *Principles and practice of stress management*. NY: Guilford Press.

Medich, C., Stuart, E. M., Deckro, J. P., & Friedman, R. (1991). Psychophysiologic control mechanisms in ischemic heart disease: Mind-heart connection. *Journal of Cardiovascular Nursing, 5*, 10–26.

Mittleman, M. A., Maclure, M., Tofler, G. H., et al. (1993). Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *The New England Journal of Medicine, 329*(23), 1677–1683.

Montogomery, G. H., David, D., Winkel, G., Silverstein, J. H., & Bovbjerg, D. H. (2002). The effectiveness of adjunctive hypnosis with surgical patients: A meta-analysis. *Anesthesia & Analgesia, 94*, 1639–1645.

Morgan, A. J., Parker, A. G., Alvarez-Jimenez, M., & Jorm, A. F. (2013). Exercise and mental health: An exercise and sports science Australia commissioned review. *Journal of Exercise Physiology, 16*(4), 64–73.

Moser, D. K., & Dracup, K. (1995). Psychosocial recovery from a cardiac event: The influence of perceived control. *Heart and Lung, 24*, 273–280.

Moser, K. V., & Jong, D. (2005). Depression and anxiety in heart failure. *Journal of Cardiac Failure, 11*(6), 463–466.

Murphy, B. M., Higgins, R. O., Jackson, A. C., Ludeman, D., Humphreys, J., Edington, J., Jackson, A., & Worcester, M. (in press). Patients want to know about the 'cardiac blues'. *Australian Family Physician.*

Nelson, D. V., Baer, P. E., Cleveland, S. E., Revel, K. F., & Montero, A. C. (1994). Six-month follow-up of stress management training versus education during hospitalization for acute myocardial infarction. *Journal of Cardiopulmonary Rehabilitation, 14*, 384–390.

Oxman, T. E., & Hull, J. G. (1997). Social support, depression, and activities of daily living in older heart surgery patients. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 52*, 1–14.

Pal, A., Srivastava, N., Tiwari, S., Verma, N. S., Narain, V. S., Agarwal, G. G., Natu, S. M., & Kumar, K. (2011). Effect of yogic practices on lipid profile and body fat composition in patients of coronary artery disease. *Complementary Therapies in Medicine, 19*, 122–127.

Petruzzello, S. J., Landers, S. J., Hatfield, D. M., Kubitz, K. A., & Salazar, W. (1991). A meta-analysis on the anxiety-reducing effects of acute and chronic exercise. *Sports Medicine, 11*(3), 143–182.

Rapee, R. M. (1985). A case of panic disorder treated with breathing retraining. *Journal of Behavioural Therapy and Experimental Psychiatry, 16*, 63–65.

Reker, G. T. (1997). Personal meaning, optimism and choice: Existential predictors of depression in community and institutional elderly. *Gerontologist, 37*, 709–716.

Roose, S. P., Laghrissi-Thode, F., Kennedy, J. S., Nelson, J. C., Bigger, J. T., Jr., Pollock, B. G., et al. (1998). Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA, 279*, 287–291.

Rothenbacher, D., Hahmann, H., Wusten, B., Koenig, W., & Brenner, H. (2007). Symptoms of anxiety and depression in patients with stable coronary heart disease: Prognostic value and consideration of pathogenetic links. *European Journal of Cardiovascular Prevention and Rehabilitation, 14*, 547–554.

Sardinha, A., & Nardi, A. E. (2012). The role of anxiety in metabolic syndrome. *Expert Reviews Endocrinology and Metabolism, 7*(1), 63–71.

Sauer, W. H., Berlin, J. A., & Kimmel, S. E. (2003). Effects of antidepressants and their relative affinity for serotonin transporter on the risk of myocardial infarction. *Circulation, 108*, 32–36.

Stewart, S. H., Mitchell, T. L., Wright, K. D., & Loba, P. (2004). The relations of PTSD symptoms to alcohol use and coping drinking in volunteers who responded to the Swissair Flight 111 airline disaster. *Journal Anxiety Disorders, 18*(1), 51–68.

Still well, S. B. (2002). *Critical care nursing* (3rd ed., pp. 357–358). London: Mosby.

Stonerock, G. L., Hoffman, B. M., Smith, P. J., & Blumenthal, J. A. (2015). Exercise as treatment for anxiety: Systematic review and analysis. *Annals of Behavioural Medicine, 49*, 542–556.

Strik, J. J., Honig, A., Lousberg, R., Lousberg, A. H., Cheriex, E. C., Tuynman-Qua, H. G., et al. (2000). Efficacy and safety of fluoxetine in treatment of patients with major depression after first myocardial infarction: Findings from a double-blind, placebo-controlled trial. *Psychosomatic Medicine, 62*, 783–789.

Strik, J. J., Denollet, J., Lousberg, R., & Honig, A. (2003). Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *Journal of American College of Cardiology, 42*, 1801–1807.

Strike, P. C., & Steptoe, A. (2005). Behavioral and emotional triggers of acute coronary syndromes: A systematic review. *Psychosomatic Medicine, 67*, 179–186.

Sunnen, G. V. (2007). *Can the mind talk to the heart? Hypnosis, self-hypnosis, autogenic training, and cardiovascular health*. New York: Basic Books.

Szekely, A., Balog, P., Benko, E., Breuer, T., Szekely, J., Kertai, M. D., Horkay, F., Kopp, M. S., & Thayer, J. F. (2007). Anxiety predicts mortality and morbidity after coronary artery and value surgery- A 4 year follow-up study. *Psychosomatic Medicine, 69*, 625–631.

Tousoulis, D., Antonopoulos, A. S., & Antoniades, C. (2010). Role of depression in heart failure-choosing the right antidepressant treatment. *International Journal Cardiology, 140*(1), 12–18.

Tully, P. J., & Cosh, S. M. (2013). Generalized anxiety disorder prevalence and co morbidity with depression in coronary heart disease. *Journal of Health Psychology, 18*, 1601–1616.

Tully, P. J., Baker, R. A., & Knight, J. L. (2008). Anxiety and depression as risk factors for mortality after coronary artery bypass surgery. *Journal of Psychosomatic Research, 64*, 285–290.

Tully, P. J., Wittert, G. A., Deborah, T. A., Beltrame, J. F., Horowitz, J. D., Cosh, S., & Baumeister, H. (2015). Panic disorder and incident coronary heart disease: A systematic review and meta-analysis protocol. *Systematic Reviews, 4*, 33.

Veith, R. C., Lewis, N., Linares, O. A., Barnes, R. F., Raskind, M. A., Villacres, E. C., et al. (1994). Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Archives General Psychiatry, 51*, 411–422.

Vikenes, K., Farstad, M., & Nordrehaug, J. E. (1999). Serotonin is associated with coronary artery disease and cardiac events. *Circulation, 100*, 483–489.

Watkins, L. L., Koch, G. G., Sherwood, A., Blumenthal, J. A., Davidson, J. R., O'Connor, C., & Sketch, M. H. (2013). Association of anxiety and depression with all-cause mortality in individuals with coronary heart disease. *Journal of American Heart Association, 19*, 2(2).

Williams, M. A., Ades, P. A., Hamm, L. F., et al. (2006). Clinical evidence for a health benefit from cardiac rehabilitation: An update. *American Heart Journal, 152*(5), 835–841.

Winterfeid, H. J., Siewert, H., Bohm, J., Frenzel, R., Aurisch, R., Ecke, A., et al. (1993). Autogenic training in hypertension dysregulation after aortocoronary venous bypass operation of coronary heart disease. *Zeitschrift fur die Gesamte Innere Medizin und Ihre Grenzgebiete, 48*, 201–204.

Yeragani, V. K., Jampala, V. C., Sobelewski, E., Kay, J., & Igel, G. (1990). Effects of paroxetine on heart period variability in patients with panic disorder: A study of Holter ECG records. *Neuropsychobiology, 40*, 124–128.

Yeung, A. C., Vekshtein, V. I., Krantz, D. S., Vita, J. A., Ryan, T. J., Jr., Ganz, P., et al. (1991). The effect of atherosclerosis on vasomotor response of coronary arteries to mental stress. *The New England Journal of Medicine, 325*, 1551–1556.

Young, Q. R., Ignaszewski, A., Fofonoff, D., et al. (2007). Brief screen to identify 5 of the most common forms of psychosocial distress in cardiac patients: Validation of the screening tool for psychological distress (STOP-D). *Journal of Cardiovascular Nursing, 22*, 525–534.

Yousefy, A., Khayyam-Nekouej, Z., Sadeghi, M., Ahmadi, S. A., Ruhafza, H., Rabiei, K., & Khayyam-Nekouei, S. A. (2006). The effect of cognitive-behavioral therapy in reducing anxiety in heart disease patients. *ARYA Journal, 2*(2), 84–88.

Psychological and Behavioral Contributions to Rehabilitation and Recovery in Heart Disease

David M. Clarke, Dinali N. Perera, and Melissa F. Casey

Contents

Abstract

From time immemorial, the mind and the body have been closely linked, and research continues to show a high association of depression and anxiety with heart disease. Depression is a risk factor for heart disease as well as risk for poor recovery after a cardiac event. The Whole Person Model described here integrates thinking about thoughts, emotions, bodily symptoms, and health behaviors, and can form the foundation of a powerful rehabilitation or disease

D.M. Clarke (✉) • D.N. Perera • M.F. Casey
Department of Psychological Medicine, Monash University, Monash Health, Clayton, VIC, Australia
e-mail: david.clarke@monash.edu; Dinali.Perera@monashhealth.org; Melissa.Casey1@monashhealth.org

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_49

management program. For real functional recovery to occur, patients need to take control of their lives, and for this to occur considerable behavioral change is often required. Integrating psychological care with physical health care will facilitate this.

Keywords

5A's approach • Cardiac rehabilitation and recovery • Behavior and behavior change • CDSM. *See* Chronic disease self-management (CDSM) • Definition • Depression and anxiety • Diet and smoking • Education • Exercise • Stress management • Telephone- and web-based interventions • Type A behavior • Weight loss programs • Collaborative care • Education programs • Effectiveness of • Whole person model • Cognitive behavioral therapy (CBT) • ICD patients, treatment of • Strategies • Telephone delivery of • Diet • Education • Exercise • Implantable cardioverter defibrillators (ICD) • Interpersonal therapy • Motivational interviewing • Recovery and cardiac rehabilitation. *See* Cardiac rehabilitation and recovery • Smoking • Stress management

Introduction

From time immemorial the mind and the heart have been closely linked. People often speak of the "broken heart" to be associated with grief, and much data provides evidence supporting the increased mortality following bereavement (Martikainen and Valkonen 1996). During the psychosomatic era of the 1930s and since, many studies have investigated the links between personality (for instance, type A, type D, hostility) and heart disease, and this volume chronicles the history and current status of knowledge of the links between the "psyche" and the heart, including the intricate biological connections provided by the autonomic nervous system and the neuroendocrine system.

Medicine, however, has mostly been taking a different path. Ever since Descartes gave permission to split the indivisible "psyche" from the divisible "soma" (Descartes 1641/1972), science and medicine have pursued a relentless reductionistic process to understand the human person: firstly with anatomy and physiology and later, with an increasingly narrower focus, molecular and genetic science.

Reductionistic science has brought enormous advances to clinical medicine and the health of the population, and this is no less evident in the area of heart disease than in other areas. Through new pharmaceuticals and amazing procedural interventions, the outcomes from coronary heart disease have vastly improved, and hospital admissions significantly reduced, over the last 20 years (Mozaffarian et al. 2015). The mortality, in absolute numbers and in proportion of overall deaths, has significantly reduced in those 20 years (NHLBI 2012). With quick intervention, heart muscle can be preserved following an ischemic episode.

However – and there is always an however – there are some areas in which reductionistic science has failed to have much impact and that is in the prevention of heart disease and in the rehabilitation and recovery following a cardiac event.

Heart disease and its common accompaniments of metabolic syndrome and diabetes mellitus are predominantly lifestyle diseases, with the risk factors of diet, exercise, obesity, and smoking being issues of behavior. Taken together – obesity, diabetes, and the metabolic syndrome – Western societies are facing an epidemic (Kereiakes and Willerson 2003). There has, perhaps, been a reduction in smoking, with strong public health messages being effective in some sectors of society. On the other hand, obesity is increasing enormously, with almost two-thirds of the Australian population being overweight or obese (Thorburn 2005), and, in parallel with that, rates of type II diabetes have been increasing worldwide (World Health Organization 2006). Notwithstanding the contribution of genetic predisposition, these are predominantly behavior-related disorders, and behavior change is difficult.

The body and mind are inextricably linked. Over the past decade, there has been an increasing awareness of the role that psychological and behavioral factors play in the onset, course, and recovery of cardiac disease (Compare et al. 2015; Dyer and Beck 2007; Srinivas and Reddy 2013). Three examples of "onset" factors include the link between acute stress (e.g., earthquake) and sudden cardiac death (Leor et al. 1996), stress and acute heat failure (Akashi et al. 2008), and the prospective relationship between depression and cardiac events, with a two to four times increased risk above that of the general population (Kuper et al. 2002). In regard to "course," evidence shows that depression is associated with poorer outcomes even in people with established heart disease (Rutledge et al. 2006). This chapter focuses on the recovery phase. Psychological and cardiac issues cannot be considered separately, and a multidisciplinary approach, adopting the use of psychological and behavioral interventions, is required (Compare et al. 2015). As the Lancet article proclaimed, "There is no health without mental health" (Prince et al. 2007). In this chapter we use, as a framework, the "Whole Person Model," built on the principles of CBT (cognitive behavioral therapy), to explain how bodily health and sickness are linked with emotions, thoughts, and behaviors. To make an impact on the difficult problem of behavior change, we need a multipronged attack. We need to take a holistic view of the problem.

The World Health Organization defines **cardiac rehabilitation** as "the sum of activities required to ensure cardiac patients the best possible physical, mental and social conditions, so that they may, by their own efforts, regain a normal place in the community and lead an active productive life" (WHO 1964). The earliest cardiac rehabilitation programs concentrated on physical training with the aim of improving physical fitness so people could return to work. Over the last 30 years, programs have evolved to use more holistic multidisciplinary approaches, focusing on patient education, modification of risk factors, psychological impact of cardiac events, and overall well-being of patients (Dusseldorp et al. 1999; Bennett 2012; Mampuya 2012). This transformation in cardiac rehabilitation has had a positive impact for those attending, with resulting reduction in mortality, symptom relief, and enhanced well-being. It is a cost-effective intervention that improves quality of life, reduces hospital admissions, and improves survival (Hedback et al. 2001; Mampuya 2012; Shepherd and While 2012). The scandal is that a minority of patients, following a

cardiac event, attend rehabilitation programs (Sundararajan et al. 2004). We need to change the behavior – of both patients and practitioners – to improve this statistic.

The concept of **recovery** is used in a number of different, and sometimes imprecise, ways in health care. In law, of course, it means the restoration of a former right or the regaining of something lost. In medicine, it generally means the restoration of health – or a return to normal, although "normal" is not usually defined.

It is a term, however, that has been used for many years in the addiction field and is now being widely used in mental health. In these settings, its definition is intentionally subjective, determined by the patient. It does not rely or depend on full recovery from the disease but seeks the highest level of functioning despite what impairments might remain and maximal, if not full, engagement in life. Recovery-oriented practice in mental health care seeks full participation of patients in their health-care decisions. It is patient-centered (Shepherd et al. 2008). This model can have enormous advantages in the management of chronic disease, in particular in regard to successful behavior change.

Chronic Disease Self-Management

For all the reasons given above – the success of acute intervention and the growing problem of chronic disease – much attention in health care is now being given to the management of chronic disease and, in particular, the "self-management" of chronic disease. This requires a different focus and a different set of skills to that required in acute medicine. Chronic disease self-management (CDSM) requires full and active engagement of the person with the disease and with health-care practitioners. This in turn requires knowledge about the disease and its causes and complications; knowledge and self-confidence in recognizing symptoms, managing medication, and negotiating the health system when and as required; a general self-efficacy and competence in goal setting and planning; and finally, the social and emotional skills to cope with stress, disappointments, and challenges and to maintain good supportive relationships.

The sometimes quoted joke about how many psychologists are required to change a light globe – one, but the light globe has got to want to change – is fairly true when it comes to behavior change. Kate Lorig, one of the early pioneers in the field of chronic disease self-management (CDSM), and her colleagues, following on from the work of Corbin and Strauss (1988), emphasized three broad categories of tasks involved in disease self-management: (1) medical management, such as taking medications, monitoring illness, and adhering to diet; (2) adapting behaviors and roles in life to fit to limitations caused by the disease; and (3) the management of emotions such as depression, demoralization, anger, hopelessness, etc. (Lorig and Holman 2003). To this we would add a fourth: managing and negotiating the health system (see Fig. 1). Furthermore, life goes on, and while a person may have

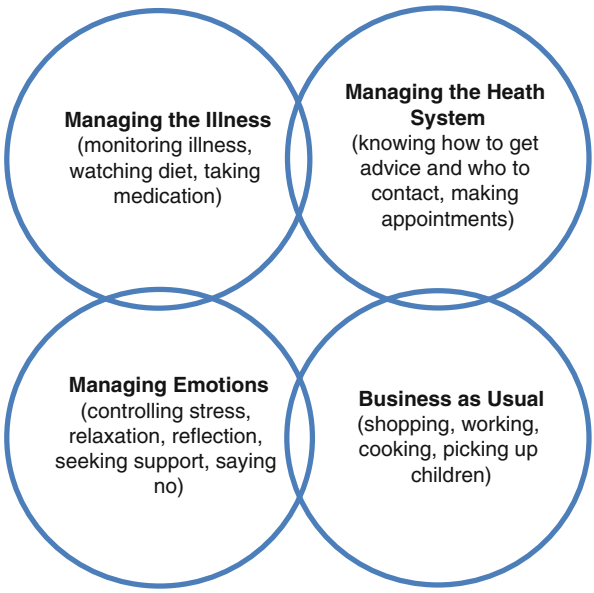


Fig. 1 Four "tasks" in managing your illness

to manage their illness, there is also "business as usual" – meals to cook, shopping to be done, and children to pick up. It takes a fair amount of organization and discipline to accomplish all of this.

In order to achieve these goals, there is a whole set of skills that patients need to learn. These have been studied in a number of programs across a range of chronic diseases by Clark et al. (1991) and are summarized thus to include:

- Recognizing and responding to symptoms and monitoring of physical indicators
- Controlling triggers to symptoms
- Using medicines
- Managing acute episodes and emergencies
- Maintaining nutrition and diet
- Maintaining adequate exercise and activity
- Giving up smoking
- Using relaxation and stress reduction techniques
- Interacting with health-care providers
- Seeking information and using community services
- Adapting to work
- Managing relationships with significant others
- Managing emotions and psychological responses to illness

Current evidence suggests that patients with effective self-management skills make better use of health-care professionals' time and have enhanced self-care (Barlow et al. 2002; Lorig et al. 1999). CDSM programs are reported to be effective

in improving health and health behavior and in reducing use of emergency departments (Lorig et al. 2001).

Despite evidence for the effectiveness of CDSM, there remain significant barriers to their implementation (Kennedy et al. 2014), and Jordan and Osborne (2007) describe the importance of enablers to overcome these barriers. These include doing multifaceted health promotion, empowering patients, strengthening multidisciplinary teams, structuring referral pathways and clinical networks, and making access easier.

Collaborative Care

A key requirement for chronic disease management is collaboration between health professionals. Collaborative care requires good communication between health professionals with clearly defined roles; patient education that facilitates their engagement with, and negotiation through, the health system; and stepped care approaches that provide additional treatments for people with persisting symptoms. A large number of randomized controlled trials have shown the effectiveness of collaborative care approaches over and above standard primary care for people with chronic disease (Katon et al. 2010). A key feature of these successful models is that they incorporate attention to feelings – particularly depression.

Rollman et al. (2009) describe a further development of collaborative care, coordinated by telephone by a nurse care coordinator. Regular contact over a 2–4-month period following CABG surgery, using this telephone-delivered collaborative care, demonstrated improved quality of life, mood symptoms, and physical functioning when compared to usual care.

The Whole Person Model

The Whole Person Model has been described by Baird and Clarke (2011, 2012) and is represented in Fig. 2. Underpinning it is a framework of cognitive behavioral therapy (CBT) that emphasizes, within a strong therapeutic relationship, assisting a patient to explore the problem, whatever it is, in terms of emotions, thoughts, and behaviors (Hawton et al. 1989). Strategies used are typical CBT strategies of behavioral analysis, problem-solving, identifying and expressing emotions, cognitive restructuring, and goal setting (Hawton et al. 1989). The Whole Person Model assists patients to see how thoughts, feelings, behavior, and bodily states are all related – each affecting the other, and it provides a framework for understanding how psychological and behavioral interventions can be used in a rehabilitation setting to maximize patient recovery, functioning, and well-being.

The Whole Person Model has been used in a chronic disease self-management program in heart failure patients, which for the patient involves working through a manual over a 4-week period, with the aid of a health coach or nurse. The manual includes information about the disease process, diet, exercise, and medication, as

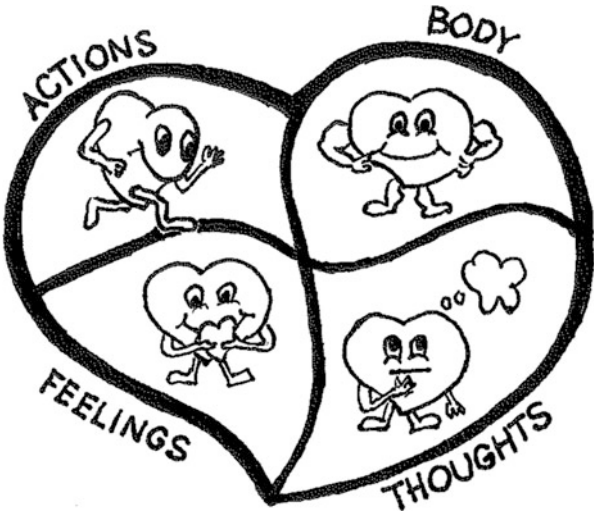


Fig. 2 The Whole Person Model (From Baird and Clarke 2011, 2012)

well as including behavioral exercises and reflective pieces. Importantly it addresses issues of feelings and thoughts as well as behaviors and bodily symptoms. Patients find it a helpful integrating framework. The model – using a manual and a health coach – has also been successfully employed in patients with type 2 diabetes (Clarke et al. 2014).

> Case A: George was a 56 year old businessman who suffered an acute episode of chest pain, with ST-elevation myocardial infarction (STEMI). He underwent a stenting procedure and remained in hospital for 5 days, after which time he was discharged home. Cardiac rehabilitation was mentioned to him as he left the hospital, although he did not take it up. One month after the event he had returned to work, though by his own report he was not performing well. He told the GP, and later the psychologist, that he seemed to be anxious – though he could not see that he had any reason to be worried – and he was not sleeping well. At work, he could not concentrate well, and would often leave early and go home. He had been divorced two years previously and lived alone. At home he seemed to mope around, and watch movies till late at night because he knew he would not sleep. When he took himself to the GP he was feeling desperate. He knew things were going in the wrong direction.

The above story is not uncommon. The heart beats continuously through our lifetime and, if it stops, we die. Problems with the heart engender strong emotions, particularly worry or worse, fear. At an unconscious level and sometimes at a conscious level, it raises very basic existential anxieties about death and mortality. This is particularly true of people who rely on implanted defibrillators (Frizelle et al. 2004).

Using a Whole Person Model, we might assume that all people with heart disease will, to some extent, be stressed. To a greater or lesser extent, they will have anxieties, will be saddened, and may be angry. To a greater or lesser extent, they will face these issues with courage or with avoidance. Their responses may be

adaptive or maladaptive. Because emotions, thoughts, and behaviors are so intertwined, a practitioner working within a Whole Person Model will attend to all areas together. Rather than, for instance, dealing with issues of medication first and then referring to another practitioner because the patient remains depressed, the Whole Person Model practitioner will see that the patient's demoralization has sapped their energy to live and reduced their drive to exercise or participate in rehabilitation (Clarke and Kissane 2002). The depression has made their thinking pessimistic, and they are not regular in taking their medication, let alone looking after themselves. The practitioner working in a Whole Person Model – and this could be a GP, rehabilitation nurse, or health psychologist – will enquire about emotions, listen to the thoughts, and observe the behaviors. They will link them all together and, in doing so, will be able to give the patient an explanation that, in many cases, unlocks their feelings of helplessness. Not understanding leads to not knowing what to do. Sometimes, using the principle of stepped care, the patient will need and benefit from referral to a specialist psychologist or psychiatrist.

In the Whole Person Model, it is not important to rush in and make a diagnosis of depression. Rather it is important to acknowledge the emotions and work with the patient to see how emotions are affecting their thinking (e.g., making them pessimistic) and in turn affecting their behavior (not getting out of bed, not exercising, not eating, not taking medication), which in turn is affecting their health (poor physical recovery).

Cardiac Rehabilitation

Cardiac rehabilitation is effective (Gellis and Kang-Yi 2012), and programs now include the optimization of medical treatment, nutritional counseling, smoking cessation, stress management, exercise, and psychosocial support (Mampuya 2012). They are run by multidisciplinary teams – often based around a physician and cardiac nurses. But they can also usefully employ health coaches, exercise physiologists, pharmacists, and behavioral medicine specialists (psychologists or psychiatrists).

Education is the mainstay of CDSM programs. CDSM education programs "aim to empower patients through providing information, and teaching skills and techniques to improve self-care and doctor-patient interaction, with the ultimate goal of improving quality of life" (Jordan and Osborne 2007). It is assumed, perhaps, that with full information, people will have the requisite knowledge to change and will change. But we know this is not true. In a recent report of an evaluation of a health education program, the authors comment, "it was not enough to effectively self manage. (Patients) were still not shifting the responsibility for their health from the doctor or nurses to themselves. . . .and were not ready to change their unhealthy lifestyles" (Tun 2014). Furthermore, psychoeducational programs effect no change on depression and anxiety (Dusseldorp et al. 1999). Information is crucially important, but it is not enough.

Exercise is also a fundamental component of modern cardiac rehabilitation programs. It is effective in improving and restoring cardiac function post infarction (Lawler et al. 2011) and is also effective in improving recovery in the presence of cardiac failure (Belardinelli et al. 2012).

Furthermore, exercise, even in the elderly and tailored to a person's limited ability, is effective in reducing depression (Bridle et al. 2012).

Despite all this evidence, there is still a tendency for people to think that exercise is dangerous for those with heart disease (Bethell 1999), and patients, and sometimes also nurses, are anxious about exercising in the presence of breathlessness – despite the potential benefits of exercise for people with cardiac failure (Coats et al. 1992). Therefore, encouraging people to exercise regularly requires more than just education. It requires behavioral activation involving graded exercise while taking seriously a person's fears and concerns – but challenging them gently. It needs goal planning, gaining little successes, a step at a time. Over time, people gain confidence and can start to enjoy exercise. Athletes training for the Olympics build up their fitness in graded and measured steps. So must cardiac patients. This requires perseverance on the part of the patient and encouragement on the part of the clinician/coach who is assisting them.

Cardiac rehabilitation programs also generally include **stress management** interventions to help patients identify, avoid, and deal with stressful situations. Stress reduction techniques include meditation, controlled breathing, and yoga (Collins and Rice 1997; Mampuya 2012) and, when used with cognitive and behavioral strategies, give good results in the cardiac rehabilitation setting (Pedersen et al. 2007).

Diet and **smoking** also need to be considered here. Each is a significant lifestyle risk factor for cardiovascular disease, and each needs to be dealt with in a rehabilitation program that seeks to improve outcomes for cardiac patients, and yet, they are notoriously difficult behaviors to change. Education – the giving of information – is important but is not enough. Each requires assessment of motivation and behavioral activation.

In a Cochrane review, Barth et al. (2015) examined 40 RCTs of smoking cessation programs involving behavioral therapies, telephone support, and self-help material. Each had positive effects on abstinence at 12 months, with more intensive interventions being associated with greater quit rates.

Reviews of the literature have demonstrated that behavioral interventions which have included behavioral counseling, telephone support, and/or self-help material have been shown to assist with smoking cessation in CHD patients (Barth et al. 2006, 2015; Bennett 2012; Dyer and Beck 2007).

Although many people are pessimistic about losing weight, a Cochrane review of **weight loss programs**, involving 18 RCTs, showed a significant overall weight loss effect, with average weight reduction ranging from 3 % to 9 % of body weight over periods of roughly 4–36 months (Mulrow et al. 2000). Heterogeneity of studies did not allow a more detailed evaluation of whether some programs were better than others.

Friedman and Rosenman (1959) first described **type A behavior** as a particular characteristic that they observed in their patients. Its key features included

ambitious and competitive behavior, impatience, aggressiveness, and hostility (Bunker et al. 2003; Friedman and Rosenman 1974; Kohli and Malhotra 2008; Sirri et al. 2012). In addition, type A behavior is associated with a tendency to minimize the impact of a life-threatening illness, and these components can adversely affect the rehabilitation process (Sirri et al. 2012).

In the 1980s, type A behavior was considered an independent risk factor for coronary heart disease, although subsequent contradictory findings have led this to be reviewed and the topic to be controversial (Bunker et al. 2003). Recent studies, however, using structured diagnostic interview – in contrast to the self-report measures used in earlier studies – have found a substantial increase in type A behavior in cardiac patients when compared to noncardiac medically ill persons (Sirri et al. 2012). Education around type A has historically been a part of some cardiac rehabilitation programs, and studies do show that type A behavior can be reduced in coronary patients through a relatively short intervention aimed at behavior change (Sebregts et al. 2005).

Managing Depression and Anxiety in the Cardiac Patient

The Problem

It is well documented in the literature that there is a high prevalence of depression, anxiety, and stress in patients who experience cardiac events (Colquhoun et al. 2013; Compare et al. 2011; Mampuya 2012; Whalley et al. 2014; Lichtman et al. 2014; O'Neil et al. 2014; Celano and Huffman 2011). Cardiac events, as well as the associated medical and surgical treatments, can be frightening, if not traumatic, and lead to the development of psychological symptoms and unhealthy behaviors (Whalley et al. 2014). Major depressive disorder (MDD) has been found to occur in 15–20 % of patients, an approximately threefold higher rate than that found in the general population (Colquhoun et al. 2013; Huffman et al. 2013). If we include milder forms of depression, the rate increases to over 40 % (Colquhoun et al. 2013).

Anxiety and stress, also, are very prevalent in patients with heart disease, with rates reported between 41 % and 80 % (Moser 2007; Abed et al. 2014). People with implanted defibrillator experience even greater levels of anxiety (Dyer and Beck 2007; Frizelle et al. 2004; Lewin et al. 2009; Pedersen et al. 2007; Maia et al. 2014).

Unfortunately, depression and anxiety often go unrecognized and untreated (Baird and Clarke 2011; Celano and Huffman 2011; Rutledge et al. 2013). It may be considered "normal" to be depressed after a cardiac event (Colquhoun et al. 2013), or the fatigue may be considered to be a symptom of the heart disease rather than an indication of depression.

Depression and anxiety have a number of significant consequences on quality of life and prognosis from heart disease. A rich literature has consistently identified depression and anxiety to be risk factors for poor prognosis, recurrent cardiac events, and increased mortality (Clarke and Currie 2009; Bennett 2012; Compare et al. 2011;

Celano and Huffman 2011; Dyer and Beck 2007; Lichtman et al. 2014; Mampuya 2012). Depression and anxiety have also been found to be associated with poor uptake of healthy lifestyle habits and cardiac risk-reducing behaviors (Abed et al. 2014). Psychological symptoms following coronary events are associated with lower exercise capacity, increased hospitalizations, fatigue, reduced QOL, and a lower sense of well-being (Abed et al. 2014; Colquhoun et al. 2013; Ladapo et al. 2012).

The Treatment

The efficacy of psychological interventions, such as CBT, in the treatment and management of depression and anxiety is unarguable (Dyer and Beck 2007; Jordan et al. 2007). However, these have not been extensively applied and tested in cardiac patients. Nevertheless, there are a small number of relevant studies. A mixture of psychological interventions have been shown to give added benefit in reducing psychological symptoms in cardiac rehabilitation settings (Colquhoun et al. 2013; Dickens et al. 2013; Linden et al. 2007; Rutledge et al. 2013; Whalley et al. 2014; Compare et al. 2015). More specifically, in the ENRICHD study, using an RCT design, CBT was found to be modestly effective in reducing depression symptoms compared to usual care (Berkman et al. 2003).

Interpersonal therapy also has a proven effectiveness in treating depression (Elkin et al. 1989) and has the appeal of focusing on the issues of grief, role transitions, and/or interpersonal role disputes – all potentially relevant to people suffering incapacity following a cardiac event. Its use has been described in cardiac patients (Koszycki 2006), although in the CREATE trial it was shown not to be effective (Lesperance et al. 2007).

Due to the limited amount of research in this area, it is difficult to know which types of psychological interventions are the most useful and in what settings. In the review by Dickens et al. (2013) of 64 trials of psychological interventions to treat depression in patients with heart disease, they found evidence for the effectiveness of problem-solving, general education, skills training, relaxation, and CBT, although they acknowledge that the effects sizes are small and, in the best quality trials, only CBT showed significant, albeit small, effects. The Cochrane systematic review conducted by Whalley et al. (2014) identified 22 studies of interventions to treat anxiety, depression, and type A behavior and to improve disease adjustment. Components of treatments included relaxation exercises, cognitive restructuring, risk education, self-awareness and self-monitoring, homework exercises, and emotional support. They found small to moderate effects for interventions treating depression and anxiety.

Although this chapter is not about pharmacological treatments, it is perhaps useful to note here that, similar to psychological treatments, there have been a small number of trials of antidepressant medication treatments in cardiac patients, with mixed results. In general antidepressant medications are effective in reducing depression in cardiac patients. The SADHART study showed that sertraline was more effective than placebo (Glassman et al. 2002), and the CREATE study showed citalopram, also, was effective in treating depression (Lesperance et al. 2007).

On the other hand, in the MIND-IT study, mirtazapine was no more effective than placebo (van den Brink et al. 2002).

The evidence that depression is a risk factor for coronary heart disease, cardiac events, and outcomes in heart disease is strong (Colquhoun et al. 2013). Given that, it would be nice to demonstrate that treatments that are effective in treating depression also have an effect on the course of heart disease. Unfortunately, this has not been robustly shown in a number of studies. The meta-analysis conducted by Rutledge et al. (2013) concludes that psychiatric treatments (pharmacotherapy or psychological interventions) did not reduce total mortality, although there was moderate efficacy for reducing CHD events and improving depression.

Implantable Cardioverter Defibrillator: A Special Case

Patients with implantable cardioverter defibrillators (ICD) arguably present special challenges and opportunities. Patients with ICDs have high levels of anxiety, chiefly around anticipation of the defibrillator being triggered and fears that the device may malfunction. This is accompanied by potentially distorted or exaggerated beliefs and avoidance behaviors. ICD patients are therefore vulnerable to developing depression and anxiety disorder (Maia et al. 2014).

Early research work suggests that psychological interventions are valuable for this group of patients (Bennett 2012; Pedersen et al. 2007; Maia et al. 2014). CBT has been shown to be effective in the treatment of ICD patients with depression and/or anxiety (Frizelle et al. 2004; Lewin et al. 2009; Maia et al. 2014; Pedersen et al. 2007). CBT applied in this population has incorporated techniques of psychoeducation, cognitive restructuring, modifying dysfunctional and catastrophic beliefs, establishing weekly goals, and developing healthy coping strategies. Furthermore, doubts and misunderstandings related to the use of the device are clarified, enhancing understanding and awareness of the patient's medical condition (Maia et al. 2014).

A study conducted by Lewin et al. (2009) showed that a home-based CBT rehabilitation program for ICD patients was able to improve QOL, reduce the incidence of clinically significant psychological distress, and significantly reduce unplanned readmissions. The home-based program included education about common fears, relaxation tapes, goal-setting diaries, and regular telephone calls and was considered a cost-effective and easily implemented method for delivering rehabilitation and psychological care to patients undergoing ICD implantation (Lewin et al. 2009).

Behavior and Behavior Change

The Problem

Depression, anxiety, and subsequent cognitions experienced by cardiac patients can lead to developments of unhealthy illness behaviors and risky health behaviors (Gallo et al. 2004; Bennett 2012). Depressed and anxious patients are likely to have

fewer appropriate coping responses to stressful conditions and commonly experience a lack of control, feelings of helplessness and powerlessness, and worry about their health and the possible recurrence of health problems (Clarke et al. 2006; Bennett 2012; Abed et al. 2014). This can cause them to engage in avoidance behaviors and fail to attend to their own health-care needs. As a result, such people are less likely to reduce risky behaviors such as smoking, unhealthy eating, and physical inactivity (Abed et al. 2014; Colquhoun et al. 2013). This is particularly relevant in cardiac failure patients with limited exercise tolerance and in patients with defibrillators. These patients readily choose not to engage in physical exercise (Frizelle et al. 2004; Lewin et al. 2009; Maia et al. 2014). Mood and expectations can also impact on a person's ability to return to work. Depression has been consistently associated with delayed or failure to return to previous work (Bennett 2012).

Psychological symptoms, and especially negative emotions and cognitions, have been shown to interfere with the rehabilitation process (Abed et al. 2014; Rutledge et al. 2013). They are a barrier to making and sustaining behavior change (Gallo et al. 2004) and are associated with reduced participation in rehabilitation programs and adherence to regimens (Beckie et al. 2011; Bennett 2012; Colquhoun et al. 2013; Dyer and Beck 2007; Rutledge et al. 2013). Distressed patients are less likely to attend cardiac rehabilitation classes than those with little distress (Bennett 2012). Furthermore, nonattendance in cardiac rehabilitation is associated with erroneous health beliefs and maladaptive coping strategies (Dyer and Beck 2007; Whitmarsh et al. 2003).

The Solution

Helping patients to become motivated and active in health behavior change has proven to be a challenging task for health-care providers (Peitrabissa et al. 2015; Shinitzky and Kub 2001). Therefore, interventions that include strategies to promote behavior change and reward changes are likely to be more effective than standard educational programs (Bennett 2012). It is for this reason that cardiac rehabilitation programs generally make explicit the goals of behavior change as well as focusing on symptom control and emotional impact (Bennett 2012). This requires both cognitive and behavioral interventions to modify unhelpful thoughts, acknowledge distressing feelings and fears, and work toward changing behaviors (Whalley et al. 2014; Beckie et al. 2011; Beswick et al. 2005; Charlson et al. 2014; Pietrabissa et al. 2015; Stawnychy et al. 2014; Thompson et al. 2011).

A number of patient characteristics have been identified as being linked with successful behavior change. Unsurprisingly, patients with positive affect, and subsequent increased self-efficacy and confidence, are more likely to sustain positive behavior change (Charlson et al. 2014), again underlining the importance of treating the whole person. Positive emotions and cognitions (i.e., optimism, perceived control, and contentment) may represent resilience in individuals with CHD (Gallo et al. 2004) and are an essential requirement for behavior change.

Common behavior change interventions separate to cognitive behavior therapy include **motivational interviewing** techniques, models adopting the transtheoretical model of change, and the 5A's approach (Beswick et al. 2005; Harris and Lloyd 2012; Pietrabissa et al. 2015; van Nes and Sawatzky 2010; Shinitzky and Kub 2001; Stawnychy et al. 2014; Thompson et al. 2011).

Motivational interviewing techniques are arguably very important in motivating and facilitating positive health behavior change (Beswick et al. 2005; Pietrabissa et al. 2015; van Nes and Sawatzky 2010; Stawnychy et al. 2014; Thompson et al. 2011). Motivation interviewing is a client-centered method for enhancing intrinsic motivation to change by exploring and resolving a patient's ambivalence (Castelnuovo et al. 2014). Techniques include the use of empathy, the identification of the discrepancy between the life the person is leading and the life they would like to lead, encouragement for the patient to develop reasons for change by engaging the patient in leading their problem-solving process, and supporting the patient's self-efficacy so they believe they can change (Miller and Rollnick 2013). There have been mixed findings regarding the effectiveness of motivational interviewing in cardiac rehabilitation, both in the short term and the long term (Castelnuovo et al. 2014). Some studies have reported motivational interviewing to be effective in changing unhealthy behaviors in cardiac patients (e.g., Beckie et al. 2011; van Nes and Sawatzky 2010; Pietrabissa et al. 2015); however, some have also demonstrated no change or a worsening of anxiety and other psychological outcomes following motivational interviewing (Chair et al. 2012, 2013).

In a review conducted by Beswick et al. (2005), specifically looking at the outcome of adherence and attendance, the use of motivational interviewing techniques and communications was found to be associated with improved attendance and involvement in cardiac rehabilitation (Beswick et al. 2005). Techniques used included the use of motivational letters, pamphlets with information, and telephone calls designed to influence acceptance and attendance.

The **5A's approach** (Ask, Assess, Advise/Agree, Assist, Arrange) is another interesting behavioral approach that has been used in primary health-care prevention and also adopted to address behavioral risk factors in cardiovascular disease. It incorporates assessment of readiness to change and provision of motivational interviewing (Harris and Lloyd 2012). Behavioral risk factors targeted using these techniques include smoking, nutrition, alcohol, physical activity, and weight. This approach may be effective in the prevention or management of behavioral risk factors, but there is much work to be done to translate this into Australian practice (Harris and Lloyd 2012).

Telephone and Web-Based Interventions

To increase uptake of psychological treatments, a number of groups have experimented with telephone- or web-based interventions, of essentially a psychoeducation nature, using a cognitive behavioral framework. These have

some positive effect. Telephone delivery of CBT has been successfully trialed in the treatment of depression and anxiety disorders (Muller and Yardley 2011).

A recent tele-health program conducted by O'Neil et al. (2014) involved cardiac patients receiving ten CBT sessions over a 6-month period primarily aimed at reducing depression. The program involved a psychologist using techniques of motivational interviewing, goal setting, behavioral activation, and cognitive restructuring. It demonstrated effectiveness in reducing depression and anxiety symptoms.

There have also recently been developed web-based treatments for cardiac patients which have been shown to reduce depression and anxiety (Dew et al. 2004; Kuhl et al. 2006; Messerli-Burgy et al. 2012). These techniques may assist in overcoming barriers to people being involved in rehabilitation programs – barriers such as distance, time, and travel – although adherence and attrition appear to be common challenges for these types of interventions also (Habibovic et al. 2014).

Improving Uptake of Rehabilitation Programs

A range of treatments – education, support, motivational interviewing, exercise, stress reduction, cognitive therapy, behavioral planning and reinforcement, etc. – are effective in aiding the recovery of cardiac patients. Such treatments can be organized into programs and offered to patients. The challenge is how to get patients to participate. Like any other behavior change, this depends on knowing the value of something, knowing how to access it, and minimizing the barriers, including cost. Cardiac rehabilitation has proven benefits. It is recommended, supported with level I evidence, by the major cardiac societies (Antman et al. 2004). But it is underutilized. In the UK, for instance, the rate of attendance is about 30 % of what best practice would dictate, and this number is falling (Bethell et al. 2006). In Australia, this figure is about 50 % (Worcester et al. 2004).

Barriers to uptake of cardiac rehabilitation include lack of awareness and referral by health services (Scott et al. 2003). On the part of patients, age and transport create significant physical impediments (Worcester et al. 2004).

People who attend cardiac rehabilitation tend to understand the consequences of their illness, are concerned about it, understand the role of cardiac rehabilitation, and believe it is necessary. They tend to use problem-focused and emotion-focused coping more than others (Cooper et al. 2007; Whitmarsh et al. 2003). On the other hand, nonattendance or early drop out is associated with a low perception of the consequences and a low perception of treatment controllability (Whitmarsh et al. 2003; Yohannes et al. 2007). Psychological distress is generally associated with early drop out (Casey et al. 2008; Yohannes et al. 2007). However, as with any treatment program where some level of distress or concern is required to motivate a person to initially seek treatment, some relief of the distress through the instilling of hope is also necessary to keep them in treatment (Yalom 1995).

There has been little practical research done to date on mechanisms to improve uptake of cardiac rehabilitation programs (Beswick et al. 2005). Clearly, the above data tells us that there needs to be better information and stronger referral pathways. It also seems, however, as if the process of rehabilitation needs to begin early – when the patient is in hospital or in the cardiology clinic having their stent. Uptake of a referral will be enhanced if patients have better and earlier information about their condition and what they can do about it and have their questions and fears (thoughts and feelings) listened to and addressed. And finally, patients need to be assisted with the practical barriers. There seems to be a role here for an "in-reach" nurse – a cardiac rehabilitation nurse visiting the clinic, spruiking the benefits of cardiac rehabilitation.

Conclusion

The data presented in this chapter shows overwhelmingly that a holistic style of cardiac rehabilitation has a lot to offer patients. Education about the disease, treatment, diet, and exercise is important but needs a behavioral program to facilitate real change. Cognitive and behavioral techniques can be used to facilitate change in diet, exercise, and compliance to medications, while addressing the fears associated with illness and barriers that exist in the way of patients making healthy life choices. Cardiac rehabilitation and self-management programs have tended to be either exercise based (Heran et al. 2011) or education based (Lorig and Holman 2003). They need to be holistic, paying due attention to the thoughts and feelings of patients. It is these thoughts and feelings that are the barriers to full participation, but paradoxically, it is the thoughts and feelings which will drive the motivation and commitment for significant change. Combined with a strong psychoeducational component, a CBT framework provides the structure and tools to do this, utilizing any of the many techniques available: stress reduction, relaxation, problem-solving, cognitive therapy, goal planning, pleasant events scheduling, graded exposure, etc. Patients can learn to look after themselves, eat well, get exercise, and treasure relationships such that they can live a full and satisfying life (Clarke 2007). The Whole Person Model is a way to help patients understand how their thoughts and feelings impact upon on their health and health choices.

The specific role of psychiatrists and psychologists in this field has been mapped out in the model of consultation-liaison psychiatry (Wise and Rundell 2002), which, as the name suggests, has a dual focus. We can work directly with patients, but we also have a role in assisting the design and structure of the programs, thinking about the referrals' pathways and the barriers, and supporting the frontline staff. Cardiac patients generally do not want to see a psychologist or a psychiatrist. They have a heart problem after all. But we can support the frontline staff to facilitate psychologically and behaviorally informed recovery-focused care. Patients who are distressed should be referred to a psychologist or psychiatrist.

Although there is a dearth of good data supporting the efficacy of treatments for anxiety and depression in cardiac patients specifically, there is plenty of general

data informing best practice, and, unless there is a particular contraindication, patients should not be denied this best practice treatment. The data shows that outcomes, when there is depression and/or anxiety, are poor. A range of first-line and, if necessary, second-line treatments for depression or anxiety should be employed (Casey et al. 2012).

To achieve optimal outcomes, therefore, in a rehabilitation setting, mental health professionals can play a major role by (1) helping design a rehabilitation program based on solid behavioral principles, (2) providing support and advice to staff and helping to maintain a positive environment, (3) providing psychoeducation and coping skills training to patient groups, and (4) and providing specific psychological or behavioral interventions for individual patients when required (Dyer and Beck 2007; Rutledge et al. 2013; Whitmarsh et al. 2013).

Case B: George was a 56 year old businessman who suffered an acute episode of chest pain, with ST-elevation myocardial infarction (STEMI). He underwent a stenting procedure, and remained in hospital for 5 days. On day 4, he was visited by a cardiac nurse named Angela, who went to talk to him about a referral to cardiac rehabilitation. She introduced herself and then pulled up a chair and sat down. She started saying a little about what she knew about George's condition, and advised him that he would be referred for rehabilitation. She then noticed that he was looking very distressed, with his eyes starting to moist up. What was wrong, she thought. What had she said? So she asked him.

George told her how frightened he was. He had been increasingly miserable, perhaps even depressed, since his divorce two years ago. His relationship with his children was terrible, and he felt increasingly isolated and lonely. The quality of his work had deteriorated because he was finding it hard to give it the full concentration. He was sure that people at work had noticed this. His life was falling apart. By this time the tears were flowing, and Angela started to feel uncomfortable. She felt she probably needed some help here. She continued, by acknowledging his awful predicament, and asking him a few more questions to allow him to continue. He expressed the idea that perhaps the heart attack was a punishment for him, and that he may not survive it.

After another fifteen minutes – though it seemed like an hour to Angela – she repeated her recommendation, coming from the cardiology team, that he go to the rehabilitation program. She acknowledged that it might be hard for him, but emphasised that it was important. Because of his intense sadness, she asked George whether he would like a visit from a psychologist who she knew could help him, and he agreed. In parting, she indicated that she would come and see him again tomorrow, and would then see him on his first day at the rehabilitation programme. She suggested she organise transport for the first day, which he accepted.

References

Abed, M. A., Kloub, M. I., & Moser, D. K. (2014). Anxiety and adverse health outcomes among cardiac patients: A biobehavioral model. *Journal of Cardiovascular Nursing, 29*(4), 354–363.

Akashi, Y. J., Goldstein, D. S., Barbaro, G., & Ueyama, T. (2008). Takotsubo cardiomyopathy: A new form of acute, reversible heart failure. *Circulation, 118*, 2754–2762.

Antman, E. M., Anbe, S. T., Armstrong, P. W., Bates, E. R., Green, L. A., Hand, M., ... Ornato, J. P. (2004). ACC/AHA guideline for the management of patients with ST-elevation myocardial infarction: Executive summary: A report of the American College of Cardiology and

American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, *44*, 671–719.

Baird, D., & Clarke, D. M. (2011). The whole person model: A collaborative approach to chronic disease management. *Health Issues, 106*, 21–26.

Baird, D., & Clarke, D. M. (2012). Thinking about the whole person: A collaborative model for chronic disease. *Primary Times, 12*(1), 8–10.

Barlow, J., Wright, C., Sheasby, J., Turner, A., & Hainsworth, J. (2002). Self-management approaches for people with chronic conditions: A review. *Patient Education and Counseling, 48*(2), 177–187.

Barth, J., Bengel, J., & Critchley, J. (2006). Efficacy of psychosocial interventions for smoking cessation in patients with coronary heart disease: A systematic review and meta-analysis. *Annals of Behavioral Medicine, 32*(1), 10–20.

Barth, J., Jacobs, T., Daha, I., & Critchley, J. A. (2015). Psychosocial interventions for smoking cessation in patients with coronary heart disease. Cochrane Database of Systematic Reviews 7: CD006886

Beckie, T. M., Beckstead, J. W., Schocken, D. D., Evans, M. E., & Fletcher, G. F. (2011). The effects of a tailored cardiac rehabilitation program on depressive symptoms in women: A randomized clinical trial. *International Journal of Nursing Studies, 48*(1), 3–12.

Belardinelli, R., Georgiou, D., Cianci, G., & Purcaro, A. (2012). 10-year exercise training in chronic heart failure: A randomized controlled trial. *Journal of the American College of Cardiology, 60*(16), 1521–1528.

Bennett, P. (2012). Cardiovascular rehabilitation. In P. Kennedy (Ed.), *The Oxford handbook of rehabilitation psychology* (pp. 337–350). New York: Oxford University Press.

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catelier, D., Cowan, M. J. … Schneiderman, N. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The enhancing recovery in coronary heart disease patients enriched randomized trial. *Journal of the American Medical Association*, *289*(23), 3106–3116.

Beswick, A. D., Rees, K., West, R. R., Taylor, F. C., Burke, M., Griebsch, I., … Ebrahim, S. (2005). Improving uptake and adherence in cardiac rehabilitation: Literature review. *Journal of Advanced Nursing*, *49*(5), 538–555.

Bethell, H. J. N. (1999). Exercise in cardiac rehabilitation. *British Journal of Sports Medicine, 33*, 79–86.

Bethell, H. J. N., Evans, J. A., Turner, S. C., & Lewin, R. J. P. (2006). The rise and fall of cardiac rehabilitation in the United Kingdom since 1998. *Journal of Public Health, 29*(1), 57–61.

Bridle, C., Spanjers, K., Patel, S., Atherton, N. M., & Lamb, S. E. (2012). Effect of exercise on depression severity in older people: Systematic review and meta-analysis of randomised controlled trials. *British Journal of Psychiatry, 201*(3), 180–185.

Bunker, S. J., Colquhoun, D. M., Esler, M. D., Hickie, I. B., Hunt, D., Jelinek, V. M., … Tonkin, A. M. (2003). " Stress" and coronary heart disease: Psychosocial risk factors. *The Medical Journal of Australia*, *178*(6), 272–276.

Casey, E., Hughes, J. W., Waechter, D., Josephson, R., & Rosneck, J. (2008). Depression predicts failure to complete phase II cardiac rehabilitation. *Journal of Behavioural Medicine, 31*(5), 421–431.

Casey, M. F., Perera, D. N., & Clarke, D. M. (2012). Psychosocial treatment approaches to difficult-to-treat depression. *MJA Open, 1*(Suppl 4), 52–55.

Castelnuovo, G., Pietrabissa, G., Manzoni, G., Cappella, E. A., Baruffi, M., Malfatto, G., … Molinari, E. (2014). The need of psychological motivational support for improving lifestyle change in cardiac rehabilitation. *Experimental and Clinical Cardiology*, *20*(Settembre), 4856–4861.

Celano, C. M., & Huffman, J. C. (2011). Depression and cardiac disease: A review. *Cardiology in Review, 19*(3), 130–142.

Chair, S. Y., Chan, S. W. C., Thompson, D. R., Leung, K. P., Ng, S. K. C., & Choi, K. C. (2012). Short-term effect of motivational interviewing on clinical and psychological outcomes and health-related quality of life in cardiac rehabilitation patients with poor motivation in Hong Kong: A randomized controlled trial. *European Journal of Preventive Cardiology, 19*(6), 1383–1392.

Chair, S. Y., Chan, S. W., Thompson, D. R., Leung, K. P., Ng, S. K., & Choi, K. C. (2013). Long-term effect of motivational interviewing on clinical and psychological outcomes and health-related quality of life in cardiac rehabilitation patients with poor motivation in Hong Kong: A randomized controlled trial. *Clinical Rehabilitation, 27*(12), 1107.

Charlson, M. E., Wells, M. T., Peterson, J. C., Boutin-Foster, C., Ogedegbe, G. O., Mancuso, C. A., ... Isen, A. M. (2014). Mediators and moderators of behavior change in patients with chronic cardiopulmonary disease: The impact of positive affect and self-affirmation. *Translational Behavioral Medicine*, *4*(1), 7–17.

Clark, N. M., Becker, M. H., Janz, N. K., Lorig, K., Rakowski, W., & Anderson, L. (1991). Self-management of chronic disease by older adults: A review and questions for research. *Journal of Aging and Health, 3*(1), 3–27.

Clarke, D. M. (2007). Growing old and getting sick: Maintaining a positive spirit at the end of life. *Australian Journal of Rural Health, 15*, 148–154.

Clarke, D. M., & Currie, K. C. (2009). Depression, anxiety and their relationship with chronic diseases: A review of the epidemiology, risk and treatment evidence. *Medical Journal of Australia, 190*, S54–S60.

Clarke, D. M., & Kissane, D. W. (2002). Demoralization: Its phenomenology and importance. *Australian and New Zealand Journal of Psychiatry, 36*, 733–742.

Clarke, D. M., Cook, K. E., Coleman, K. J., & Smith, G. C. (2006). A qualitative examination of the experience of 'depression' in hospitalized medically ill patients. *Psychopathology, 39*, 303–312.

Clarke, D. M., Baird, D. E., Perera, D. N., Hagger, V. L., & Teede, H. J. (2014). The INSPIRED study: A randomised controlled trial of the Whole Person Model of disease self-management for people with type 2 diabetes. *BMC Public Health, 14*(1), 134.

Coats, A. J., Adamopoulos, S., Radaelli, A., McCance, A., Meyer, T. E., Bernardi, L., ... Forfar, C. (1992). Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation*, *85*, 2119–2131.

Collins, J. A., & Rice, V. H. (1997). Effects of relaxation intervention in phase II cardiac rehabilitation: Replication and extension. *Heart & Lung, 26*(1), 31–44.

Colquhoun, D. M., Bunker, S. J., Clarke, D. M., Glozier, N., Hare, D. L., Hickie, I. B., ... Branagan, M. G. (2013) Screening, referral and treatment for depression in patients with coronary heart disease. *Medical Journal of Australia*, *198*, 483–484.

Compare, A., Germani, E., Proietti, R., & Janeway, D. (2011). Clinical psychology and cardiovascular disease: An up-to-date clinical practice review for assessment and treatment of anxiety and depression. *Clinical Practice & Epidemiology in Mental Health, 7*, 148–156.

Compare, A., Zarbo, C., & Bonaiti, A. (2015). Psychocardiology and the role of the psychologist in acquired and congenital heart disease. In E. Callus & E. Quadri (Eds.), *Clinical psychology and congenital heart disease: Lifelong aspects and interventions* (pp. 133–146). Milan: Springer.

Cooper, A. F., Weinman, J., Hankins, M., Jackson, G., & Horne, R. (2007). Assessing patients' beliefs about cardiac rehabilitation as a basis for predicting attendance after myocardial infarction. *Heart, 93*, 53–58.

Corbin, J., & Strauss, A. (1988). *Unending work and care: Managing chronic illness at home*. San Francisco: Jossey-Bass.

Descartes, R. (1972). 1641. *Meditations on first philosophy*.

Dew, M. A., Goycoolea, J. M., Harris, R. C., Lee, A., Zomak, R., Dunbar-Jacob, J., ... Kormos, R. L. (2004). An internet-based intervention to improve psychosocial outcomes in heart transplant recipients and family caregivers: Development and evaluation. *Journal of Heart and Lung Transplantation*, *23*(6), 745–758.

Dickens, C., Cherrington, A., Adeyemi, I., Roughley, K., Bower, P., Garrett, C., … Coventry, P. (2013). Characteristics of psychological interventions that improve depression in people with coronary heart disease: A systematic review and meta-regression. *Psychosomatic Medicine*, *75*(2), 211–221.

Dusseldorp, E., van Elderen, T., Maes, S., Meulman, J., & Kraaij, V. (1999). A meta-analysis of psychoeducational programs for coronary heart disease patients. *Health Psychology, 18*(5), 506.

Dyer, J., & Beck, N. (2007). Psychocardiology: Advancing the assessment and treatment of heart patients. *Electronic Journal of Applied Psychology – Psychocardiology, 3*(2), 3–12.

Elkin, I., Shea, T., Watkins, J. T., Imber, S. D., Sotsky, S. M., Collins, J. F., … Parloff, MB. (1989). National Institute of Mental Health Treatment of Depression Collaborative Research Program: General effectiveness of treatments. *Archives of General Psychiatry*, *46*(11), 971–982.

Friedman, M., & Rosenman, R. H. (1959). Association of specific overt behavior pattern with blood and cardiovascular findings: Blood cholesterol level, blood clotting time, incidence of arcus senilis, and coronary artery disease. *JAMA, 169*(12), 1286–1296.

Friedman, M., & Rosenman, R. H. (1974). *Type A behaviour and your heart*. New York: Knopf.

Frizelle, D. J., Lewin, R. J. P., Kaye, G., Hargreaves, C., Hasney, K., Beaumont, N., & Moniz-Cook, E. (2004). Cognitive-behavioural rehabilitation programme for patients with an implanted cardioverter defibrillator: A pilot study. *British Journal of Health Psychology, 9*(3), 381–392.

Gallo, L. C., Ghaed, S. G., & Bracken, W. S. (2004). Emotions and cognitions in coronary heart disease: Risk, resilience, and social context. *Cognitive Therapy and Research, 28*(5), 669–694.

Gellis, Z. D., & Kang-Yi, C. (2012). Meta-analysis of the effect of cardiac rehabilitation interventions on depression outcomes in adults 64 years of age and older. *American Journal of Cardiology, 110*(9), 1219–1224.

Glassman, A. H., O'Connor, C. M., Califf, R. M., Swedberg, K., Schwartz, P., Bigger, J. T., … McIvor, M. (2002). Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*, *288*(6), 701–709.

Habibovic, M., Cuijpers, P., Alings, M., van der Voort, P., Theuns, D., Bouwels, L., … Pedersen, S. (2014). Attrition and adherence in a web-based distress management program for implantable cardioverter defibrillator patients (WEBCARE): Randomized controlled trial. *Journal of Medical Internet Research*, *16*(2), e52.

Harris, M., & Lloyd, J. (2012). *The role of Australian primary health care in the prevention of chronic disease*. Canberra: Australian National Preventive Health Agency.

Hawton, K., Salkovskis, P. M., Kirk, J., & Clark, D. M. (1989). *Cognitive behaviour therapy for psychiatric problems: A practical guide*. New York: Oxford Medical Publications.

Hedbäck, B., Perk, J., Hörnblad, M., & Ohlsson, U. (2001). Cardiac rehabilitation after coronary artery bypass surgery: 10-year results on mortality, morbidity and readmissions to hospital. *Journal of Cardiovascular Risk, 8*(3), 153–158.

Heran, B. S., Chen, J. M., Ebrahim, S., Moxham, T., Oldridge, N., Rees, K., … Taylor, R. S. (2011). Exercise-based cardiac rehabilitation for coronary heart disease. *The Cochrane Library*.

Huffman, J. C., Celano, C. M., Beach, S. R., Motiwala, S. R., & Januzzi, J. L. (2013). Depression and cardiac disease: Epidemiology, mechanisms, and diagnosis. *Cardiovascular Psychiatry and Neurology, 2013*, 695925.

Jordan, J. E., & Osborne, R. H. (2007). Chronic disease self-management education programs: Challenges ahead. *Medical Journal of Australia, 186*, 84–87.

Jordan, J. E., Bardé, B. E., & Zeiher, A. M. E. (Eds.). (2007). *Contributions toward evidence-based psychocardiology: A systematic review of the literature*. Washington, DC: American Psychological Association.

Katon, W. J., Unutzer, J., Wells, K., & Jones, L. (2010). Collaborative depression care: History, evolution and ways to enhance dissemination and sustainability. *General Hospital Psychiatry, 32*, 456–464.

Kennedy, A., Rogers, A., Chew-Graham, C., Blakeman, T., Bowen, R., Gardner, C., ... Protheroe, J. (2014). Implementation of a self-management support approach (WISE) across a health system: A process evaluation explaining what did and did not work for organisations, clinicians and patients. *Implementation Science*, *9*, 129.

Kereiakes, D. J., & Willerson, J. T. (2003). Metabolic syndrome epidemic. *Circulation, 108*, 1552–1553.

Kohli, S., & Malhotra, S. (2008). Interplay of type A behaviour and emotional immaturity as psychological risk factors of coronary heart disease. *Journal of the Indian Academy of Clinical Medicine, 9*(3), 179–183.

Koszycki, D. (2006). Interpersonal psychotherapy for depression in patients with coronary heart disease. In E. Molinari, A. Compare, & G. Parati (Eds.), *Clinical psychology and heart disease*. Italia: Springer.

Kuhl, E. A., Sears, S. F., & Conti, J. B. (2006). Internet-based behavioral change and psychosocial care for patients with cardiovascular disease: A review of cardiac disease-specific applications. *Heart & Lung, 35*(6), 374–382.

Kuper, H., Marmot, M., & Hemingway, H. (2002). Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. *Seminars in Vascular Medicine, 2*, 267–314.

Ladapo, J. A., Shaffer, J. A., Fang, Y., Ye, S., & Davidson, K. W. (2012). Cost-effectiveness of enhanced depression care after acute coronary syndrome: Results from the Coronary Psychosocial Evaluation Studies randomized controlled trial. *Archives of Internal Medicine, 172*, 1682–1684.

Lawler, P. R., Filion, K. B., & Eisenberg, M. J. (2011). Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. *American Heart Journal, 162*(4), 571–584.

Leor, J., Poole, W. K., & Kloner, R. A. (1996). Sudden cardiac death triggered by an earthquake. *New England Journal of Medicine, 334*, 413–419.

Lesperance, F., Frasure-Smith, N., Koszycki, D., Laliberte, M. A., van Zyl, L. T., Baker, B., ... Guertin, M. C. (2007). Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA*, *297*, 367–379.

Lewin, R. J., Coulton, S., Frizelle, D. J., Kaye, G., & Cox, H. (2009). A brief cognitive behavioural preimplantation and rehabilitation programme for patients receiving an implantable cardioverter-defibrillator improves physical health and reduces psychological morbidity and unplanned readmissions. *Heart, 95*(1), 63–69.

Lichtman, J. H., Froelicher, E. S., Blumenthal, J. A., Carney, R. M., Doering, L. V., Frasure-Smith, N., ... Wulsin, L. (2014). Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: Systematic review and recommendations a scientific statement from the American Heart Association. *Circulation*, *129*(12), 1350–1369.

Linden, W., Phillips, M. J., & Leclerc, J. (2007). Psychological treatment of cardiac patients: A meta-analysis. *European Heart Journal, 28*(24), 2972–2984.

Lorig, K. R., & Holman, H. R. (2003). Self-management education: History, definition, outcomes and mechanisms. *Annals of Behavioral Medicine, 26*(1), 1–7.

Lorig, K. R., Sobel, D. S., Stewart, A. L., Brown, B. W., Bandura, A., Ritter, P. ... Holman, H. R. (1999). Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: A randomized trial. *Medical Care*, *37*(1), 5–14.

Lorig, K. R., Ritter, P., Stewart, A. L., Sobel, D. S., Brown, B. W., Bandura, A., ... Holman, H. R. (2001). Chronic disease self-management program: 2-year health status and health care utilization outcomes. *Medical Care*, *39*(11), 1217–1223.

Maia, A. C. C. O., Braga, A. A., Soares-Filho, G., Pereira, V., Nardi, A. E., & Silva, A. C. (2014). Efficacy of cognitive behavioral therapy in reducing psychiatric symptoms in patients with implantable cardioverter defibrillator: An integrative review. *Brazilian Journal of Medical and Biological Research, 47*(4), 265–272.

Mampuya, W. M. (2012). Cardiac rehabilitation past, present and future: An overview. *Cardiovascular Diagnosis and Therapy, 2*(1), 38–49.

Martikainen, P., & Valkonen, T. (1996). Mortality after the death of a spouse: Rates and causes of death in a large Finnish cohort. *American Journal of Public Health, 86*(8), 1087–1093.

Messerli-Bürgy, N., Barth, J., & Berger, T. (2012). The InterHerz project-a web-based psychological treatment for cardiac patients with depression: Study protocol of a randomized controlled trial. *Trials, 13*(1), 245.

Miller, W. R., & Rollnick, S. (2013). *Motivational interviewing: Helping people change* (3rd ed.). New York: Guilford Press.

Moser, D. K. (2007). "The rust of life": Impact of anxiety on cardiac patients. *American Journal of Critical Care, 16*(4), 361–369.

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., … Turner, M. B. (2015). Heart disease and stroke statistics: 2015 update. *Circulation*, *131*(4), e29–e322.

Muller, I., & Yardley, L. (2011). Telephone-delivered cognitive behavioural therapy: A systematic review and meta-analysis. *Journal of Telemedicine and Telecare, 17*(4), 177–184.

Mulrow, C. D., Chiquette, E., Angel, L., Cornell, J., Summerbell, C., Anagnostelis, B., … Brand, M. B. (2000). Dieting to reduce body weight for controlling hypertension in adults. *Cochrane Database of Systematic Reviews*.

National Heart Lung and Blood Institute (NHLBI). (2012). NHLBI fact book, Chapter 4, disease statistics: Prevalence of common cardiovascular and lung diseases, US, 2007–2011.

O'Neil, A., Taylor, B., Sanderson, K., Cyril, S., Chan, B., Hawkes, A. L., … Oldenburg, B. (2014). Efficacy and feasibility of a tele-health intervention for acute coronary syndrome patients with depression: Results of the "MoodCare" randomized controlled trial. *Annals of Behavioral Medicine*, *48*(2), 163–174.

Pedersen, S. S., Van den Broek, K. C., & Sears, S. F. (2007). Psychological intervention following implantation of an implantable defibrillator: A review and future recommendations. *Pacing and Clinical Electrophysiology, 30*(12), 1546–1554.

Pietrabissa, G., Ceccarini, M., Borrello, M., Manzoni, G. M., Titon, A., Nibbio, F., … Castelnuovo, G. (2015). Enhancing behavioral change with motivational interviewing: a case study in a Cardiac Rehabilitation Unit. *Frontiers in Psychology*, *6*, 298.

Prince, M., Patel, V., Saxena, S., Maj, M., Maselko, J., Phillips, M. R., & Rahman, A. (2007). No health without mental health. *Lancet, 370*(9590), 859–877.

Rollman, B. L., Belnap, B. H., LeMenager, M. S., Mazumdar, S., Houck, P. R., Counihan, P. J., … Reynolds, C. F. (2009). Telephone-delivered collaborative care for treating post-CABG depression: A randomized controlled trial. *JAMA*, *302*(19), 2095–2103.

Rutledge, T., Reis, V. A., Linke, S. E., Greenberg, B. H., & Mills, P. M. (2006). Depression in heart failure: A meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology, 48*(8), 1527–1537.

Rutledge, T., Redwine, L. S., Linke, S. E., & Mills, P. J. (2013). A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease. *Psychosomatic Medicine, 75*(4), 335–349.

Scott, I. A., Lindsay, K. A., & Harden, H. E. (2003). Utilisation of outpatient cardiac rehabilitation in Queensland. *Medical Journal of Australia, 179*, 341–345.

Sebregts, E. H. W. J., Falger, P. R. J., Appels, A., Kester, A. D. M., & Bar, F. W. H. M. (2005). Psychological effects of a short behavior modification program in patients with acute myocardial infarction or coronary artery bypass grafting. A randomized controlled trial. *Journal of Psychosomatic Research, 58*(5), 417–424.

Shepherd, C. W., & While, A. E. (2012). Cardiac rehabilitation and quality of life: A systematic review. *International Journal of Nursing Studies, 49*(6), 755–771.

Shepherd, G., Boardman, J., & Slade, M. (2008). *Making recovery a reality*. London: Sainsbury Centre for Mental Health.

Shinitzky, H. E., & Kub, J. (2001). The art of motivating behavior change: The use of motivational interviewing to promote health. *Public Health Nursing, 18*(3), 178–185.

Sirri, L., Fava, G. A., Guidi, J., Porcelli, P., Rafanelli, C., Bellomo, A., ... Sonino, N. (2012). Type A behaviour: a reappraisal of its characteristics in cardiovascular disease. *International Journal of Clinical Practice*, *66*(9), 854–861.

Srinivas, G., & Reddy, K. (2013). Psychocardiology: Recognizing and addressing the profound impact of psychosocial factors on cardiac health. *Indian Journal of Applied Research, 3*(8), 526–529.

Stawnychy, M., Creber, R. M., & Riegel, B. (2014). Using brief motivational interviewing to address the complex needs of a challenging patient with heart failure. *Journal of Cardiovascular Nursing, 29*(5), E1–E6.

Sundararajan, V., Bunker, S. J., Begg, S., Marshall, R., & McBurney, H. (2004). Attendance rates and outcomes of cardiac rehabilitation in Victoria, 1998. *Medical Journal of Australia, 180*, 268–271.

Thompson, D. R., Chair, S. Y., Chan, S. W., Astin, F., Davidson, P. M., & Ski, C. F. (2011). Motivational interviewing: A useful approach to improving cardiovascular health? *Journal of Clinical Nursing, 20*, 1236–1244.

Thorburn, A. W. (2005). Prevalence of obesity in Australia. *Obesity Reviews, 6*, 187–189.

Tun, K. S. (2014). Self-management education in patients with cardiovascular disease: A best practice implementation project. *JBI Database of Systematic Reviews and Implementation Reports*, *12*(9).

Van den Brink, R. H. S., van Melle, J. P., Honig, A., Schene, A. H., Crijns, H. J. G. M., Lambert, F. P. G., & Ormel, J. (2002). Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: Rationale and outline of the Myocardial Infarction and Depression-Intervention Trial (MIND-IT). *American Heart Journal, 144*(2), 219–225.

Van Nes, M., & Sawatzky, J. A. V. (2010). Improving cardiovascular health with motivational interviewing: A nurse practitioner perspective. *Journal of the American Academy of Nurse Practitioners, 22*(12), 654–660.

Whalley, B., Thompson, D. R., & Taylor, R. S. (2014). Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. *International Journal of Behavioral Medicine, 21*(1), 109–121.

Whitmarsh, A., Koutantji, M., & Sidell, K. (2003). Illness perceptions, mood and coping in predicting attendance at cardiac rehabilitation. *British Journal of Health Psychology, 8*(2), 209–221.

Wise, M. G., & Rundell, J. R. (2002). *Textbook of consultation-liaison psychiatry*. Washington, DC: American Psychiatric Publishing.

Worcester, M. U. C., Murphy, B. M., Mee, V. K., Roberts, S. B., & Goble, A. J. (2004). Cardiac rehabilitation programmes: Predictors of non-attendance and drop-out. *European Journal of Preventive Cardiology, 11*(4), 328–335.

World Health Organisation. (1964). *Report of a WHO Expert Committee: Rehabilitation of patients with cardiovascular diseases. Technical report No. 270*. Geneva: World Health Organisation.

World Health Organization. (2006). *Diabetes. Fact sheet No. 312*. Geneva: World Health Organization.

Yalom, I. D. (1995). *The theory and practice of group psychotherapy*. New York: Basic Books.

Yohannes, A. M., Yalfani, A., Doherty, P., Bundy, C. (2007). Predictors of drop-out from an outpatient cardiac rehabilitation programme. *Clinical Rehabilitation*, *21*(3), 222–229.

Adding Psychological Intervention to High-Tech Care for Patients with Implantable Cardioverter Defibrillators

Lindsey Rosman, Amanda Whited, Jessica H. Ford, Raj Nekkanti, John Cahill, and Samuel F. Sears

Contents

Abstract

Psychosocial challenges for ICD patients have been well established in research and clinical practice. Anxiety secondary to disease management and/or fear of ICD shock is among the most common concerns that lead to development and maintenance of psychological distress in ICD patients. Researchers and clinicians

L. Rosman • J.H. Ford
Department of Psychology, East Carolina University, Greenville, NC, USA
e-mail: rosmanl@ecu.edu; jessica.d.ford7.civ@mail.mil

A. Whited • S.F. Sears (✉)
Department of Psychology, East Carolina University, Greenville, NC, USA

Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Greenville, NC, USA
e-mail: whitedam@ecu.edu; searss@ecu.edu

R. Nekkanti • J. Cahill
Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Greenville, NC, USA
e-mail: nekkantir@ecu.edu; cahillj@ecu.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_50

have developed a broad range of cognitive-behavioral, pharmacological, and nontraditional approaches to address the unique needs of ICD patients. Findings from two recent meta-analyses suggest that cognitive-behavioral interventions of high intensity were effective in reducing anxiety and depressive symptoms (effect sizes ranging from small to moderate large). However, the high degree of heterogeneity in treatment duration and content across studies has made it difficult to formulate broad conclusions on the feasibility and effectiveness of existing interventions. The purpose of this chapter is to highlight the evidence and breadth of empirically supported psychological treatments for ICD patients and their families. A list of resources for ICD patients and mental health professionals is also provided at the end of the chapter.

Keywords
ICD • Psychosocial treatment • Treatment • Intervention • Quality of life

Introduction

For patients with underlying cardiovascular disease, the confirmation of high risk for sudden cardiac arrest, or survival thereof, can be profound, and their emotional response may be further amplified by the need for an implantable cardioverter defibrillator (ICD). ICD patients often describe initial feelings of confusion, disbelief, fear, anger, frustration, and helplessness. For many, these initial emotions can be intense but attenuate over time. However, in a subgroup of ICD patients, psychological symptoms persist or worsen and may lead to the development of clinically significant anxiety (13–38 %), depression (10–41 %), and/or PTSD (21 %) (Sears et al. 2009; Kapa et al. 2010). Patients and their families may also face additional challenges related to cardiac disease management, medication adherence, fear of ICD shock, body image concerns, fear of resuming intimacy, heightened feelings of vulnerability, perceived loss/grief, inadequate social support, and end-of-life issues (Sears and Conti 2002).

The need for routine assessment and treatment for these patients is clear, but available and effective long-term management of psychological symptoms secondary to ICD implantation has been a challenge for healthcare providers. Over the past two decades, a broad range of cognitive-behavioral, pharmacological, and nontraditional (i.e., patient support groups, yoga, cardiac rehabilitation programs, biofeedback) interventions have been developed for patients with ICDs and their families (Dunbar et al. 2012). Technology-based treatments are also being increasingly used to improve access to psychosocial care, particularly among underserved patient populations (Bennett and Glasgow 2009). Nonetheless, practical considerations for mental health providers remain about where, when, and which types of interventions are most effective in ICD patients. The purpose of this chapter is to highlight the evidence and breadth of empirically supported psychological treatments for ICD patients and their families. Additional clinician resources and patient education materials are provided at the end of the chapter.

ICD Patient Referral and Case Conceptualization

The referral of a patient with an implantable cardioverter defibrillator (ICD) for psychological care can be a daunting task for a mental health professional. Mental health professionals are often less familiar with the cause, course, and treatment of cardiac patients dealing with the potential for life-threatening arrhythmias. However, the medical details are essential for conceptualizing and empathizing with the patient experience of living with an ICD. For example, many ICD patients have a tendency to overestimate their risk for experiencing ICD shock, which often leads to a cascade of catastrophic cognitions, affective restriction, and behavioral avoidance. Although patients may feel that they are "always at risk" for experiencing shock, the annual risk of shock for the prototypic primary prevention ICD patient can be approximated to be 6 % (Sears et al. under review). Thus, understanding the patient's medical history, disease severity, and the spontaneous nature of cardiac arrhythmias and subsequent risk for ICD shocks helps the clinician to effectively conceptualize and manage the psychosocial challenges of living with an ICD.

It is also important to note that a majority of ICD patients do not have a premorbid history of clinically significant psychological problems or mental health treatment. ICD patients without a history of psychological disturbance may be initially reluctant to engage in mental health treatment due to misconceptions about psychologists and psychological treatment. Therefore, it is essential for mental health providers to normalize an ICD patient's reaction to an abnormal event (ICD implantation or shock) and articulate a clear plan for recovery that may involve ICD-specific psychological intervention. When communicating the goals of treatment to patients, it can be useful to describe treatment as "several sessions to increase your knowledge and confidence about your device and get you back to doing the things you love." This approach appears to normalize patients' reactions, promote recovery, reduce stigma associated with mental healthcare, and facilitate patient engagement in treatment.

Additionally, medical and nursing communities are increasingly recognizing the psychosocial challenges of ICD patients and are often readily enlisted partners for mental health providers. The reasonably experienced mental health professional can be briefed by the medical team and be effective in the treatment of most ICD patients. The care and recovery of an ICD patient represents a "modern-day" psychological challenge for ICD patients to trust a medical device for protection and to make a "cardiac comeback" in their own life following the many challenges of living with cardiac disease.

Psychological Intervention Research

The initial rationale and interest for psychological intervention for ICD patients were strongly influenced by patients' fear of ICD shock and the high rate of maladaptive behavioral and psychosocial sequelae that emerge secondary to shock. Mowrer's two-factor theory of conditioned avoidance (Mowrer 1960) provides a theoretical

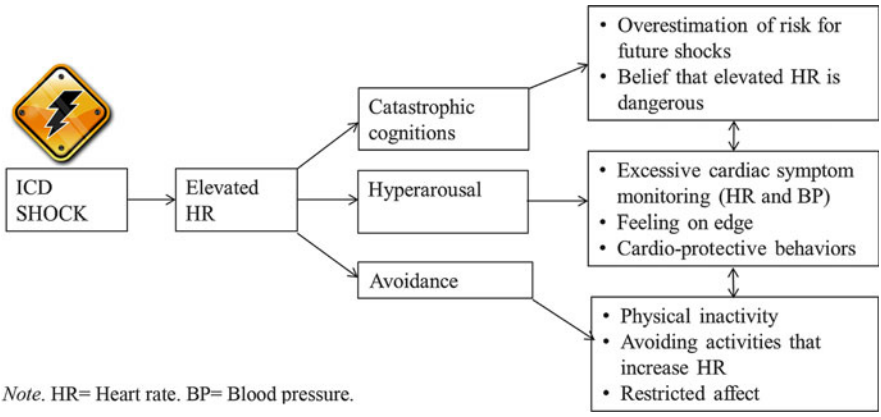


Fig. 1 Development of anxiety secondary to ICD shock. *Note. HR* heart rate. *BP* blood pressure

framework for conceptualizing conditioned reactions and disruptive patterns of recovery among ICD patients. For this reason, anxiety and shock-specific anxiety (also known as *shock anxiety*) have been the primary target of psychosocial research, and the evidence has been encouraging related to preventing anxiety (Irvine et al. 2011) and reducing anxiety following ICD shock (Sears et al. 2007).

Figure 1 demonstrates a simplified, generic model of the development and maintenance of shock anxiety in ICD patients following an episode of shock. As depicted in this model, catastrophic cognitions can include overestimation of risk for future shock, beliefs that any increase in heart rate is dangerous and will lead to ICD shock, and beliefs that certain activities will cause their ICD to discharge (e.g., activities engaged in when their device previously fired and are therefore dangerous). Symptoms of hyperarousal or somatic hypervigilance can also occur, leading some ICD patients to engage in excessive cardiac symptom monitoring (heart rate and blood pressure) and cardioprotective safety behaviors (seeking medical reassurance for normal alterations in cardiac function) (Broek et al. 2009). Cognitive, affective, and behavioral avoidance are also common and may lead patients to avoid thinking about their ICD or cardiac condition, to restrict affective expression due to fears that intense emotions (anger or elation) may increase their heart rate and cause their device to fire, and to engage in behavioral avoidance of activities that raise their heart rate (e.g., sex, housework, walking, exercise).

As cognitive-behavioral theories have predominated, treatments have typically utilized approaches targeting catastrophic cognitions, behavioral avoidance, arousal reduction, and social support. Empirically supported individual and group-based psychological interventions for patients with ICDs have been emphasized in the existing research literature and have varied widely in their duration, theoretical orientation, content, and method of delivery (Habibovic et al. 2013). Many utilize a randomized controlled trial (RCT) study design; however, patient self-selection is common and may reduce the external validity of some studies. Further, sample sizes

in ICD intervention research are generally small, which reduces researchers' ability to control for potential confounds or examine interaction effects. Small sample sizes may also contribute to Type II errors (i.e., failing to statistically detect an effect when one is actually present) and problems related to insufficient power in statistical analyses to capture meaningful changes. Despite these challenges in regard to research design and methods, the results from three decades of empirical research are compelling and demonstrate an ability to reduce psychological distress and improve quality of life in patients with ICD and their families (Dunbar et al. 2012). For the purpose of this review, psychological interventions for ICD patients and their families are broadly categorized as cognitive-behavioral, pharmacological, nontraditional, or technology-based treatments.

Cognitive-Behavioral Therapy Interventions

Brief cognitive-behavioral interventions. Brief cognitive-behavioral interventions focused on subclinical specific behavioral or psychological symptoms may help to address mild elevations in mood, medication adherence problems, reduce health risk behaviors, and increase ICD device knowledge and acceptance in most ICD patients. However, the initial research examining brief therapies has not yielded significant effects on psychosocial outcomes in small studies (Carlsson et al. 2002). Nonetheless, this type of single-session intervention may be helpful for patients seen by professionals providing consultation/liaison services in a hospital setting where clinical interactions are short term and goal oriented (see Table 1). Typically, psychoeducational interventions are employed because many of the challenges that ICD patients and families face are novel. For example, and of great significance, *few people have to acquire a strategy to cope with electrical shock in the daily life*. Simply providing information about the occurrence and an initial strategy to manage the problem can give many people the feeling of confidence and support needed to employ effective strategies for subclinical concerns.

Clinical example. Many ICD patients have a relatively poor understanding of how their device works and how to respond to an ICD shock (Hauptman et al. 2013). Without adequate education from healthcare providers, some patients develop a pathological pattern of avoidance behaviors, excessive cardiac symptom monitoring (e.g., heart rate and blood pressure), or experience increased arousal symptoms (Broek et al. 2009). ICD patients with a history of shock or shock storm (i.e., $\geq$5 shocks) are particularly at risk for adverse psychological outcomes (Sears and Conti 2002). To reduce or even prevent shock-related psychological sequelae, it is recommended that all ICD patients receive psychoeducation about their device and clear directions for how to respond to ICD shock, known as a *shock plan* (Table 2). Patient handouts for how to respond to ICD shock are free and available online, as indicated at the end of this chapter. In a clinical setting, a mental health professional can provide patients and their families with this written information and verbally review shock plan procedures to ensure patient understanding and reduce ambiguity/fears of future shock events.

Table 1 Brief CBT interventions for common psychological symptoms in ICD patients

Behavioral or psychological symptoms	Suggested CBT intervention
Medication nonadherence	Motivation interviewing, problem-solving techniques
Tobacco use or substance abuse	Motivational interviewing
	Provide referral for tobacco cessation or substance abuse counseling, if indicated
Poor knowledge about ICD and ICD shock	Review established mortality benefit of ICD vs. medications alone from large clinical trials
	Provide patient handout on *How to Respond to ICD Shock* (see end of chapter)
	Review shock plan verbally with patient and family
Concerns about sexual activity with an ICD	Engage medical providers to confirm safety of sexual activity with patient
	Provide patient handout on *Sexual Activity in ICD Patients* (see end of chapter). Review verbally with patient
Concerns about ICD device recall	Provide patient handout on *How to Respond to a Device Recall* (see end of chapter). Review verbally with patient
	Review low probability of device malfunction and extensive monitoring of device reliability
Family expresses questions or concerns about patient's ICD	Acknowledge, normalize, and discuss the relatively increased stress in ICD partners and families
	Provide patient handout on *Coping with My Partners ICD* (see end of chapter). Review verbally with patient
Mild, intermittent depressive symptoms	Behavioral activation. Provide referral for further psychological treatment, if indicated
Weight management	Introduce goal setting as a strategy to make small, manageable changes in daily food consumption. Provide referral to nutritionist (if available). Ask cardiologist to prescribe a walking program or referral to cardiac rehabilitation program, if indicated
Physical inactivity	Review medical chart or consult with cardiologist about activity restrictions
	Introduce goal setting as a strategy to make small, manageable increases in daily physical activity
	Encourage use of personal activity trackers like *Fitbit*

Table 2 Recommended shock action plan for ICD patients

Shock delivered	Patient experience	Patient action
One shock	No problematic symptoms	Call cardiac device clinic and schedule appointment or remote monitor transmission
One shock	Persistent problematic symptoms (e.g., chest pain, dizziness, coughing, weakness)	Seek emergency medical attention
Two or more shocks in 24 h period	With or without any symptoms	Seek emergency medical attention

Traditional Cognitive-Behavioral Interventions (3–12 Sessions)

Comprehensive qualitative and quantitative reviews of traditional multi-session cognitive-behavioral therapy treatment interventions are available in the literature (Habibovic et al. 2013; Dunbar et al. 2012). Collectively, these reviews examined 17 clinical trials that have empirically evaluated intervention effectiveness in ICD patients. More comprehensive interventions were associated with reduced anxiety and depressive symptoms, with the effect sizes ranging from small to moderate large (0.10–1.79). These results are encouraging, but every review notes the challenges of drawing conclusions across the trials with small sample sizes, various recruitment time points, and tedious generalizations. Reviews also highlight that heterogeneity in intervention duration, modality (individual, group, technology-based delivery), professionals involved in treatment delivery (psychologists, nursing and allied health professionals), and session content (health behaviors, adherence, psychosocial adjustment) make generalizations across studies difficult.

Nonetheless, cognitive-behavioral interventions appear effective in producing substantial and long-lasting reductions in psychological distress ICD patients. Across studies, common components of effective treatments were utilization of a group format, ICD-specific education (Dougherty 1994; Fitchett et al. 2003; Frizelle et al. 2004; Lewin et al. 2009; Sears et al. 2007), cognitive restructuring and relaxation/stress management (Chevalier et al. 2006; Frizelle et al. 2004; Lewin et al. 2009; Kuhl et al. 2009; Sears et al. 2007), and shock planning (Sears et al. 2007). Additional components of other interventions were check-in phone calls (usually from nurses), exercise programming, and social support (Salmoirago-Blotcher and Ockene 2009). Educational components usually include management of arrhythmia, medication review, purpose and function of ICD, safety of return to activities, common symptoms, and device monitoring (Sreeram et al. 2008).

Clinical example. After experiencing a multiple shock episode or shock storm (five or more ICD shocks in a single episode), patients may develop a pathological pattern of symptoms that require several sessions of cognitive-behavioral intervention. These often include a mixture of distorted cognitions (mistakenly associate a specific activity with the occurrence of ICD shock), avoidance behaviors (complete cessation of physical activity), and hyperarousal symptoms (cardiac symptom monitoring). In the absence of comorbid or severe psychological disturbance, the ICD shock and stress management program (Sears et al. 2007) is a useful empirically validated intervention that targets ICD-specific distress. Details of the treatment protocol and intervention effectiveness are published in the original article.

To summarize, the ICD shock and stress management program was theoretically based on cognitive-behavioral therapy for anxiety and specifically tailored to address common cognitive, affective, and behavioral difficulties experienced by patients with ICDs. The standard intervention protocol typically includes four to six sessions and has four key components: patient education, relaxation/stress management training, cognitive reframing techniques, and promotion of social support. The first component focuses on increasing patient knowledge about their device and ICD shock which, in turn, should lead to reductions in uncertainty and ambiguity that

maintain shock-related anxiety. This step also promotes patient self-efficacy by equipping them with the knowledge to understand, manage, and effectively communicate about their medical condition. Peer-reviewed *Patient Pages* from the journal, *Circulation*, or other patient education resources are verbally reviewed in session and provided to patients and their families during the initial phase of treatment. Patient education materials can also be used to effectively target significant avoidance symptoms and provide a mechanism to gradually expose patients to potentially aversive cognitions and emotions associated with their ICD.

The second component of the ICD-specific intervention aims to teach patients to identify the signs and symptoms of stress and provide them with a standard operating procedure for how to reduce psychological distress. Diaphragmatic breathing and progressive muscle relaxation techniques are introduced, practiced in session, and assigned as daily homework. Professionals may also wish to consider incorporating grounding and mindfulness strategies, particularly for patients exhibiting a traumatic stress response secondary to ICD shock or shock storm. When indicated, provide patients with information on technology-based resources and smartphone apps to facilitate daily practice of stress management techniques. In the third phase of treatment, cognitive reframing techniques are introduced to help ICD patients identify and reframe distorted or "unhelpful" cognitions related to their ICD or shock. The Challenging Questions technique developed for cognitive processing therapy may also be an effective tool for teaching patients a step-by-step approach to reframe distorted cognitions (Resick et al. 2008). With these skills established, the final phase of treatment focuses on improving ICD patient support and acquiring new outlets for support (ICD support groups, online communities, etc.) when indicated. Collectively, this program aims to normalize patients' reactions to living with an ICD, provide device-related education, reduce fear-based cognitions and behavioral avoidance, as well as promote device confidence and recovery.

Pharmacological Interventions

The clinical reality of a distressed patient on a cardiology consultation service with relatively few specialty mental health providers in immediate availability often prompts a call for psychopharmacological intervention. Research has demonstrated that psychological distress is particularly pronounced in the 30 days following an ICD shock event (Mark et al. 2008), and attending cardiologists often feel the need to start psychiatric medications. However, psychopharmacological treatments for ICD patients have not been the subject of any clinical trials to date. Small-scale trials appear to be underway, but no published information on this patient population is yet available.

Nonetheless, a great deal of research has focused on the cardiovascular side effects of psychotropic medications. See Beach et al. (2013) for a detailed review of cardiovascular risks associated with psychotropic medications. Overall, results from these studies suggest that certain classes of medications should be avoided in cardiac patients due to their risk for increased heart rate (sinus tachycardia) and/or problems with cardiac conduction or rhythm disturbance (O'Brien and Oyebode 2003). Tricyclic antidepressants, typical and atypical antipsychotics, and

nonselective monoamine oxidase inhibitors (MAOIs) can lead to sinus tachycardia (O'Brien and Oyebode 2003), which is a common cause of inappropriate shocks in patients with ICDs (Raitt 2013). Tricyclic antidepressants are known to produce delays in cardiac conduction due to prolongation of the QRS interval (O'Brien and Oyebode 2003). In ICD patients, this can lead to the development of arrhythmias and cause their ICD to deliver a shock. QT interval disruption and rhythm disturbance has also been documented in patients prescribed typical and atypical antipsychotics, lithium, anticonvulsant agents, and in some antidepressants (i.e., citalopram, trazodone, and venlafaxine) (Vieweg et al. 2012). Given the known association between ICD shock and adverse psychological outcomes, efforts should be made to avoid drugs that potentially increase risk for unnecessary ICD discharge. Selective serotonin reuptake inhibitors (SSRIs) are generally considered safe in patients with ICDs (O'Brien and Oyebode 2003). However, as noted, citalopram has been associated with adverse QT outcomes and therefore is one SSRI that is not recommended as a first-line approach for patients with cardiovascular disease (Vieweg et al. 2012). In sum, ICD patients who experience frequent, persistent, or severe symptoms of psychological distress may benefit from pharmacological intervention in conjunction with another psychological treatment. In all cases, clinicians need to be aware of the cardiovascular risks associated with various psychotropic medications and work closely with cardiology providers to monitor and assess for adverse outcomes.

Nontraditional Interventions

Support groups. The rapid acceleration of the use of the ICD over the past decade has produced new needs for the management of patients. Efficient methods of providing patient education and support have been employed. Many of these methods are reasonable to support the health literacy and adjustment of ICD patients and families. The most common approach by medical treatment centers has been the initiation of support groups. ICD support groups can take many forms ranging between provider-led question and answer groups or didactic classes, to patient-led groups encouraging emotional expression or peer-to-peer support. The efficacy or effectiveness of ICD support groups has not been sufficiently studied (Sears and Conti 2002), but they likely activate the known benefits of group interventions such as universality of concerns, generation of hope, information sharing, and acquisition of coping skills via vicarious learning. Despite the lack of clinical studies, support groups encourage attention to the psychological adjustment of the novel concerns that many ICD patients can face and likely provide at least some support to many patients.

Yoga and mindfulness. The availability and utility of complementary and alternative approaches, such as yoga and mindfulness, to address the emotional needs of ICD patients represent a new avenue of potential benefit to aid ICD patient adjustment. Initial results from research studies suggest that yoga interventions may be beneficial for reducing psychological distress in ICD patients. Moreover, a trial of randomized 46 patients to an 8-week group-based yoga program vs. usual care (Toise et al. 2014) demonstrated a significant reduction in shock anxiety that was maintained 6 months after the intervention. The yoga group also showed benefit in yoga-specific metrics such as greater self-compassion and mindfulness. Further, an intriguing finding

included a significantly lower number of anti-tachycardia pacing (ATP) events in the yoga group vs. the control group. This exploratory finding suggested that yoga might have some broader effects for ICD patients. Supporting this hypothesis, Salmoirago-Blotcher et al. (2013) recently studied mindfulness in a sample of ICD patients ($N = 45$) and demonstrated similar improvements in mindfulness and anxiety in the treatment group who received eight weekly individual phone calls vs. scripted phone calls. However, additional well-constructed randomized controlled trials are needed to determine the impact of yoga and mindfulness interventions on ICD patients. Research with larger samples is also essential to clarify what components of these interventions are most beneficial to ICD patients, and what types of patients receive the greatest benefit from yoga and mindfulness interventions.

Cardiac rehabilitation. The engagement of ICD patients in rehabilitation programs can provide a setting for safe exposure to increased heart rate and partially address the fear of shock. For some patients, the fear of shock can generalize to the fear of any action that might increase heart rate above resting rate, which they erroneously perceive as increasing their chance of triggering an ICD shock. Cardiac rehabilitation can further allow for a safe venue to test the limits, per se, where patients can gradually increase exertion and heart rate elevation without experiencing negative feedback (ICD shock). Researchers have successfully established these approaches are safe and effective in initial research (Isaksen et al. 2012). Another recent randomized controlled trial of an exercise program that included over 1,000 patients with congestive heart failure and ICDs demonstrated no increased risk of shock for patients on an exertive regimen vs. usual care over the course of a 2.2-year follow-up period (Piccini et al. 2013). Additional research trials are underway to determine the potential direct benefit on arrhythmia occurrence from various levels of exercise, but the results are pending.

Although some positive results have been reported, variability across studies limits the extent to which exercise programs can be considered effective psychological interventions in ICD patients. In a small sample of ICD patients ($N = 16$) in the UK, Fitchett et al. (2003) found evidence of improvement in anxiety and depression in patients that completed an exercise training program plus CBT. Dougherty et al. (2008) demonstrated that exercise training alone demonstrated improvement in the mental component of generic quality of life, anxiety, and depressive symptoms at the 8-week follow-up. However, these improvements were not sustained at 6 months. Most recently, Berg and colleagues (2011) randomized a large Danish sample of ICD patients ($N = 196$) to standard cardiac rehabilitation combined with a brief psychosocial nursing intervention vs. usual care (COPE-ICD trial). Results from the study revealed no significant differences in psychological outcomes between the intervention and control groups after 3 months. Collectively, cardiac rehabilitation approaches need additional study but may provide ICD patients some benefits across both physical and psychosocial domains, particularly if no ICD-specific mental health services are available.

Technology-based treatments. Given the large number of current and future ICD patients, the expansion of e-health applications in the field of cardiovascular medicine will likely continue across coming years. Web-based and mobile phone

Table 3 Examples of ICD patient information websites

Example website	Sponsor
www.asktheicd.com	Medtronic
www.arrhthymiaanswers.com	St Jude Medical
www.heartdevicechoice.com	Boston scientific
Icdsupportgroup.com	ICD patients
Inspire.com	Cardiac patients

platforms are already available and provide patients with the opportunity to learn about and track their cardiac functioning. This reality has great promise for increased access and availability of information tempered by the validity and biases of the provider of the information. Table 3 presents a list of websites developed by medical device companies and patient groups that attempt to address the informational needs of ICD patients.

The possibilities for mobile phone-based applications for ICD patients are encouraging. The ubiquitous presence of mobile phones could provide the ICD patient with personal medical information, coping support, or diagnostic discrimination. At present, ICD patients cannot access their own device data via the mobile phone. However, smartphone applications such as AliveECG and Instant Heart Rate can monitor heart rate and provide real-time EKG. For the right patient, this could be a reassuring strategy to combat catastrophic cognitions related to perceived risk of imminent danger, death, or ICD shock. However, clinical judgment should be exercised as this type of strategy could be contraindicated for some patients. For example, patients exhibiting symptoms of somatic hypervigilance may become preoccupied with their cardiac function and spend an excessive amount of time examining their heart rate, leading to increased behavioral dysfunction. Non-ICD-specific sources of mobile mental health treatment are also available and offer tremendous benefit to ICD patients. The popular "PTSD Coach," created by the US Veterans Administration Hospital, represents this kind of innovation. Collectively, e-health is a frontier that will likely continue to attract ICD patients and may have some clinical value. Continued research is needed to validate the most efficacious and beneficial aspects of these technologies.

Conclusion

This chapter reviewed the extant literature on psychosocial interventions for patients living with ICDs. Overall, these data empirically demonstrate the value of psychosocial treatments for ICD patients. Moreover, evidence from randomized clinical trials supports the feasibility and efficacy of various treatment modalities to improve patient's emotional well-being and reduce ICD-specific distress. Innovative technologies may also help providers research previously underserved populations and increase patient's access to information about their device and ICD shock, participate in online peer support groups, and engage in treatment via web-based psychological interventions. Nonetheless, efforts to translate research findings into actionable

evidence-based care remain an ongoing challenge for mental health professionals. Often, a multitude of patient, provider, and environmental factors may interfere with treatment fidelity to an evidence-based intervention protocol. Despite these challenges, skilled providers can equip themselves with the knowledge to conceptualize and deliver evidence-based care to ICD patients in brief consultation and longer-term clinical settings. The use of peer-reviewed patient education resources and multidisciplinary collaboration, whenever feasible, is also strongly encouraged to promote continuity of care.

Published data on psychological outcomes of ICD-specific interventions are encouraging but further research is warranted. Future studies need to include larger samples that are diverse in terms of age, ethnicity, and sociocultural backgrounds to increase the generalizability of research findings to the broader population of ICD patients. Research is also needed to clarify what type of patient is most likely to benefit from specific ICD interventions. Moreover, the impact of psychological interventions on medical care costs, morbidity, and mortality is poorly understood in this population and should be the focus of future research investigations.

To be successful in the long term, mental health providers need to fully understand the complex array of medical, psychological, and social factors that lead to the development and maintenance of psychological distress in ICD patients. Providers also should utilize the full spectrum of evidence-based interventions that can be adapted to consultation and traditional treatment settings. The strategies discussed in this chapter are essential to help patients survive and thrive with their ICD and can be individually tailored to meet the unique needs of each ICD patient.

Educational Resources for Clinicians, ICD Patients, and Their Families

Cardiology Patient Pages. Cardiology patient pages are free and available online from *Circulation*, a leading, peer-reviewed cardiology journal. They are specifically written in patient-friendly language to address frequently reported questions and concerns from ICD patients and their families. Go to http://circ.ahajournals.org/ for more information or to print patient handouts listed in the chart below.

Resources for ICD patients	Topics addressed
The implantable cardioverter defibrillator: patient perspective	Provides a description of what an ICD is and how it works
Coping with trauma and stressful events as a patient with an implantable cardioverter defibrillator	Reviews stressful reactions and post-traumatic stress symptoms in ICD patients. Provides an action plan for developing effective coping responses
Coping with my partner's ICD and cardiac disease	Describes common challenges associated with the psychological adjustment of ICD partners and offers possible strategies to consider in managing these difficulties

(*continued*)

Resources for ICD patients	Topics addressed
How to respond to an implantable cardioverter defibrillator shock	Describes ICD shock and provides instructions (shock plan) for patients and family on how to respond to an ICD shock
How to respond to an implantable cardioverter defibrillator recall	Help ICD patients be prepared for and psychologically cope with a potential device recall
Sexual health for patients with an implantable cardioverter defibrillator	Review common sexual problems in patients with ICDs and describe strategies for effective management

ICD Shock Plans. Websites that provide free printable ICD shock plans are listed below. Professionally printed patient shock plan brochures can also be requested from device manufacturers.

Boston scientific – my shock plan
http://www.bostonscientific.com/lifebeat-online/live/my-shock-plan.html
Device-advice.org
http://www.device-advice.org/shock-plan.htm

Support Programs for Young ICD Patients and Their Families

Camp Odayin

Supportive camp experiences and community building opportunities for young people with heart disease and their families. Located in Stillwater, MN, this camp is open to all patients and families coping with heart disease, including ICD patients. They offer support programs throughout the year and have a scholarship program to help with program costs. For more information, go to http://campodayin.org/.

University of Michigan Young ICD Connection Conference
Location: Ann Arbor City Club, Ann Arbor, MI
Contact: Donna Wilkin (734) 936-9218 email: dawilkin@umich.edu

Books

McFarland, H. (2012). *ICD connection*: *Living with an implantable cardioverter defibrillator. A collection of patient & family stories*. Ann Arbor: MPublishing.

Nobble, M. D. (2005). *One beat at a time – Living with sudden cardiac death*. Russell Douglas Publishing.

Nobble, M. D., Fallon, R. S., & Hayes, D. L. (2012). *Understanding your pacemaker or defibrillator*: *What patients and families need to know*. Cardiotext Publishing.

References

Beach, S. R., Celano, C. M., Noseworthy, P. A., Januzzi, J. L., & Huffman, J. C. (2013). QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics, 54*(1), 1–13. doi:10.1016/j.psym.2012.11.001.

Bennett, G. G., & Glasgow, R. E. (2009). The delivery of public health interventions via the internet: Actualizing their potential. *Annual Review of Public Health, 30*, 273–292. doi:10.1146/annurev.publhealth.031308.100235.

Berg, S. K., Svendsen, J. H., Zwisler, A. D., Pedersen, B. D., Preisler, P., Siersbaek-Hansen, L., … Pedersen, P. U. (2011). COPE-ICD: A randomised clinical trial studying the effects and meaning of a comprehensive rehabilitation programme for ICD recipients -design, intervention and population. *BMC Cardiovascular Disorders, 11*, 33-2261-11-33. doi: 10.1186/1471-2261-11-33.

Broek, K., Nyklícek, I., & Denollet, J. (2009). Anxiety predicts poor perceived health in patients with an implantable defibrillator. *Psychosomatics, 50*, 483–492.

Carlsson, E., Olsson, S. B., & Hertevig, E. (2002). The role of the nurse in enhancing quality of life in patients with an implantable cardioverter defibrillator: The Swedish experience. *Progress in Cardiovascular Nursing, 17*, 18–25.

Chevalier, P., Cottraux, J., Mollard, E., Yao, S., Brun, S., Burri, H., … Adeleine, P. (2006). Prevention of implantable defibrillator shocks by cognitive behavioral therapy: A pilot trial. *American Heart Journal, 151*, 191. doi: 10.1016/j.ahj.2005.10.007.

Dougherty, C. (1994). Longitudinal recovery following sudden cardiac arrest and internal cardioverter defibrillator implantation: Survivors and their families. *American Journal of Critical Care, 3*, 145–154. PMID:8167775.

Dougherty, C. M., Glenny, R., & Kudenchuk, P. J. (2008). Aerobic exercise improves fitness and heart rate variability after an implantable cardioverter defibrillator. *Journal of Cardiopulmonary Rehabilitation and Prevention, 28*(5), 307–311. doi:10.1097/01.HCR.0000336140.56322.1f.

Dunbar, S. B., Dougherty, C. M., Sears, S. F., Carroll, D. L., Goldstein, N. E., Mark, D. B., … American Heart Association Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Cardiovascular Disease in the Young. (2012). Educational and psychological interventions to improve outcomes for recipients of implantable cardioverter defibrillators and their families: A scientific statement from the american heart association. *Circulation, 126* (17), 2146–2172. doi: 10.1161/CIR.0b013e31825d59fd.

Fitchett, A., Doherty, P. J., Bundy, C., Bell, W., Fitzpatrick, A. P., & Garratt, C. J. (2003). Comprehensive cardiac rehabilitation programme for implantable cardioverter-defibrillator patients: A randomised controlled trial. *Heart (British Cardiac Society), 89*(2), 155–160.

Frizelle, D., Lewin, R., Kaye, G., Hargreaves, C., Hasney, K., Beaumont, N., & Moniz-Cook, E. (2004). Cognitive behavioural rehabilitation programme for patients with an implanted cardioverter defibrillator: A pilot study. *British Journal of Health Psychology, 9*, 381–392. doi:10.1348/1359107041557039.

Habibovic, M., Burg, M. M., & Pedersen, S. S. (2013). Behavioral interventions in patients with an implantable cardioverter defibrillator: Lessons learned and where to go from here? *Pacing and Clinical Electrophysiology: PACE, 36*(5), 578–590. doi:10.1111/pace.12108.

Hauptman, P. J., Chibnall, J. T., Guild, C., & Armbrecht, E. S. (2013). Patient perceptions, physician communication, and the implantable cardioverter-defibrillator. *JAMA Internal Medicine, 173*(7), 571–577. doi:10.1001/jamainternmed.2013.3171.

Irvine J, Firestone J, Ong L, Cribbie R, Dorian P, Harris L, Ritvo P, et al. (2011) A randomized controlled trial of cognitive behavior therapy tailored to psychological adaptation to an implantable cardioverter defibrillator. *Psychosom Med*. *73*:226–233.

Isaksen K, Morken IM, Munk PS, Larsen AI. (2012). Exercise training and cardiac rehabilitation in patients with implantable cardioverter defibrillators: a review of current literature focusing on safety, effects of exercise training, and the psychological impact of programme participation. *Eur J Prev Cardiol*. *19*:804.

Kapa, S., Rotondi-Trevisan, D., Mariano, Z., Aves, T., Irvine, J., Dorian, P., & Hayes, D. L. (2010). Psychopathology in patients with ICDs over time: Results of a prospective study. *Pacing and Clinical Electrophysiology, 33*(2), 198–208. doi:10.1111/j.1540-8159.2009.02599.x.

Kuhl, E., Sears, S., Vazquez, L., & Conti, J. (2009). Patient-assisted computerized education for recipients of implantable cardioverter-defibrillators: A randomized controlled trial of the

PACER program. *The Journal of Cardiovascular Nursing, 24*, 225–231. doi:10.1097/JCN.0b013e31819c143d.

Lewin, R., Coulton, S., Frizelle, D., Kaye, G., & Cox, H. (2009). A brief cognitive behavioural pre-implantation and rehabilitation programme for patients receiving and implantable cardioverter defibrillator improves physical health and reduces psychological morbidity and unplanned re-admission. *Heart, 95*, 63–69. doi:10.1136/hrt.2007.129890.

Mark DB, Anstrom KJ, Sun JL, et al. (2008). Quality of Life with Defibrillator Therapy or Amiodarone in Heart Failure. *The New England journal of medicine*. *359*(10):999-1008. doi:10.1056/NEJMoa0706719.

Mowrer, O. H. (1960). *Learning theory and behavior*. New York: Wiley.

O'Brien, P., & Oyebode, F. (2003). Psychotropic medication and the heart. *Advances in Psychiatric Treatment, 9*(6), 414–423. doi:10.1192/apt.9.6.414.

Piccini, J. P., Hellkamp, A. S., Whellan, D. J., Ellis, S. J., Keteyian, S. J., Kraus, W. E., . . . HF-ACTION Investigators. (2013). Exercise training and implantable cardioverter-defibrillator shocks in patients with heart failure: Results from HF-ACTION (heart failure and A controlled trial investigating outcomes of exercise TraiNing). *Journal of the American College of Cardiology Heart Failure, 1*(2), 142–148. doi: 10.1016/j.jchf.2013.01.005.

Raitt, M. H. (2013). Inappropriate implantable defibrillator shocks: An adverse outcome that can be prevented. *Journal of the American College of Cardiology, 62*(15), 1351–1352. doi:10.1016/j.jacc.2013.05.055.

Resick, P. A., Uhlmansiek, M. O., Clum, G. A., Galovski, T. E., Scher, C. D., & Young-Xu, Y. (2008). A randomized clinical trial to dismantle components of cognitive processing therapy for posttraumatic stress disorder in female victims of interpersonal violence. *Journal of Consulting and Clinical Psychology, 76*, 243–258. doi:10.1037/0022-006X.76.2.243.

Salmoirago-Blotcher, E., & Ockene, I. S. (2009). Methodological limitations of psychosocial interventions in patients with an implantable cardioverter-defibrillator (ICD) A systematic review. *BMC Cardiovascular Disorders, 9*, 56-2261-9-56. doi: 10.1186/1471-2261-9-56.

Salmoirago-Blotcher, E., Crawford, S. L., Carmody, J., Rosenthal, L., Yeh, G., Stanley, M., . . . Ockene, I. S. (2013). Phone-delivered mindfulness training for patients with implantable cardioverter defibrillators: Results of a pilot randomized controlled trial. *Annals of Behavioral Medicine, 46*(2), 243–250. doi: 10.1007/s12160-013-9505-7.

Sears, S. F., & Conti, J. B. (2002). Quality of life and psychological functioning of icd patients. *Heart, 87*(5), 488–493. doi:10.1136/heart.87.5.488.

Sears, S. F., Sowell, L. D., Kuhl, E. A., Kovacs, A. H., Serber, E. R., Handberg, E., . . . Conti, J. B. (2007). The ICD shock and stress management program: A randomized trial of psychosocial treatment to optimize quality of life in ICD patients. *Pacing and Clinical Electrophysiology, 30*(7), 858–864. doi: PACE773

Sears, S. F., Matchett, M., & Conti, J. B. (2009). Effective management of ICD patient psychosocial issues and patient critical events. *Journal of Cardiovascular Electrophysiology, 20*(11), 1297–1304. doi:10.1111/j.1540-8167.2009.01526.x.

Sears, S. F., Whited, A., & Volosin, K. (2014). Enhancing patient care by estimation and discussion of risk for ICD shock. Manuscript under review.

Sreeram, N., Trieschmann, U., & Haan, E. (2008). Device therapy in children: Current indications. *Indian Pacing and Electrophysiology Journal, 8*, s92–s104. doi:10.1002/9780470750797.ch4.

Toise, S. C., Sears, S. F., Schoenfeld, M. H., Blitzer, M. L., Marieb, M. A., Drury, J. H., . . . Donohue, T. J. (2014). Psychosocial and cardiac outcomes of yoga for ICD patients: A randomized clinical control trial. *Pacing and Clinical Electrophysiology, 37*(1), 48–62. doi: 10.1111/pace.12252.

Vieweg, W. V., Hasnain, M., Howland, R. H., Hettema, J. M., Kogut, C., Wood, M. A., & Pandurangi, A. K. (2012). Citalopram, QTc interval prolongation, and torsade de pointes. How should we apply the recent FDA ruling? *The American Journal of Medicine, 125*(9), 859–868. doi:10.1016/j.amjmed.2011.12.002.

In-Hospital Management of Psychological Responses to Acute Cardiac Events

Marian Una Worcester

Contents

M.U. Worcester (✉)
School of Public Health, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia
e-mail: marian.worcester@monash.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_51

Abstract

Many patients experience significant psychological distress after admission to hospital following acute coronary syndrome or to undergo percutaneous coronary angioplasty, coronary artery bypass surgery, or other cardiac surgery. Anxiety and depression are common emotional responses to these acute cardiac events and may be preexisting conditions. Symptoms of cognitive impairment, post-traumatic stress disorder, delirium, and major denial may also be present in hospitalized cardiac patients. Although gaps in knowledge exist concerning the impact and course of these disorders, there is now sufficient evidence showing their detrimental effects upon patients' recovery. The importance of early detection and management of depression, in particular, is essential to help prevent unwarranted psychological disability. Screening of patients is recommended in hospital and at appropriate intervals during follow-up. Brief screening tools are available which can be routinely administered. In addition, doctors and other health professionals should be aware of the clinical features of common psychological reactions of hospitalized patients to ensure prompt recognition and assessment. The important role of doctors in the clinical management of patients with anxiety and depression symptoms is stressed. However, referrals for the management of acutely distressed patients should be made to health professionals who have specific training in the treatment of psychological problems. Past studies have reported benefits from some depression treatments, especially those based on cognitive behavioral therapy. However, further rigorous research is required to develop, implement, and evaluate interventions for the early alleviation of symptoms of depression and other psychological conditions. Coordinated care of patients by a multidisciplinary team is essential. Encouragement of patients to attend a group cardiac rehabilitation program is highly recommended.

Keywords

Psychology • Psychiatry • Cardiac patient • Anxiety • Depression • Acute coronary syndrome • Coronary artery bypass graft surgery • Cardiology • Hospital • Cardiac rehabilitation

Introduction

Patients admitted to hospital after acute coronary syndrome (ACS) or to undergo coronary revascularization usually experience considerable emotional and physical distress. Unless detected early and treated effectively, psychological conditions such as anxiety and depression can have a negative impact upon recovery. Indeed, psychological disability is usually greater than physical disability in patients who have experienced an acute cardiac event.

Early pioneers in the field recognized the significant impact of negative emotions upon recovery following acute myocardial infarction (AMI) (Hackett

et al. 1968, 1969; Goble et al. 1963; Goble 1983; Wynn 1967). Their insightful clinical reports describing the symptoms, course, and treatment of anxiety and depression, in particular, have been frequently cited in the literature over the past 50 years.

The present chapter focuses on psychological and psychiatric issues of cardiac patients in hospital following ACS or to undergo coronary artery bypass graft surgery (CABGS) or percutaneous coronary intervention (PCI). It provides a brief overview of the typical symptoms, course, and impact of anxiety, depression, and denial. Other psychological complications, including post-traumatic stress disorder, delirium, and cognitive impairment, are also briefly described. Screening to enable early detection of anxiety, depression, and other conditions is addressed. Issues concerning the clinical management of cardiac patients in hospital are discussed, including the importance of exploring and modifying negative beliefs, providing clear explanations about the illness and the recovery process, and addressing patients' fears and concerns. Interventions for the management of depression, including pharmacological treatment, are reviewed. The need for a multidisciplinary approach to patient care is highlighted. The importance of careful discharge planning and follow-up is stressed, including referral to cardiac rehabilitation. Finally, recommendations are made concerning urgently needed research into the prevention and management of disabling conditions, especially depression.

Earlier chapters of this handbook cover anxiety, depression, and other psychological conditions in greater depth, including their prevalence, long-term impact upon mortality and morbidity, and possible mechanisms linking these conditions to cardiac outcomes.

Psychological Responses to Acute Cardiac Events

Anxiety after Acute Coronary Syndrome

Admission to a coronary care unit (CCU) often leads to acute anxiety and fear, especially the fear of dying. Other common fears of patients in the CCU include a further cardiac event, invalidism, unemployment, loss of income, and family distress. The CCU is a highly technological setting which is potentially frightening to critically ill patients (Sanders and Cassem 1993). The presence of cardiac monitoring devices and witnessing a cardiac arrest may exacerbate anxiety in some patients.

Anxiety is usually the immediate emotional response to an AMI and ACS (An et al. 2004), commonly peaking on admission to the CCU and again upon transfer to the ward (Stern 1985). Although anxiety often decreases spontaneously over time after hospital discharge, high levels of anxiety can persist for 1 year or more (Lane et al. 2002). The prevalence of anxiety following AMI has been reported to be between 24 % and 31 % (Frasure-Smith et al. 1995), with women experiencing higher levels of anxiety than men (An et al. 2004).

While anxiety is a normal response to life-threatening illness and admission to hospital, persisting or disabling anxiety can inhibit satisfactory recovery. Highly anxious patients have a lower quality of life (Lane et al. 2001) and delayed resumption of work (Havik and Maeland 1990). High anxiety early after AMI is independently predictive of increased morbidity (Frasure-Smith et al. 1995), including a higher risk of in-hospital complications (Moser and Dracup 1996), a longer stay in hospital (Lane et al. 2001), and an increased risk of recurrent cardiac events (Frasure-Smith et.al. 1995). Compared with the literature on depression, there have been relatively few studies investigating the effects of anxiety after AMI, and those which have been undertaken have produced inconsistent results. In particular, there is inconclusive evidence regarding the effect of anxiety on mortality (Lane et al. 2003).

Depression after Acute Coronary Syndrome

Depressive symptoms are common after AMI and ACS. Approximately 20 % of patients with ACS meet diagnostic criteria for a major depression disorder, and an even larger percentage show subclinical levels of depressive symptoms (Lichtman et al. 2014).

Symptoms of depression may be first experienced in hospital but commonly peak during convalescence. In other patients, there may be a delayed onset of depression which emerges only after the collapse of the defense of denial which concealed earlier depressive symptoms. Depression often persists for several months or more (Lane et al. 2002), intensifying in some patients after a further loss or crisis later in the recovery period (Brown and Harris 1978). Fluctuations in depressive symptoms over time are not uncommon.

Milder depressive symptoms are common after ACS. They are similar to a grief or bereavement reaction and may be referred to as a "depressed mood," in which a sense of real or feared loss is experienced, including the loss of immortality and independence (Goble et al. 1989). Common symptoms include poor concentration, restlessness, disturbed sleep, irritability, fatigue, withdrawal, loss of interest, pleasure and motivation, sentimentality, and tearfulness. Symptoms are often transient and their manifestations are usually subtle.

Numerous studies have been undertaken in recent years to examine the association between depression, mortality, and morbidity in cardiac patients (Lichtman et al. 2014). The severity, time of onset, and duration of depressive symptoms in relation to mortality and morbidity have been investigated, producing some conflicting findings. Depression after AMI has been associated with increased mortality and morbidity in several studies (Parashar et al. 2006; Frasure Smith et al. 1995; Mallik et al. 2006) but not in others (Lane et al. 2001). Mild as well as severe depressive symptoms have been found to be independent predictors of mortality and morbidity after AMI (Frasure-Smith et al. 1993). An increased risk of mortality in patients with a prior history of depression has also been reported (Lesperance et al. 2002). Irrespective of a history of depression, transient and

persistent depressive symptoms, as well as new symptoms found at 1 month, have all been shown to be significantly associated with adverse outcomes (Parashar et al. 2006). Depression predicts a slower recovery from AMI and poor quality of life (Lane et al. 2001; Frasure-Smith et al. 1993). Importantly, depression increases the risk of noncompliance with medical treatment (Ziegelstein et al. 2000) and is associated with lower participation in cardiac rehabilitation (Ades et al. 1992).

There is now a general consensus that depression remains associated with an increased risk of cardiac events and should be elevated to the status of a risk factor for adverse medical outcomes in patients with ACS (Lichtman et al. 2014). Depression may be a more important risk factor for women than for men, especially younger women (Mallik et al. 2006).

Anxiety and Depression in Patients Undergoing Revascularization

Anxiety is the dominant feeling before coronary artery bypass graft surgery (CABGS) (Duits et al. 1998) and has been reported to be present in 34 % of patients, especially younger patients (Krannich et al. 2007). Among preoperative concerns are fears relating to the impending surgery, postoperative pain, and having a fatal heart attack prior to surgery. After surgery some patients react with a decrease in anxiety (Krannich et al. 2007), whereas others exhibit increased feelings of anxiety and depression (Duits et al. 1998).

The prevalence of depression postoperatively has been estimated to be between 19 % and 61 % (Pignay-Demaria et al. 2003). Connerney and colleagues found that 20 % of patients met the criteria for major depressive disorder after CABGS and had higher rates of nonfatal cardiac events during the first 12 months after surgery (Connerney et al. 2001). The incidence of clinical depression in one study of women undergoing CABGS was 36 % before hospital discharge, with 9.3 % meeting criteria for major depression (Doering et al. 2006).

High levels of preoperative depression ranging from 23 % to 47 % have been reported (Pignay-Demaria et al. 2003; Krannich et al. 2007). Patients with a prior history of depression are at greater risk of postoperative depression (McKhann et al. 1997; Timberlake et al. 1997). Unfortunately the patient's preoperative depression status has not always been taken into account. Thus, the frequency of new depression after CABGS is unknown (Selnes et al. 1999).

Depression is an important independent risk factor for adverse outcomes following CABGS, including further events (Connerney et al. 2001). Contrary to other reports (O'Neil et al. 2010), depression was not found to predict resumption of work in one recent study, although depressive symptoms did predict a slower return to work (Worcester et al. 2014).

Relatively few studies have investigated in-hospital emotional responses to percutaneous coronary intervention (PCI), largely because of patients' short hospital stays. Patients' concerns usually relate to the outcome of the procedure, including a fear that surgery might be required. A high prevalence of anxiety and depression has been found in patients prior to PCI, with relief of angina symptoms

and improved psychosocial functioning in most patients after PCI (White and Frasure-Smith 1995). However, the procedure can be distressing to some patients, and high expectations before PCI can set patients up for depression or anxiety afterwards (Fitzgerald et al. 1989).

Denial

Denial is the most common defense mechanism used by cardiac patients to cope with symptoms of anxiety and depression (Stenstrom et al. 2005). Deniers tend to respond to an acute cardiac event by negating or minimizing its severity, symptoms, and possible outcomes, including death or invalidism. Denial of fear is common, with deniers often projecting their fears onto others or displacing their symptoms to indigestion, influenza, or other organs. Denial can be expressed verbally, behaviorally, or both. For most deniers, denial has been a lifelong defense.

Denial may serve either a functional or dysfunctional role, with both excessive and insufficient levels of denial leading to unacceptable outcomes (Dimsdale and Hackett 1982). Early after AMI, arrhythmias and other complications can occur which worsen the patient's prognosis. Since strong denial lessens these responses, chances of survival may improve for the first 48–72 hours (Levine et al. 1987). Unfortunately, patients with a high level of denial typically disregard their cardiac symptoms and delay seeking medical treatment (Stenstrom et al. 2005). Denial is also associated with decreased retention of information (Fowers 1992), nonadherence to advice (Levine et al. 1987; Stenstrom et al. 2005), and nonattendance at cardiac rehabilitation (Stenstrom et al. 2005).

Denial is common in the immediate postoperative period among CABGS patients who have a short history of angina and who undergo emergency surgery with little time to adjust (Pignay-Demaria et al. 2003). Interestingly, high levels of denial shortly after CABGS were associated in one study with less anxiety and depression and better psychosocial adjustment postoperatively (Folks et al. 1988).

Post-traumatic Stress Disorder

Acute cardiac events can cause significant distress and may trigger symptoms of post-traumatic stress disorder (PTSD) (Alonzo 2000) within days of AMI or CABGS (Kutz et al. 1994). Rates of PTSD after AMI have been reported to range between 8 % and 24 % (Kutz et al. 1994).

Preexisting PTSD may be present in some patients following the accumulation of previous traumatic events (Alonzo 2000). The diagnosis of PTSD requires the patient's response to a life-threatening event to include severe helplessness, fear, or horror. Reexperiencing symptoms is a central feature of PTSD, provoking intense negative emotions associated with the initial traumatic event (Alonzo 2000).

In cardiac patients, PTSD is associated with increased levels of anxiety, depression, hostility, and overall psychopathology. PTSD symptoms are strongly

correlated with failure to return to work (Kutz et al. 1994), poor overall quality of life (Shemesh et al. 2001), and nonadherence (Alonzo 2000). Patients who are traumatized may avoid being reminded of their acute event by not taking their medication or delaying seeking medical attention (Shemesh et al. 2001).

Delirium

Delirium is a clinical state in which patients exhibit fluctuating levels of consciousness and arousal, disorientation, diminished ability to concentrate, and either agitation or stupor (Barr et al. 2013). It is a frequent complication of cardiac surgery, especially in older patients, and is associated with a longer stay in hospital and adverse outcomes, including mortality (Saczynski et al. 2012). In one recent study, postoperative delirium developed in 46 % of cardiac surgical patients (Saczynski et al. 2012). A greater incidence of delirium has been found in patients who have undergone valve repair or replacement surgery (with or without CABGS), compared with patients undergoing CABGS alone (Hudetz et al. 2011).

Cognitive Impairment

Cognitive dysfunction is well documented in CABGS patients and may be present in up to 50 % of patients after CABGS (Newman et al. 2001; Selnes et al. 1999; Jensen et al. 2006). Impairment usually diminishes in the months after hospital discharge (Newman et al. 2001).

Awareness of cognitive impairment is a frequent source of anxiety or depression in cardiac patients after surgery. Some patients have a subjective sense of impairment, commonly involving memory disturbances, which might not be detected by standardized neuropsychological testing and which can reduce one's ability to enjoy intellectual pursuits (Selnes et al. 2012). Anxiety and depression are possible contributing factors to subjective memory problems (Selnes et al. 2012). However, while some have argued that postoperative depression accounts for cognitive decline, others assert that many patients who are depressed after CABGS were also depressed before surgery. Thus, postoperative depression alone cannot account for cognitive decline (McKhann et al. 1997; Selnes et al. 1999). While neurocognitive deficiencies were widely attributed to the use of cardiopulmonary bypass in earlier reports, recent studies have not shown a significant risk reduction associated with the use of off-pump surgery (Ernest et al. 2006).

More recently, the focus has shifted from procedure-related to patient-related risk factors to explain cognitive dysfunction (Selnes et al. 2012). Evidence now exists that many patients have impaired cognitive performance before cardiac surgery, with a frequency ranging from 20 % to 46 % (Jensen et al. 2006). The risk of cognitive decline after CABGS appears to be closely linked to the degree of preoperative cerebrovascular disease. Thus, preoperative cognitive impairment may be a surrogate marker for the degree of underlying cerebrovascular disease (Selnes et al. 2012).

For most patients in whom new cognitive symptoms develop postoperatively, symptoms generally resolve within 3 months (Selnes et al. 2012). According to this recent review, the incidence of cognitive dysfunction after CABGS has probably been greatly overestimated in earlier studies due to a lack of control groups, the use of inappropriate statistical methods, and the lack of a uniform definition of what constitutes cognitive decline (Selnes et al. 2012).

Identification and Assessment of Psychological Problems

It is essential that anxiety, depression, and other psychological or psychiatric conditions are detected and treated early to reduce suffering and improve the prognosis of hospitalized cardiac patients.

Recognition of Anxiety and Depression

Unfortunately anxiety and depression are often difficult to recognize. Symptoms of anxiety are frequently covert in cardiac patients. Overt symptoms such as hyperventilation or excessive perspiration are usually absent. Similarly, patients with depressive symptoms do not generally present with overt signs of emotional distress such as crying (Freedland et al. 1992). Many patients fail to communicate spontaneously, either verbally or nonverbally, that they are feeling apprehensive (Hackett et al. 1969). However, constant requests for reassurance or sedation can signify anxiety, as can outbursts of anger and impatience or threats to leave the hospital (Sanders and Cassem 1993).

Distinguishing somatic symptoms of anxiety and depression from physical symptoms attributable to the cardiac event can be difficult. Symptoms such as fatigue, appetite change, weight loss, and sleep disturbances are common to both conditions (Doerfler and Paraskos 2004; An et al. 2004). In addition, patients who are depressed often display mild symptoms which are not dissimilar to those experienced by patients who are not depressed (Freedland et al. 1992). Another difficulty in diagnosing depression is that it can share the same symptoms as anxiety, such as irritability, reduced concentration, and sleep disturbances. Indeed, it frequently coexists with anxiety (Connerney et al. 2001; Lane et al. 2002). Depression is often not recognized because it is overshadowed by more overt anxiety (Goble et al. 1989). Further, the presence of denial can effectively mask anxiety and, to a lesser extent, depression (Froese et al. 1974).

Failure of clinicians to recognize anxiety and depression is not unusual (Ziegelstein et al. 2005; O'Brien et al. 2001; Frasure-Smith et al. 1995; Mallik et al. 2006). Such failure can occur because insufficient time has been spent adequately exploring patients' symptoms in order to make an accurate diagnosis. Further, some clinicians might not recognize that anxiety has an important influence upon recovery and therefore fail to record its presence (O'Brien et al. 2001). In one study, fewer than 5 % of critical care nurses considered a patient's verbalization

of anxiety as an important element in the assessment of anxiety (Moser et al. 2003). Similarly, some cardiologists view depression simply as a marker of disease severity (Lane et al. 2003) and are not convinced that depression has any direct effects upon prognosis following AMI in addition to the severity of the cardiac damage (Carney et al. 1995). They may be reluctant to treat depression because they consider it to be a normal reaction to a life-threatening event which will lessen when patients resume their usual activities (Lichtman et al. 2008). Finally, it has been argued that many clinicians lack the skills to diagnose anxiety and depression (Ziegelstein et al. 2005). Evidence confirms that depression and anxiety in hospitalized cardiac patients are undertreated (Carney and Jaffe 2002; Parashar et al. 2006; Ziegelstein et al. 2005; Lesperance and Frasure-Smith 2000).

Screening for Depression and Anxiety

There has been a robust debate in recent years concerning the desirability of routine screening of patients for depression after an acute cardiac event (Whooley 2009; Thombs et al. 2008). Although no clinical trials have assessed whether screening improves depressive symptoms or cardiac outcomes in patients with cardiovascular disease (Thombs et al. 2008), the current consensus of expert opinion is that screening for depression is recommended because of the negative impact of depression upon outcomes, including quality of life and adherence (Lichtman et al. 2008). Routine screening tests should identify patients who require further assessment, treatment, or referral to a mental healthcare provider (Lichtman et al. 2008). The use of the Patient Health Questionnaire-2 (PHQ-2) (Kroenke et al. 2003) has been advocated as a first step in screening for depression. If there is an affirmative answer to either or both questions, all 9 PHQ items should be asked (Kroenke et al. 2001). Screening for depression is also recommended for patients about to undergo cardiac surgery. In addition, a past history of depression should be explored.

Given the potentially negative impact of anxiety on mortality and quality of life (Frasure-Smith et al. 1995; Moser and Dracup 1996; An et al. 2004), early screening for anxiety is also important so that it can be effectively managed. Possible screening tools include the seven-item anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983), although the development of briefer questionnaires to measure levels of anxiety has been recommended (O'Brien et al. 2001).

For routine screening to be useful, effective management protocols need to be devised (Thompson and Froelicher 2006) that clearly set out who should undertake the screening, how results should be handled, and who should make decisions about treatment. Importantly, the availability of well-trained professionals to provide psychological and psychiatric care should be guaranteed (Luttik et al. 2011). A recent study confirmed that systematic screening for depression by nurses was feasible and not markedly resource intensive (Sowden et al. 2010).

Earlier chapters cover in greater detail the debates concerning the desirability of routine screening and the choice of screening tools.

Screening for Other Conditions

Preoperative screening of cognitive function is recommended to provide a baseline measure against which to compare the postoperative performance of surgical patients. Suitable brief tools for the assessment of cognitive function include the 6CIT, Mini-Cog, and SIS (Australian Commission on Safety and Quality in Health Care 2013).

Cognitive screening should enable early identification of patients with postoperative delirium, using a tool such as the CAM-ICU, followed by a psychiatric assessment to refute or confirm the diagnosis (Barr et al. 2013).

Patients with high levels of denial should be identified in hospital and monitored. Brief screening tools have been developed (Fowers 1992). However, excessive denial should be easily recognized clinically.

Screening for PTSD symptoms can be undertaken by diagnostic clinical interview or self-report assessment, but preferably both. A prior diagnosis of PTSD should also be investigated (Griffiths et al. 2007). Screening for PTSD is important to identify patients who are at increased risk of nonadherence (Shemesh et al. 2001).

Managing Psychological Responses of Patients in Hospital

Modifying Negative Perceptions and Beliefs

Much of the psychological distress experienced by cardiac patients, both in hospital and subsequently, can be attributed to misconceptions and folklore beliefs about the disease and the acute event itself. The detrimental effects of misconceptions were first described by clinicians in the 1960s (Goble et al. 1963; Wynn 1967). They noted that patients considered many activities to be injurious or dangerous, such as raising their hands above their head, lying on their left side, or losing their temper. These restrictive misconceptions were often reinforced by family members and others. More recent research confirms that damaging misconceptions and folklore beliefs persist in many cardiac patients (Goulding et al. 2010).

Diagrams drawn by patients reveal considerable misunderstanding of the impact of their heart attack (Broadbent et al. 2004; Logan 1986) and can therefore help to identify maladaptive beliefs, providing a starting point for patient education. Perceptions of a permanently damaged heart can contribute to the development of depression (Broadbent et al. 2004). The correction of misconceptions revealed in patient drawings has been associated with a decline in anxiety and depressive symptoms (Logan 1986).

Patients' assessments of the severity of their acute event and likely prognosis often fail to match clinical indicators but appear to be better predictors of outcomes (Broadbent et al. 2006; Laferton et al. 2013). Positive expectations regarding resumption of work have been found to be good predictors of actual return to work, regardless of the severity of the event (Maeland and Havik 1987). Negative

expectations have been associated with a slower return to work and poorer occupational adjustment (Petrie et al. 1996; Maeland and Havik 1987). Further, patients with more optimistic expectations that their illness was amenable to cure or control have been found to be more likely than others to attend cardiac rehabilitation (Petrie et al. 1996). Improving the accuracy of risk perceptions might help to reduce unnecessary cardiac anxiety and invalidism in some patients while prompting favorable behavior change in others (Broadbent et al. 2006).

Many PCI patients believe that their illness is not serious and that after their procedure they are cured of coronary artery disease. As a result, such patients may fail to adhere to medical and lifestyle advice. Such underestimation of the significance of the PCI procedure might be reinforced by short hospital stays (White and Frasure-Smith 1995). The reality of the underlying disease and prognosis must be discussed early with PCI patients in order to correct any misconceptions (Corones et al. 2009).

Many patients demonstrate a limited awareness of major risk factors for cardiovascular disease. Further, they frequently attribute their illness to external factors, commonly work or other stress (Maeland and Havik 1987; Thompson and Lewin 2000) and fail to recognize the causal role of lifestyle and physiological risk factors (Murphy et al. 2005). Investigation of patients' perceptions of causal factors is essential in order to correct any erroneous beliefs, since faulty attributions about causal factors can lead to nonadherence (Maeland and Havik 1987). Attitudes toward return to work need to be carefully explored in case reluctance to resume is based upon patients' ill-founded fears about the role of work stress in causing their heart disease.

A systematic review of interventions to change maladaptive illness beliefs in cardiac patients found that some interventions were successful. Cognitive behavioral interventions appeared to be the most consistently effective (Goulding et al. 2010). For example, a brief hospital-based intervention using cognitive behavioral therapy (CBT) was successful in changing illness perceptions after AMI and in improving recovery (Petrie et al. 2002). A later replication study found that the intervention was also effective in patients with ACS, those with repeat MI (Broadbent et al. 2009a), and spouses (Broadbent et al. 2009b). Beliefs should be explored and modified early in the recovery process to avoid protracted disability at a later stage.

Providing Information to Patients

Patients require simple and clear explanations of the acute event, symptoms, and projected treatment, including investigations or procedures. The typical recovery process should be outlined and specific advice provided about resumption of activities of daily living. The chronic nature of cardiovascular disease should be emphasized. Modification of risk factors to reduce the risk of further events should be discussed. Secondary prevention programs using behavioral techniques, including the Women's Initiative for Non-Smoking (WINS) trial, have been successfully

implemented in hospital. This intervention was an effective nurse-managed smoking cessation program for cardiac patients based on the cognitive behavioral model of relapse prevention (Froelicher et al. 2004).

Patients commonly prefer specific information in writing as well as verbal advice (Corones et al. 2009). In addition, the timing of information provision is crucial. Information might have been provided but not absorbed by patients because of their high levels of anxiety or denial, pain, or cognitive difficulties. The physical and psychological status of patients must to be taken into account prior to delivering education. Further, contradictory information given by different health professionals needs to be avoided to reduce confusion (Goble and Worcester 1999). Retention of information is enhanced if it is tailored to the patient's particular needs and if patients are actively involved in developing and prioritizing their learning goals (Veronovici et al. 2014).

Education is best delivered in an interactive fashion, with opportunities provided for patients to ask questions and seek clarification (Goble and Worcester 1999). Unfortunately, many health professionals are poor educators, tending to deliver information in a didactic manner. In addition, they commonly lack adequate listening skills and the ability to uncover pressing educational and emotional needs of patients. Further, if the patient's physical symptoms are acute and the need for medical management is urgent, clinicians may avoid addressing the informational and mental health needs of the patient altogether. More research is needed to determine how best to provide individualized patient-centered care and how to educate nurses and other health professionals in the provision of such care (Veronovici et al. 2014).

Discussing Patients' Fears and Concerns

In addition to providing patients with clear explanations about their illness, careful listening to their concerns can alleviate psychological distress (Pignay-Demaria et al. 2003). Early discussion of the patient's fears pays enormous dividends in terms of the prevention of anxiety and unwarranted invalidism (Goble et al. 1963). Fear of death or a further event is present in most patients in the CCU and ICU. However, as previously noted, patients are generally reluctant to initiate discussion of their fears or to ask for reassurance directly (Freedland et al. 1992). Thus, the responsibility for enquiring about fears lies with the doctor or other health professional. Simply asking patients if they are frightened can help to uncover anxiety not otherwise apparent. Initial denial is usual, but once rapport has been established, admission of fear becomes more common. Depression can be detected from careful history taking and observation. Simple questions to open the issue of emotional distress but without using the word "depression" are recommended (Lesperance and Frasure-Smith 2000).

It is obviously important not to foster iatrogenic anxiety by poor communication, including making over-guarded statements or giving vague advice (Goble 1983; Thompson and Lewin 2000). Medical advice, if not given with great care and

recognition of what is already believed by the patient, may harm rather than help the patient and considerably heighten anxiety (Goble et al. 1963). The daily medical round can create anxiety in patients. If doctors discuss the patient's condition at the bedside, terminology and prognostic information will be heard but probably not understood by the patient. It is preferable for the medical team to conduct such discussions elsewhere. At the bedside, reassurance of progress is more appropriate. It is also an opportunity to invite patients to ask questions about any matters which are concerning them. It can be extremely helpful to reassure patients that "the worst is over" after their first day in hospital. In addition to explanation and discussion, normalization of emotional responses is important. Patients need reassurance that an anxious or depressed mood is common after an acute cardiac event and is usually transient (Goble et al. 1989; Thompson and Lewin 2000).

Fostering Optimism and Enhancing Self-Efficacy

Cardiac rehabilitation should begin on day 1 of the patient's admission. Because the fear of weakness and disability is present in most patients, early ambulation is essential to dispel these fears, followed by increasing mobilization to reassure patients that they are improving and that physical activity is safe. Active mobilization is especially helpful for patients with depressive symptoms (Pignay-Demaria et al. 2003).

Forewarning patients about what to expect as they transition to the next stage of recovery can help them to avoid unnecessary emotional distress. In particular, educating patients about what to expect after discharge from hospital helps to decrease depression and anxiety. It can be especially important to forewarn patients that a depressed mood is common during convalescence and that such "homecoming depression" should be regarded as a normal, transient response (Thompson and Lewin 2000; Utriyaprasit et al. 2010). In one study, patients who received an intervention of education and emotional support soon after their admission to the CCU were found to be better prepared and more positive about their homecoming and had significantly less anxiety and depression (Thompson and Meddis 1990a). Similarly, education delivered prior to revascularization can have a positive effect upon recovery, leading to less anxiety, greater self-confidence, more realistic expectations, and increased compliance with medical advice (Veronovici et al. 2014; White and Frasure-Smith 1995).

Observing other patients who have undergone the same procedure or experienced a similar event can raise a patient's expectations of mastering similar situations. The vicarious experience of observing discharged patients leading active lives can increase self-efficacy in hospitalized patients concerning their own ability to engage in post-discharge activities. According to anecdotal evidence, patients about to undergo surgery benefit from a visit by a patient who is recovering well from recent CABGS. Similarly reassuring is a visit by inpatients to the cardiac rehabilitation program, if sited within the hospital. Such visits reassure patients who are about to undergo CABGS as well as those who are still in hospital recovering

from surgery. A trial of an intervention linking former patients who had recovered from cardiac surgery with patients about to undergo cardiac surgery showed that the intervention significantly reduced anxiety, improved self-efficacy expectations, and accelerated recovery (Parent and Fortin 2000). In another study, patients randomly assigned prior to surgery to a room with a postoperative roommate were less anxious preoperatively, more ambulatory postoperatively, and discharged 1.4 days earlier than patients assigned to a room with a preoperative roommate (Kulik and Mahler 1987).

Psychological Interventions

There are relatively few controlled studies of interventions which specifically aim to reduce psychological distress in cardiac patients in hospital. Most are offered after patients' discharge from hospital or preoperatively to patients awaiting CABGS. Because positive expectations have been associated with favorable outcomes, a randomized controlled trial is currently in progress to determine whether a brief psychoeducational intervention can optimize patients' expectations prior to CABGS (Laferton et al. 2013).

CBT, psychotherapy, and interpersonal psychotherapy have been recommended as suitable approaches for managing depression in cardiac patients, either alone or in combination with pharmacological therapies (Lichtman et al. 2008). However, nearly all randomized controlled trials of depression treatments to date have been conducted in patients without coronary heart disease (Lett et al. 2005). Some CBT interventions, such as that implemented in the ENRICHD trial, have successfully reduced depressive symptoms in cardiac patients (Berkman et al. 2003). However, in that study the relative improvement in the intervention group compared with the usual care group was less than expected due to substantial improvement in usual care patients. A brief cognitive behavioral intervention delivered prior to CABGS demonstrated small but significant differences in depression, but not anxiety, in favor of patients receiving the HeartOp program (Furze et al. 2009). A recent Australian trial of a group secondary prevention program based on CBT and motivational interviewing, delivered 7–8 weeks after hospital discharge, led to significantly greater improvement in depressive symptoms in depressed patients (Turner et al. 2014).

A meta-analysis of psychological treatments for cardiac patients offered in addition to usual care found a reduction of 27 % in mortality over 2 years in men, but there were no mortality benefits for women. Studies included in this meta-analysis in which patients were recruited at least 2 months after a cardiac event showed much greater mortality benefits from psychological treatments than patients receiving interventions which took place soon after the cardiac event (Linden et al. 2007). Interventions for depression management which start later might demonstrate greater effects, since they would have excluded patients whose depression had already remitted spontaneously by the time of recruitment to the study, or those who responded well to usual care (Schrader et al. 2004).

Collaborative Care Programs

Collaborative care programs have been recently introduced to improve the coordinated management of depression in cardiac and other patients. Such programs include systematic psychiatric assessment and the use of a nonphysician care manager to monitor symptoms, treatment interventions, specialist-provided stepped-care recommendations, and care coordination (Huffman et al. 2014; Rollman et al. 2009). Collaborative care interventions for psychiatric disorders are cost effective and are reported to be successful in improving outcomes (Huffman et al. 2014). A recent trial of collaborative care for depressed cardiac patients found significantly increased rates of appropriate care for the intervention group, defined as either a discharge prescription of an antidepressant at a clinically effective dose by the time of discharge from hospital or referral to a mental health provider for psychotherapy (Huffman et al. 2011). A telephone-delivered collaborative care program for CABGS patients also led to improved mood symptoms at the 8-month follow-up (Rollman et al. 2009).

Pharmacological Treatment

According to recent policy guidelines, severely or persistently depressed patients should receive comprehensive evaluation and treatment or referral to a mental health specialist for management (Lichtman et al. 2014). For cardiac patients with moderate, severe, or recurrent depression, selective serotonin reuptake inhibitors (SSRIs) are both safe and effective, as discussed more fully elsewhere. Some patients may respond better to a combination of an antidepressant and psychotherapy than to either treatment alone (Lichtman et al. 2008; Krannich et al. 2007). Anxiolytic drugs, even in small doses, can be prescribed for the treatment of anxiety (Krannich et al. 2007).

Delirium can usually be managed effectively with frequent reassurance and early mobilization. Prompt pharmacological treatment of extremely agitated patients is recommended (Barr et al. 2013). Antidepressants and CBT are recommended therapies for the alleviation of symptoms of PTSD (Meyer and Hall 2006). Psychiatric evaluation of patients with high levels of denial is recommended to assess the possibility of modifying undesirable behaviors and increasing patients' insight into the realities of their disease (Dimsdale and Hackett 1982).

Supporting Partners of Cardiac Patients

It is desirable to include partners of cardiac patients in counseling sessions in hospital whenever possible, since partners often experience considerable stress. Commonly underlying their distress is a fear that the patient will die or have a further event. Levels of spouses' anxiety and depression are often greater than those of patients and can persist for some time. Counseling in hospital has been shown to

be effective in reducing the anxiety of spouses, with benefits persisting up to 6 months (Thompson and Meddis 1990b).

The Multidisciplinary Team

In Australian hospitals, patients with pronounced psychological or psychiatric problems are generally referred to the liaison psychiatry unit. The liaison psychiatrist's role is to assess the patient's condition, institute appropriate treatment, and liaise closely with the cardiologist or cardiac surgeon and nursing staff.

The physician or surgeon should ideally be responsible for providing the patient with clear explanations about the illness and reassurance. However, these roles are often fulfilled by nurses rather than doctors. Nurses can make a significant input into alleviating the psychological distress of patients by providing counseling and psychological support. Indeed, mental health nurses and experienced registered nurses can detect and assess depression in most patients relatively easily and accurately without needing to refer patients for specialist assessment and management. With appropriate training, nurses can also deliver interventions to patients and family members (Thompson and Froelicher 2006).

Psychologists can play an important role in screening patients for depression and other disorders, assessing the psychological needs of patients, undertaking counseling, and delivering CBT or other interventions. With their extensive training in interviewing and experience in mental health, social workers have a key role in helping to uncover psychological or social problems and counseling patients. They also have an important linking function, communicating with the patient's partner and ensuring patient and family goals are incorporated into discharge plans (Goble and Worcester 1999). In a recent collaborative care trial, the social worker was designated as care manager (Huffman et al. 2011).

The psychological recovery of patients in hospital is best facilitated by a multidisciplinary approach to patient care, with close collaboration between staff involved in critical care. In practice, however, there is clearly the potential for a much greater input from nurses, psychologists, and social workers into the psychological management of cardiac inpatients, with liaison psychiatrists helping to develop the mental healthcare skills of medical and other staff, as required. In addition, a greater emphasis needs to be placed in nursing and medical education on the clinical assessment of emotional responses to illness (O'Brien et al. 2001).

Discharge Planning and Follow-Up

Primary Care Professionals

The general practitioner and other primary care professionals are usually responsible for the long-term monitoring and management of patients' mental health, with referral to specialists, as required. It is critically important for hospital staff to liaise

with these practitioners to ensure the coordinated care of patients after their discharge from hospital (Goble and Worcester 1999), especially patients with persistent depression (Rollman et al. 2009). Patients with high levels of denial also need to be regularly monitored. Such patients commonly fail to adhere to medical advice and ignore cardiac-related symptoms. They are likely to be among those patients experiencing a further event who die before reaching hospital (Carney and Jaffe 2002). Patients who successfully concealed their depressive symptoms initially become more vulnerable once their defense of denial collapses. Patients with PTSD also need ongoing monitoring. They typically avoid reminders of traumatic events, including symptoms associated with their acute cardiac event (Doerfler and Paraskos 2004).

Cardiac Rehabilitation and Secondary Prevention

Several guidelines recommend that ACS and CABGS patients should attend a cardiac rehabilitation program soon after discharge from hospital (WHO Expert Committee 1993; Wenger et al. 1995; Goble and Worcester 1999; Perk et al. 2012). Numerous benefits of cardiac rehabilitation have been demonstrated (Wenger et al. 1995). While other effective cardiac rehabilitation models have recently been developed, a group program has important advantages. Exercise can help to reduce depressive symptoms in patients (Lett et al. 2005), as can participation in a group where patients recognize that others are experiencing similar emotions and that their own responses are not unique. Patients also gain by observing a rapid recovery in others (Goble et al. 1989; Thompson and Lewin 2000). Importantly, cardiac rehabilitation programs provide significant social support during convalescence. Further, given the increasingly shortened hospital stays after ACS and CABGS, outpatient cardiac rehabilitation programs offer an opportunity for reinforcing education and providing more comprehensive and individualized advice. Cardiac rehabilitation can also be an effective launching pad for secondary prevention of CVD.

Further screening of patients for depression after hospital discharge has been strongly recommended (Parashar et al. 2006). While spontaneous improvement occurs in some patients, depression worsens in others or emerges only during convalescence. Therefore resources for screening and treating depression might be best directed at patients who are depressed during convalescence rather than in hospital (Schrader et al. 2004). Rescreening patients for depression can be easily incorporated into the routine of cardiac rehabilitation.

Referrals to cardiac rehabilitation need to be organized efficiently before patients leave the hospital. A designated cardiac rehabilitation coordinator is essential. Unfortunately, participation rates in many countries are disappointingly low (Goble and Worcester 1999; Balady et al. 2011). However, a recent study found that by adhering to best practice guidelines, some common barriers to attendance were overcome, with a high attendance rate of 72 % being achieved (Higgins et al. 2008). The policy in Australia of automatic referral to a cardiac rehabilitation

program unless medical contraindications exist is strongly recommended, since it is not possible to predict which patients are likely to benefit most from cardiac rehabilitation on the basis of their in-hospital characteristics alone. Strong encouragement from doctors has been shown to be a major predictor of cardiac rehabilitation attendance (Ades et al. 1992). A recommendation to attend is especially important for high-risk patients who typically fail to participate, such as those with high levels of depression (Ades et al. 1992), excessive denial (Stenstrom et al. 2005), and women (Ades et al. 1992).

Conclusions

There is now considerable evidence confirming the significant impact psychological responses can have upon outcomes of acute cardiac events. This chapter has briefly reviewed common emotional problems experienced by ACS and CABGS patients in hospital, especially anxiety and depression, and how best these conditions can be recognized early, assessed, and managed.

Despite the increasing focus in the literature on psychological dysfunction in cardiac patients, there remain many gaps which need to be addressed in future studies. Subtypes and characteristics of depression most associated with an increased risk of mortality and morbidity after ACS need to be identified (Lichtman et al. 2014). In particular, further research is urgently needed to differentiate the characteristics of patients whose depression will remit spontaneously from patients whose symptoms will persist or worsen and who need aggressive treatment (Carney and Jaffe 2002; Schrader et al. 2004). Because many past studies have reported only a snapshot of depression at one timepoint, fluctuations in the course of depression over time have been masked (Timberlake et al. 1997). More research using appropriate statistical techniques should be undertaken into patterns of depression and anxiety at multiple timepoints to identify different trajectories and to distinguish transient from more chronic disturbances. Expressing results of studies as group means obscures individual variations in affect, and therefore, subgroups of patients who improve or decline are not detected (Millar et al. 2001).

Unfortunately, although some studies have produced encouraging results, there are presently no definitive data to guide depression treatments in cardiac patients. There is an urgent need for further research in this area. More controlled studies are required to determine whether cognitive behavioral, interpersonal, or other forms of therapy are effective in treating depression in cardiac patients (Carney et al. 1995; Lesperance and Frasure-Smith 2000). Some evidence exists to show that medication and cognitive behavioral therapy are associated with modest benefits in depression outcomes but no improvement in cardiac outcomes (Thombs et al. 2008). Well-designed studies are needed to determine whether treatment of depression after ACS improves clinical outcomes (Lichtman et al. 2014). It should be noted that many past studies of depression and its impact were primarily designed as cardiology studies to which psychological questions were added.

More research is required concerning certain groups of patients, in particular, including those who are resistant to treatment of their depression (Rollman et al. 2009), so that different strategies can be developed for them. Interventions specifically designed for women are also required (Luttik et al. 2011), especially for younger women in whom the prevalence of depression is high (Mallik et al. 2006). Additional interventions for the management of anxiety and other disorders also need to be developed and tested.

Since most patients currently remain in hospital for just a few days after their acute cardiac event, there is only a limited time in which to detect and manage excessive anxiety, depression, or other negative emotions. Interventions should be developed which can be initiated in hospital and continued during convalescence and beyond in order to help prevent depression and other psychological problems from persisting and worsening. Careful discharge planning is especially important to ensure a seamless transition to primary care for ongoing management of the patient's mental health. Further, more effective strategies are needed to increase attendance rates at cardiac rehabilitation and secondary prevention programs where additional opportunities exist for the screening and treatment of anxiety, depression, or other psychological conditions.

Given that psychological distress is often associated with negative perceptions and beliefs, it is important to explore patients' views about the causes and expected outcomes of their illness, modifying any erroneous beliefs, if present. Patients should receive clear explanations about their illness, and an optimistic outlook for the future should be encouraged. Finally, a multidisciplinary approach is essential to good clinical management of cardiac patients in hospital and beyond.

References

Ades, P. A., Waldmann, M. L., Polk, D. M., & Coflesky, J. T. (1992). Referral patterns and exercise response in the rehabilitation of female coronary patients aged $\geq$ 62 years. *American Journal of Cardiology, 69*(17), 1422–1425.

Alonzo, A. A. (2000). The experience of chronic illness and post-traumatic stress disorder: The consequences of cumulative adversity. *Social Science & Medicine, 50*(10), 1475–1484.

An, K., de Jonge, M. J., Riegel, B. J., McKinley, S., Garvin, B. J., Doering, L. V., & Moser, D. K. (2004). A cross-sectional examination of changes in anxiety early after acute myocardial infarction. *Heart & Lung: The Journal of Acute and Critical Care, 33*(2), 75–82.

Australian Commission on Safety and Quality in Health Care. (2013). *Evidence for the safety and quality issues associated with the care of patients with cognitive impairment in acute care settings: A rapid review*. Sydney: ACSQHC.

Balady, G. J., Ades, P. A., Bittner, V. A., Franklin, B. A., Gordon, N. F., Thomas, R. J., Tomaselli, G. F., & Yancy, C. W. (2011). Referral, enrollment, and delivery of cardiac rehabilitation/secondary prevention programs at clinical centers and beyond: A presidential advisory from the American Heart Association. *Circulation, 124*, 2951–2960.

Barr, J., Fraser, G. L., Puntillo, K., Ely, E. W., Gélinas, C., Dasta, J. F., ... Jaeschke, R. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine*, *41*(1), 263–306.

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catellier, D., Cowan, M. J., et al. (2003). Effects of treating depression and low perceived social support on clinical events after

myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA: Journal of the American Medical Association, 289* (23), 3106–3116.

Broadbent, E., Petrie, K. J., Ellis, C. J., Ying, J., & Gamble, G. (2004). A picture of health – Myocardial infarction patients' drawings of their hearts and subsequent disability: A longitudinal study. *Journal of Psychosomatic Research, 57*(6), 583–587.

Broadbent, E., Petrie, K. J., Ellis, C. J., Anderson, J., Gamble, G., Anderson, D., & Benjamin, W. (2006). Patients with acute myocardial infarction have an inaccurate understanding of their risk of a future cardiac event. *Internal Medicine Journal, 36*(10), 643–647.

Broadbent, E., Ellis, C. J., Thomas, J., Gamble, G., & Petrie, K. J. (2009a). Can an illness perception intervention reduce illness anxiety in spouses of myocardial infarction patients? A randomized controlled trial. *Journal of Psychosomatic Research, 67*(1), 11–15.

Broadbent, E., Ellis, C. J., Thomas, J., Gamble, G., & Petrie, K. J. (2009b). Further development of an illness perception intervention for myocardial infarction patients: A randomized controlled trial. *Journal of Psychosomatic Research, 67*(1), 17–23.

Brown, G. W., & Harris, T. (1978). *Social origins of depression: A study of psychiatric disorder in women*. London: Tavistock Publications.

Carney, R. M., & Jaffe, A. S. (2002). Treatment of depression following acute myocardial infarction. *JAMA: Journal of the American Medical Association, 288*(6), 750–751.

Carney, R. M., Freedland, K. E., Rich, M. W., & Jaffe, A. S. (1995). Depression as a risk factor for cardiac events in established coronary heart disease: A review of possible mechanisms. *Annals of Behavioral Medicine, 17*(2), 142–149.

Connerney, I., Shapiro, P. A., McLaughlin, J. S., Bagiella, E., & Sloan, R. P. (2001). Relation between depression after coronary artery bypass surgery and 12-month outcome: A prospective study. *The Lancet, 358*(9295), 1766–1771.

Corones, K., Coyer, F. M., & Theobald, K. A. (2009). Exploring the information needs of patients who have undergone PCI. *British Journal of Cardiac Nursing, 4*(3), 123–130.

Dimsdale, J. E., & Hackett, T. P. (1982). Effect of denial on cardiac health and psychological assessment. *American Journal of Psychiatry, 139*(11), 1477–1480.

Doerfler, L. A., & Paraskos, J. A. (2004). Anxiety, posttraumatic stress disorder, and depression in patients with coronary heart disease: A practical review for cardiac rehabilitation professionals. *Journal of Cardiopulmonary Rehabilitation and Prevention, 24*(6), 414–421.

Doering, L. V., Magsarili, M. C., Howitt, L. Y., & Cowan, M. J. (2006). Clinical depression in women after cardiac surgery. *Journal of Cardiovascular Nursing, 21*(2), 132–139.

Duits, A. A., Duivenvoorden, H. J., Boeke, S., Taams, M. A., Mochtar, B., Krauss, X. H., … Erdman, R. A. M. (1998). The course of anxiety and depression in patients undergoing coronary artery bypass graft surgery. *Journal of Psychosomatic Research*, *45*(2), 127–138.

Ernest, C. S., Worcester, M. U., Tatoulis, J., Elliott, P. C., Murphy, B. M., Higgins, R. O., … Goble, A. J. (2006). Neurocognitive outcomes in off-pump versus on-pump bypass surgery: A randomized controlled trial. *Annals of Thoracic Surgery*, *81*(6), 2105–2114.

Fitzgerald, S. T., Becker, D. M., Celentano, D. D., Swank, R., & Brinker, J. (1989). Return to work after percutaneous transluminal coronary angioplasty. *The American Journal of Cardiology, 64*(18), 1108–1112.

Folks, D. G., Freeman, A. M., Sokol, R. S., & Thurstin, A. H. (1988). Denial: Predictor of outcome following coronary bypass surgery. *International Journal of Psychiatry in Medicine, 18*(1), 57–66.

Fowers, B. J. (1992). The cardiac denial of impact scale: A brief, self-report research measure. *Journal of Psychosomatic Research, 36*(5), 469–475.

Frasure-Smith, N., Lespérance, F., & Talajic, M. (1993). Depression following myocardial infarction: Impact on 6-month survival. *JAMA: Journal of the American Medical Association, 270*(15), 1819–1825.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1995). The impact of negative emotions on prognosis following myocardial infarction: Is it more than depression? *Health Psychology, 14*(5), 388–398.

Freedland, K. E., Lustman, P. J., Carney, R. M., & Hong, B. A. (1992). Underdiagnosis of depression in patients with coronary artery disease: The role of nonspecific symptoms. *International Journal of Psychiatry in Medicine, 22*(3), 221–229.

Froelicher, E. S. S., Miller, N. H., Christopherson, D. J., Martin, K., Parker, K. M., Amonetti, M., . . . Bacchetti, P. (2004). High rates of sustained smoking cessation in women hospitalized with cardiovascular disease: The Women's Initiative for Nonsmoking (WINS). *Circulation*, *109*(5), 587–593.

Froese, A., Hackett, T. P., Cassem, N. H., & Silverberg, E. L. (1974). Trajectories of anxiety and depression in denying and nondenying acute myocardial infarction patients during hospitalization. *Journal of Psychosomatic Research, 18*(6), 413–420.

Furze, G., Dumville, J. C., Miles, J. N., Irvine, K., Thompson, D. R., & Lewin, R. J. (2009). "Prehabilitation" prior to CABG surgery improves physical functioning and depression. *International Journal of Cardiology, 132*(1), 51–58.

Goble, A. J. (1983). Folklore and disability in heart disease. *National Heart Foundation of Australia Notes on Cardiovascular Diseases, 19*(6), 21–24.

Goble, A. J., & Worcester, M. U. (1999). *Best practice guidelines for cardiac rehabilitation and secondary prevention*. Victoria: Department of Human Services.

Goble, A. J., Adey, G. M., & Bullen, J. F. (1963). Rehabilitation of the cardiac patient. *Medical Journal of Australia, 2*, 975–982.

Goble, A. J., Biddle, N., & Worcester, M. C. (1989). Depression after acute cardiac illness. *Quality of Life and Cardiovascular Care, 2*, 60–63.

Goulding, L., Furze, G., & Birks, Y. (2010). Randomized controlled trials of interventions to change maladaptive illness beliefs in people with coronary heart disease: Systematic review. *Journal of Advanced Nursing, 66*(5), 946–961.

Griffiths, J., Fortune, G., Barber, V., & Young, J. D. (2007). The prevalence of post traumatic stress disorder in survivors of ICU treatment: A systematic review. *Intensive Care Medicine, 33*(9), 1506–1518.

Hackett, T. P., Cassem, N. H., & Wishnie, H. A. (1968). The coronary care unit. An appraisal of its psychologic hazards. *New England Journal of Medicine, 279*(25), 1365–1370.

Hackett, T. P., Cassem, N. H., & Wishnie, H. (1969). Detection and treatment of anxiety in the coronary care unit. *American Heart Journal, 78*(6), 727–730.

Havik, O. E., & Maeland, J. G. (1990). Patterns of emotional reactions after a myocardial infarction. *Journal of Psychosomatic Research, 34*(3), 271–285.

Higgins, R. O., Murphy, B. M., Goble, A. J., Le Grande, M. R., Elliott, P. C., & Worcester, M. U. (2008). Cardiac rehabilitation program attendance after coronary artery bypass surgery: Overcoming the barriers. *Medical Journal of Australia, 188*(12), 712–714.

Hudetz, J. A., Iqbal, Z., Gandhi, S. D., Patterson, K. M., Byrne, A. J., & Pagel, P. S. (2011). Postoperative delirium and short-term cognitive dysfunction occur more frequently in patients undergoing valve surgery with or without coronary artery bypass graft surgery compared with coronary artery bypass graft surgery alone: Results of a pilot study. *Journal of Cardiothoracic and Vascular Anesthesia, 25*(5), 811–816.

Huffman, J. C., Mastromauro, C. A., Sowden, G. L., Wittmann, C., Rodman, R., & Januzzi, J. L. (2011). A collaborative care depression management program for cardiac inpatients: Depression characteristics and in-hospital outcomes. *Psychosomatics, 52*(1), 26–33.

Huffman, J. C., Niazi, S. K., Rundell, J. R., Sharpe, M., & Katon, W. J. (2014). Essential articles on collaborative care models for the treatment of psychiatric disorders in medical settings: A publication by the Academy of Psychosomatic Medicine Research and Evidence-based Practice Committee. *Psychosomatics, 55*(2), 109–122.

Jensen, B. O., Hughes, P., Rasmussen, L. S., Pedersen, P. U., & Steinbrüchel, D. A. (2006). Cognitive outcomes in elderly high-risk patients after off-pump versus conventional coronary artery bypass grafting: A randomized trial. *Circulation, 113*(24), 2790–2795.

Krannich, J. H. A., Weyers, P., Lueger, S., Herzog, M., Bohrer, T., & Elert, O. (2007). Presence of depression and anxiety before and after coronary artery bypass graft surgery and their relationship to age. *BMC Psychiatry, 7*(1), 47–52.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine, 16*(9), 606–613.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2003). The patient health questionnaire-2: Validity of a two-item depression screener. *Medical Care, 41*(11), 1284–1292.

Kulik, J. A., & Mahler, H. I. (1987). Effects of preoperative roommate assignment on preoperative anxiety and recovery from coronary bypass surgery. *Health Psychology, 6*(6), 525–543.

Kutz, I., Shabtai, H., Solomon, Z., Neumann, M., & David, D. (1994). Post-traumatic stress disorder in myocardial infarction patients: Prevalence study. *Israel Journal of Psychiatry and Related Sciences, 31*(1), 48–56.

Laferton, J. A., Shedden Mora, M., Auer, C. J., Moosdorf, R., & Rief, W. (2013). Enhancing the efficacy of heart surgery by optimizing patients' preoperative expectations: Study protocol of a randomized controlled trial. *American Heart Journal, 165*(1), 1–7.

Lane, D., Carroll, D., Ring, C., Beevers, D. G., & Lip, G. Y. (2001). Mortality and quality of life 12 months after myocardial infarction: Effects of depression and anxiety. *Psychosomatic Medicine, 63*(2), 221–230.

Lane, D., Carroll, D., Ring, C., Beevers, D. G., & Lip, G. Y. (2002). The prevalence and persistence of depression and anxiety following myocardial infarction. *British Journal of Health Psychology, 7*, 11–21.

Lane, D., Carroll, D., & Lip, G. Y. (2003). Anxiety, depression, and prognosis after myocardial infarction – Is there a causal association? *Journal of the American College of Cardiology, 42*(10), 1808–1810.

Lespérance, F., & Frasure-Smith, N. (2000). Depression in patients with cardiac disease: A practical review. *Journal of Psychosomatic Research, 48*(4), 379–391.

Lesperance, F., Frasure-Smith, N., Talajic, M., & Bourassa, M. G. (2002). Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation, 105*, 1049–1053.

Lett, H. S., Davidson, J., & Blumenthal, J. A. (2005). Nonpharmacological treatments for depression in patients with coronary heart disease. *Psychosomatic Medicine, 67*(suppl 1), S58–S62.

Levine, J., Warrenburg, S., Kerns, R., Schwartz, G., Delaney, R., Fontana, A., … Cascione, R. (1987). The role of denial in recovery from coronary heart disease. *Psychosomatic Medicine*, *49*(2), 109–117.

Lichtman, J. H., Bigger, J. T., Blumenthal, J. A., Frasure-Smith, N., Kaufmann, P. G., Lespérance, F., … Froelicher, E. S. (2008). Depression and coronary heart disease recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. *Circulation*, *118*(17), 1768–1775.

Lichtman, J. H., Froelicher, E. S., Blumenthal, J. A., Carney, R. M., Doering, L. V., Frasure-Smith, N., … Wulsin, L. (2014). Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: Systematic review and recommendations: A scientific statement from the American Heart Association. *Circulation*, *129*(12), 1350–69.

Linden, W., Phillips, M. J., & Leclerc, J. (2007). Psychological treatment of cardiac patients: A meta-analysis. *European Heart Journal, 28*(24), 2972–2984.

Logan, R. L. (1986). Patient drawings as aids to the identification and management of causes of distress and atypical symptoms of cardiac patients. *New Zealand Medical Journal, 99*(802), 368–371.

Luttik, M. L. A., Jaarsma, T., Sanderman, R., & Fleer, J. (2011). The advisory brought to practice: Routine screening on depression (and anxiety) in coronary heart disease: Consequences and implications. *European Journal of Cardiovascular Nursing, 10*(4), 228–233.

Mæland, J. G., & Havik, O. E. (1987). Psychological predictors for return to work after a myocardial infarction. *Journal of Psychosomatic Research, 31*(4), 471–481.

Mallik, S., Spertus, J. A., Reid, K. J., Krumholz, H. M., Rumsfeld, J. S., Weintraub, W. S., … Vaccarino, V. (2006). Depressive symptoms after acute myocardial infarction: Evidence for highest rates in younger women. *Archives of Internal Medicine*, *166*(8), 876–883.

McKhann, G. M., Borowicz, L. M., Goldsborough, M. A., Enger, C., & Selnes, O. A. (1997). Depression and cognitive decline after coronary artery bypass grafting. *Lancet, 349*(9061), 1282–1284.

Meyer, N. J., & Hall, J. B. (2006). Bench-to-bedside review: Brain dysfunction in critically ill patients–the intensive care unit and beyond. *Critical Care, 10*(4), 223–231.

Millar, K., Asbury, A. J., & Murray, G. D. (2001). Pre-existing cognitive impairment as a factor influencing outcome after cardiac surgery. *British Journal of Anaesthesia, 86*(1), 63–67.

Moser, D. K., & Dracup, K. (1996). Is anxiety early after myocardial infarction associated with subsequent ischemic and arrhythmic events? *Psychosomatic Medicine, 58*(5), 395–401.

Moser, D. K., Chung, M. L., McKinley, S., Riegel, B., An, K., Cherrington, C.C., . . . Garvin, B. J., et.al. (2003). Critical care nursing practice regarding patient anxiety assessment and management. *Intensive Critical Care Nursing*, *19,* 276–288.

Murphy, B., Worcester, M., Higgins, R., Le Grande, M., Larritt, P., & Goble, A. (2005). Causal attributions for coronary heart disease among female cardiac patients. *Journal of Cardiopulmonary Rehabilitation and Prevention, 25*(3), 135–143.

Newman, M. F., Kirchner, J. L., Phillips-Bute, B., Gaver, V., Grocott, H., Jones, R. H., … Blumenthal, J. A. (2001). Longitudinal assessment of neurocognitive function after coronary artery bypass surgery. *New England Journal of Medicine*, *344*(6), 395–402.

O'Brien, J. L., Moser, D. K., Riegel, B., Frazier, S. K., Garvin, B. J., & Kim, K. A. (2001). Comparison of anxiety assessments between clinicians and patients with acute myocardial infarction in cardiac critical care units. *American Journal of Critical Care, 10*(2), 97–103.

O'Neil, A., Sanderson, K., & Oldenburg, B. (2010). Depression as a predictor of work resumption following myocardial infarction (MI): A review of recent research evidence. *Health Quality of Life Outcomes, 8*(1), 95–105.

Parashar, S., Rumsfeld, J. S., Spertus, J. A., Reid, K. J., Wenger, N. K., Krumholz, H. M., et al. (2006). Time course of depression and outcome of myocardial infarction. *Archives of Internal Medicine, 166*(18), 2035–2043.

Parent, N., & Fortin, F. (2000). A randomized, controlled trial of vicarious experience through peer support for male first-time cardiac surgery patients: Impact on anxiety, self-efficacy expectation, and self-reported activity. *Heart & Lung: The Journal of Acute and Critical Care, 29*(6), 389–400.

Perk, J., De Backer, G., Gohlke, H., Graham, I., Reiner, Z., Verschuren, M., Albus, C., Benlian, P., Boysen, G., Cifkova, R., Deaton, C., Ebrahim, S., Fisher, M., Germano, G., Hobbs, R., Hoes, A., Karadeniz, S., Mezzani, A., Prescott, E., Ryden, L., Scherer, M., Syvänne, M., op Reimer WJ, S., Vrints, C., Wood, D., Zamorano, J. L., Zannad, F., & European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). (2012). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *European Heart Journal, 33*(13), 1635–1701.

Petrie, K. J., Weinman, J., Sharpe, N., & Buckley, J. (1996). Role of patients' view of their illness in predicting return to work and functioning after myocardial infarction: Longitudinal study. *British Medical Journal, 312*(7040), 1191–1194.

Petrie, K. J., Cameron, L. D., Ellis, C. J., Buick, D., & Weinman, J. (2002). Changing illness perceptions after myocardial infarction: An early intervention randomized controlled trial. *Psychosomatic Medicine, 64*(4), 580–586.

Pignay-Demaria, V., Lespérance, F., Demaria, R. G., Frasure-Smith, N., & Perrault, L. P. (2003). Depression and anxiety and outcomes of coronary artery bypass surgery. *Annals of Thoracic Surgery, 75*(1), 314–321.

Rollman, B. L., Belnap, B. H., LeMenager, M. S., Mazumdar, S., Houck, P. R., Counihan, P. J., … Reynolds, C. F. (2009). Telephone-delivered collaborative care for treating post-CABG depression: A randomized controlled trial. *Journal of the American Medical Association*, *302*(19), 2095–2103.

Saczynski, J. S., Marcantonio, E. R., Quach, L., Fong, T. G., Gross, A., Inouye, S. K., & Jones, R. N. (2012). Cognitive trajectories after postoperative delirium. *New England Journal of Medicine, 367*(1), 30–39.

Sanders, K. M., & Cassem, E. H. (1993). Psychiatric complications in the critically ill cardiac patient. *Texas Heart Institute Journal, 20*, 180–187.

Schrader, G., Cheok, F., Hordacre, A. L., & Guiver, N. (2004). Predictors of depression three months after cardiac hospitalization. *Psychosomatic Medicine, 66*(4), 514–520.

Selnes, O. A., Goldsborough, M. A., Borowicz, L. M., & McKhann, G. M. (1999). Neurobehavioural sequelae of cardiopulmonary bypass. *The Lancet, 353*(9164), 1601–1606.

Selnes, O. A., Gottesman, R. F., Grega, M. A., Baumgartner, W. A., Zeger, S. L., & McKhann, G. M. (2012). Cognitive and neurologic outcomes after coronary artery bypass surgery. *New England Journal of Medicine, 366*(3), 250–257.

Shemesh, E., Rudnick, A., Kaluski, E., Milovanov, O., Salah, A., Alon, D., … Cotter, G. (2001). A prospective study of posttraumatic stress symptoms and nonadherence in survivors of a myocardial infarction (MI). *General Hospital Psychiatry*, *23*(4), 215–222.

Sowden, G., Mastromauro, C. A., Januzzi, J. L., Fricchione, G. L., & Huffman, J. C. (2010). Detection of depression in cardiac inpatients: Feasibility and results of systematic screening. *American Heart Journal, 159*(5), 780–787.

Stenström, U., Nilsson, A. K., Stridh, C., Nijm, J., Nyrinder, I., Jonsson, A., … Jonasson, L. (2005). Denial in patients with a first-time myocardial infarction: Relations to pre-hospital delay and attendance to a cardiac rehabilitation programme. *European Journal of Cardiovascular Prevention and Rehabilitation*, *12*(6), 568–571.

Stern, T. A. (1985). The management of depression and anxiety following myocardial infarction. *Mount Sinai Journal of Medicine, 52*(8), 623–633.

Thombs, B. D., de Jonge, P., Coyne, J. C., Whooley, M. A., Frasure-Smith, N., Mitchell, A. J., … Ziegelstein, R. C. (2008). Depression screening and patient outcomes in cardiovascular care: A systematic review. *Journal of the American Medical Association*, *300*(18), 2161–2171.

Thompson, D. R., & Froelicher, E. S. (2006). Depression in cardiac patients: What can nurses do about it? *European Journal of Cardiovascular Nursing, 5*(4), 251–252.

Thompson, D. R., & Lewin, R. J. (2000). Management of the post-myocardial infarction patient: Rehabilitation and cardiac neurosis. *Heart, 84*(1), 101–105.

Thompson, D. R., & Meddis, R. (1990a). A prospective evaluation of in-hospital counselling for first time myocardial infarction men. *Journal of Psychosomatic Research, 34*(3), 237–248.

Thompson, D. R., & Meddis, R. (1990b). Wives' responses to counselling early after myocardial infarction. *Journal of Psychosomatic Research, 34*(3), 249–258.

Timberlake, N., Klinger, L., Smith, P., Venn, G., Treasure, T., Harrison, M., & Newman, S. P. (1997). Incidence and patterns of depression following coronary artery bypass graft surgery. *Journal of Psychosomatic Research, 43*(2), 197–207.

Turner, A., Murphy, B. M., Higgins, R. O., Elliott, P. C., Le Grande, M. R., Goble, A. J., & Worcester, M. U. (2014). An integrated secondary prevention group programme reduces depression in cardiac patients. *European Journal of Preventive Cardiology, 21*, 153–162.

Utriyaprasit, K., Moore, S. M., & Chaiseri, P. (2010). Recovery after coronary artery bypass surgery: Effect of an audiotape information programme. *Journal of Advanced Nursing, 66*(8), 1747–1759.

Veronovici, N. R., Lasiuk, G. C., Rempel, G. R., & Norris, C. M. (2014). Discharge education to promote self-management following cardiovascular surgery: An integrative review. *European Journal of Cardiovascular Nursing, 13*(1), 22–31.

Wenger, N. K., Froelicher, E. S., Smith, L. K., et al. (1995). Cardiac Rehabilitation. Clinical Practice Guideline No. 17. *US Department of Health and Human Services, AHCPR Publication*, (96–0672).

White, R. E., & Frasure-Smith, N. (1995). Uncertainty and psychologic stress after coronary angioplasty and coronary bypass surgery. *Heart & Lung: The Journal of Acute and Critical Care, 24*(1), 19–27.

Whooley, M. A. (2009). To screen or not to screen? Depression in patients with cardiovascular disease. *Journal of the American College of Cardiology, 54*(10), 891–893.

Worcester, M. U., Elliott, P. C., Turner, A., Pereira, J. J., Murphy, B. M., Le Grande, M. R., et al. (2014). Resumption of work after acute coronary syndrome or coronary artery bypass graft surgery. *Heart Lung and Circulation, 23*(5), 444–453.

World Health Organization. Rehabilitation after cardiovascular diseases, with special emphasis on developing countries. Report of a WHO Expert Committee. Geneva, Switzerland; 1993. WHO Technical Report Series, No. 831.

Wynn, A. (1967). Unwarranted emotional distress in men with ischaemic heart disease. *Medical Journal of Australia, 2*, 847–851.

Ziegelstein, R. C., Fauerbach, J. A., Stevens, S. S., Romanelli, J., Richter, D. P., & Bush, D. E. (2000). Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Archives of Internal Medicine, 160*(12), 1818–1823.

Ziegelstein, R. C., Kim, S. Y., Kao, D., Fauerbach, J. A., Thombs, B. D., McCann, U., . . . Bush, D. E. (2005). Can doctors and nurses recognize depression in patients hospitalized with an acute myocardial infarction in the absence of formal screening? *Psychosomatic Medicine*, *67*(3), 393–397.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361–370.

Mindfulness- and Meditation-Based Healthcare Approach Implications for Prevention, Detection, and Treatment in Cardiology

Graham Meadows and Frances Shawyer

Contents

G. Meadows (✉)
Department of Psychiatry, Monash University, Clayton, VIC, Australia

School of Global and Population Health, The University of Melbourne, Clayton, VIC, Australia
e-mail: graham.meadows@monash.edu

F. Shawyer
Department of Psychiatry, Monash University, Clayton, VIC, Australia
e-mail: frances.shawyer@monash.edu

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_52

Abstract

The chapter opens with an account from an American physician of a meeting with a Tibetan Buddhist practitioner for whom mindful awareness was central to resolving a cardiological diagnostic question, and rather more than that.

After a note on the quality and level of evidence base in this area, a general introduction to mindfulness and other meditative traditions follows, including something of relevant history and cultural origins and the range of interventions that may be considered related in contemporary healthcare.

The role of mindfulness- and meditation-based approaches will briefly be considered as they may be relevant for the practicing clinician and as they have been introduced into a number of medical educational settings.

This leads to considering the role of mindfulness-based interventions in reducing risk factors (Yusuf et al. Lancet 364(9438):937–952, 2004), particularly behavior and lifestyle factors but also psychiatric disorders, particularly depression (Rosengren et al. Lancet 364(9438):953–962, 2004) as shown substantially to influence risk for cardiac conditions.

In the context of treatment of specific cardiac disorders, studies that involve the application of mindfulness- or meditation-based approaches will be considered.

As the chapter considers specific disorder contexts, there will in each case be a drawing of the evidence together by the authors into some suggestions for how mindfulness-based interventions may be relevant for clinical management.

Keywords

Mindfulness • Yoga • Meditation • Heart disease • Buddhist philosophy • Bible • Risk factors • Hypertension • Overweight • Obese

Introduction

Yeshi Dhonden Does Rounds: By Richard Selzer

On the bulletin board in the front hall of the hospital where I work, there appeared an announcement. "Yeshi Dhonden," it read, "will make rounds at six o'clock on the morning of June 10." The particulars were then given, followed by a notation: "Yeshi Dhonden is Personal Physician to the Dalai Lama." I am not so leathery a skeptic that I would knowingly ignore an emissary from the gods. Not only might

such sangfroid be inimical to one's earthly well-being, it could take care of eternity as well. Thus, on the morning of June 10, I join the clutch of whitecoats waiting in the small conference room adjacent to the ward selected for the rounds. The air in the room is heavy with ill-concealed dubiety and suspicion of bamboozlement. At precisely six o'clock, he materializes, a short, golden, barelly man dressed in a sleeveless robe of saffron and maroon. His scalp is shaven, and the only visible hair is a scanty black line above each hooded eye. He bows in greeting while his young interpreter makes the introduction. Yeshi Dhonden, we are told, will examine a patient selected by a member of the staff. The diagnosis is as unknown to Yeshi Dhonden as it is to us. The examination of the patient will take place in our presence, after which we will reconvene in the conference room where Yeshi Dhonden will discuss the case. We are further informed that for the past two hours Yeshi Dhonden has purified himself by bathing, by fasting, and by prayer. I, having breakfasted well, performed only the most desultory of ablutions, and given no thought at all to my soul, glance furtively at my fellows. Suddenly, we seem a soiled, uncouth lot.

The patient had been awakened early and told that she was to be examined by a foreign doctor and had been asked to produce a fresh specimen of urine, so when we enter her room, the woman shows no surprise. She has long ago taken on that mixture of compliance and resignation that is the facies of chronic illness. This was to be but another in an endless series of tests and examinations. Yeshi Dhonden steps to the bedside while the rest stand apart, watching. For a long time he gazes at the woman, favoring no part of her body with his eyes, but seeming to fix his glance at a place just above her supine form. I, too, study her. No physical sign nor obvious symptom gives a clue to the nature of her disease.

At last he takes her hand, raising it in both of his own. Now he bends over the bed in kind of a crouching stance, his head drawn down into the collar of his robe. His eyes are closed as he feels for her pulse. In a moment he has found the spot, and for the next half hour, he remains thus, suspended above the patient like some exotic bird with folded wings, holding the pulse of the woman beneath his fingers, cradling her hand in his. All the power of the man seems to have been drawn down into this one purpose. It is palpitation of the pulse raised to the state of ritual. From the foot of the bed, where I stand, it is as though he and the patient have entered a special place of isolation, of apartness, about which a vacancy hovers, and across which no violation is possible. After a moment the woman rests back upon her pillow. From time to time, she raises her head to look at the strange figure above her, then sinks back once more. I cannot see their hands joined in a correspondence that is exclusive, intimate, his fingertips receiving the voice of her sick body through the rhythm and throb she offers at her wrist. All at once I am envious - not of him, not of Yeshi Dhonden for his gift of beauty and holiness, but of her. I want to be held like that, touched so, *received*. And I know that I, who have palpated a hundred thousand pulses, have not felt a single one.

At last Yeshi Dhonden straightens, gently places the woman's hand upon the bed, and steps back. The interpreter produces a small wooden bowl and two sticks. Yeshi Dhonden pours a portion of the urine specimen into the bowl, and proceeds to

whip the liquid with the two sticks. This he does for several minutes until a foam is raised. Then, bowing above the bowl, he inhales the odor three times. He sets down the bowl and turns to leave. All this while, he has not uttered a single word. As he nears the door, the woman raises her head and calls out to him in a voice at once urgent and serene. "Thank you, doctor," she says, and touches with her other hand the place he had held on her wrist, as though to recapture something that had visited there. Yeshi Dhonden turns back for a moment to gaze at her, then steps into the corridor. Rounds are at an end.

We are seated once more in the conference room. Yeshi Dhonden speaks now for the first time, in soft Tibetan sounds that I have never heard before. He has barely begun when the young interpreter begins to translate, the two voices continuing in tandem - a bilingual fugue, the one chasing the other. It is like the chanting of monks. He speaks of winds coursing through the body of the woman, currents that break against barriers, eddying. These vortices are in her blood, he says. The last spendings of an imperfect heart. Between the chambers of her heart, long, long before she was born, a wind had come and blown open a deep gate that must never be opened. Through it charge the full waters of her river, as the mountain stream cascades in the springtime, battering, knocking loose the land, and flooding her breath. Thus he speaks, and is silent.

"May we now have the diagnosis?" a professor asks.

The host of these rounds, the man who knows, answers.

"Congenital heart disease," he says, "inter ventricular septal defect, with resultant heart failure."

A gateway in the heart, I think. That must not be opened. Through it charge the full waters that flood of her breath. So! Here then is the doctor listening to the sounds of the body to which the rest of us are deaf. He is more than doctor. He is priest.

I know. . . I know. . . the doctor to the gods is pure knowledge, pure healing. The doctor to man stumbles, must often wound; his patient must die, as must he.

Now and then it happens, as I make my own rounds, that I hear the sounds of his voice, like an ancient Buddhist prayer, its meaning long since forgotten, only the music remaining. Then a jubilation possesses me, and I feel myself touched by something divine.

The Relevant Evidence Base

Phases in the Development of the Evidence Base

The empirical work of relevance presented in this chapter could be considered in two phases.

From the 1970s forward, there is work on meditation and yoga practices addressing, particularly, risk factors such as hypertension. Much early work focused on mantra-based meditation, specifically Transcendental Meditation (TM).

From the late 1990s forward, work more specifically coheres around the term "mindfulness." This is an alignment with a very strong growth in the general volume of research in this area. The strongest strands of work in this area are with group-based meditation techniques, by way of variants on mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT).

Levels of Evidence

In the case of conditions that are established risk factors and relating levels of evidence to the GRADE classification (Owens et al. 2010), then for some clinical questions, the evidence may be approaching "high" levels. However, in much of this literature, especially as the concentration moves to smaller bodies of published work, the evidence levels encountered will be more in alignment with GRADE definitions of moderate, low, or very low, and not uncommonly there is insufficient evidence to reach a conclusion.

Systematic reviews, where they exist so providing the potential to lift evidence into higher categories, often will feature studies going back many years and publication bias as an influence on findings cannot be excluded. It is only since 2005 that the International Committee of Medical Journal Editors (ICMJE) determined not to publish trials other than those formally registered, and much of the literature is not in the ICMJE journals. It is only since 2008 that the revised declaration of Helsinki (World Medical Association 2013) required trial registration. A systematic review published in 2008 of this area concluded that "Most clinical trials on meditation practices are generally characterized by poor methodological quality with significant threats to validity in every major quality domain assessed." Some 10 % of surveyed studies were considered as of good quality (Ospina et al. 2008). So until there are appreciable bodies of work with improved quality and accumulated since the 2005 and 2008 safeguards were put in place, practice will often need to be conducted in the context of a somewhat limited empirical evidence base.

General Introduction to Mindfulness

What Is Mindfulness

History

> What is a man, that myndeful thou art of him?
> Wycliffe's Bible, Psalm viii. 6

The first generally recognized occurrence of the word mindful in the English language is in 1382 in Wycliffe's Bible, specifically in Psalms where the question is asked of God why he is "myndeful" of man; much later (1970), the New English Bible renders this as "what is man that thou should remember him?" Used in

English, then, for several centuries reflected a quality of recollection, also heedfulness and acting with care. Since the late nineteenth century, the term mindfulness has been the most common translation of the term from the Pali Buddhist scriptures "sati." The earlier English usage, often regarded as obsolete, nevertheless probably has some influence over how the term typically is understood and interpreted.

Defining, Characterizing, or Evoking Mindfulness

> Anyone who isn't confused, really doesn't understand the situation.
> Edward R. Murrow

Considerable attention in the literature is devoted to discussion of how mindfulness can be briefly captured for definition, and there are many examples where authors have attempted to capture the term in one sentence or phrase. An example from a careful review of this area would be: "self-regulating attention toward the immediate present moment and adopting an orientation marked by curiosity, openness, and acceptance." This can usefully be extended into two components (Bishop et al. 2004) of which the first "involves the self-regulation of attention so that it is maintained on immediate experience, thereby allowing for increased recognition of mental events in the present moment." The second involves "adopting a particular orientation toward one's experiences in the present moment, an orientation that is characterized by curiosity, openness, and acceptance."

A widely used questionnaire to assess development of mindfulness includes five facets: observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity to inner experience. To this commonly may be added self-compassion, receiving increased attention as a likely mediator of important effects (Kuyken et al. 2010). An important related concept in psychology is that of metacognitive awareness or the development of an internal element of mind habitually devoted to monitoring mental states.

Mindfulness often is cultivated in programs that involve a substantial component of meditation practice with exploration of mindful states, although as can be seen from the above attempts to capture or define it, the goal is something more like a shift in trait or habitual mental ways of relating to internal mental content. Such programs (Kabat-Zinn 2005; Segal et al. 2012) therefore, often involve out of session tasks intended to bring the kind of awareness cultivated in meditation as states into becoming regular habits.

The complexity of capturing mindfulness in a simple definition may arise because, taking into consideration the origins of the term within Buddhist philosophy and practice, it was taught as an interactive set of processes or practices. These seem to have been intended as quite carefully interlocking and promoting a progressive upward spiral of progress. When the historical Buddha taught what is often referred to as the key teaching on this, the Satipatthana Sutta (Thera 2010), he did so within teachings grouped under four mindfulnesses. These are those of body, sensations/feelings, mind/consciousness, and mental contents. Within this, he advised a wide range of contemplations intended to promote motivation toward development of mindfulness and through the exercise of particular objects of

attention, to assist the practitioner. These included, for instance, contemplation of death and impermanence and his key teachings on the nature of existence and experience, often referred to as the four noble truths. An ongoing task within the psychology and other literatures is that of extracting to what extent mindfulness as employed for therapeutic interventions can be understood, transmitted, or modeled without some acquaintance at least with the teachings from out of which it has arisen. Here may be included Buddhist teachings, perhaps traditions such as yoga or other spiritual contemplative traditions. Many courses aiming to support cultivation of the skills needed for practitioners to deliver mindfulness-based interventions now include some exposure to Buddhist and other philosophical systems of relevance; this exposure may be important for the development of the necessary background knowledge and capacity to deliver the interventions. Also commonly emphasized for mindfulness-based intervention practitioners is the need to develop and maintain some level of mindfulness practice as needed to support an authentic presence in the context of the delivery of the intervention.

Mindfulness, Therapies, and Meditation

Mindfulness-Based Approaches

Not all mindfulness approaches involve formal meditation, and not all meditation involves promotion of mindfulness. Meditation-based approaches that may be introduced into healthcare and which are mindfulness-based include MBSR, MBCT, Vipassana, and Zen meditation among others. MBCT and MBSR both are described as mindfulness-based and this is very clear in their structure. Both of them usually are presented as group-based experiences. They share a common format of 8 weeks of approximately 2-hour group sessions, often with a full day of meditation offered at some point. In both, the early focus is strongly toward the development of meditation practices and, through that and other elements of homework, the incorporation of mindful presence into daily life. Later on in the usual 8-week course, with the expectation of being able to build on some acquired capacity for mindful awareness, the focus shifts more toward the employment of mindful approaches to specific coping strategies or developing new habitual ways of responding intended as health promoting. MBCT and MBSR both make use of poetry to evoke and facilitate the development of mindfulness. Here they draw on materials from various cultural sources ranging from the Persian poet Rumi to the American poet Mary Oliver.

The richness of such poetry can vividly illuminate the key qualities of mindfulness and help inspire the possibility of a radical shift in perspective from the future-oriented and often predominant "doing" mode (such as when problem solving, making plans, and achieving goals) to "being" (allowing things to be as they are in the present moment).

In MBCT, for example, this quality of acceptance is considered to be critical for preventing relapse in recurrent depression. Allowing difficult feelings to remain in awareness, just as they are, is an important alternative to the automatic response of

aversion which can easily become the first link in the chain of habitual ruminative patterns of thinking that can then lead to relapse of depression (Segal et al. 2013). There is a risk, however, that "acceptance" can imply for some a sense of passivity and resignation (Segal et al. 2013), while, for others, the prospect of allowing difficult emotions may be frightening (Shapiro 2001). "The Guest House" poem by Rumi (Barks and Moyne 1997) can dramatically transform these reactions, inspiring a profoundly different and warm-hearted stance of welcoming difficult feelings as transient but honorable guests in one's metaphorical "house." Another poem, "The Summer Day" by Mary Oliver (1990), powerfully expresses to participants the importance of taking care of themselves, also critical for preventing depressive relapse. By reminding us of our mortality and that we can choose how we live our "one wild and precious life" (p. 60), this poem opens up the possibility of getting off the treadmill of rules that seem to constrain life to a series of tasks and obligations that "should" be done. "Wild Geese," also by Mary Oliver (1986), conveys the sense of spaciousness that mindfulness can bring to experience, where thoughts, feelings, and sensations can be held in awareness without being engulfed by them, enabling an appreciation of the wider context (Segal et al. 2013).

Mindfulness-based approaches are available in a range of spiritual techniques and also in lay settings. Interventions such as MBSR and MBCT are typically conducted in secular environments and often with deliberate avoidance of overtly spiritual symbolism. MBSR is quite readily available in many Western societies – fees vary with healthcare systems. Mindfulness-based meditation courses also are available in many spiritual traditions especially Buddhist ones. Naturally, these will typically have overtly spiritual content and will include presentation of Buddhist philosophical content as part of the course. This may be a source of attraction to some but for others may make such opportunities inaccessible or inappropriate.

Therapeutic Approaches That Involve Mindfulness to Varying Degrees

Meditation-based approaches that may or may not include promotion of mindfulness (Goyal et al. 2014a, b) may include TM, other mantra meditations, also dialectical behavior therapy (DBT), acceptance and commitment therapy (ACT), and movement-based meditations, such as yoga (e.g., Iyengar, hatha, shavasana), tai chi, and qigong (chi kung). Other approaches that may be considered by some as having a meditative component at least, but where this is not the foundation and majority of the intervention could include: aromatherapy, biofeedback, neurofeedback, hypnosis, autogenic training, psychotherapy, laughter therapy, therapeutic touch, eye movement desensitization reprocessing, relaxation therapy, spiritual therapy, and breathing exercises.

TM is a mantra-based technique that promotes attention control with intent through this to promote positive physical health and well-being. Internal repetition of a mantra is taught with instruction as to the preferred mental attitude toward this. It is typically taught in a seven-step course that takes six days and needs to be delivered by a certified TM teacher. While it does not necessarily promote mindfulness in the way that say MBSR or MBCT does, it is a meditative approach that works on attention control, and so it is included in the scope of this chapter. TM is

promoted by members of a worldwide organization associated with Maharishi Mahesh Yogi who died in 2008. As something that is not part of mainstream healthcare, fees consistently are charged and can be substantial, though also discounts or scholarships may be provided for those unable to pay. The TM movement has associations with a political group – the Natural Law Party. It involves the use of a mantra with Vedic origins. The TM movement has received criticisms and allegations that it has something of a cult status. For some, these associations and those with other practices in the tradition such as Yogic Flying may undermine the credibility of TM, but for others, such associations may be a source of appeal.

Yoga considered as a therapy has foundations in philosophical systems that have commonality with other mindfulness practices and so is included here, although the emphasis on mindfulness as contrasted with the physical exercise component of yoga may vary between practitioners.

Cultural Congruence

In considering recommending meditation or related approaches for patients in Western clinical care settings, the practitioner needs to consider the cultural congruence and acceptability of such suggestion. Mindfulness- and meditation-based activities are increasing across many Western countries. The United States has been described as possibly being in the context of a "mindful revolution" (Pickert 2014). In Australia, there is some information on community prevalence of mindfulness or yoga practice, at least among women, where about 30 % of respondents in a major national survey said they practice something of this nature on a regular basis (Sibbritt et al. 2011).

For adherents of the Indian or East Asian religions, particularly Buddhists, or people from countries or cultures where these are the dominant religious affiliations, then meditation or a mindful approach to life may well be culturally congruous, but this should not automatically be assumed. In many Buddhist societies, for instance, meditation is generally a monastic activity, practiced much less by lay people. In Western society, it often would be questionable for a Christian practitioner to recommend prayer as an approach to management of health problems. For some people from Indian or East Asian religious backgrounds, proposing that they engage in meditation similarly may be seen as problematic in affiliating with a religious or spiritual position.

Although meditation is most usually associated with the Indian or East Asian religions, there are branches of religions in the Abrahamic tradition (Christianity, Judaism, Islam) that may include meditative or contemplative practices, and for their adherents, proposing meditation may be quite culturally congruous. But occasionally, patients with a strong and specific religious adherence within these traditions may take the view that engaging in a meditation or yoga practice involves an exposure to an alien and potentially dangerous philosophical system, and such individuals may be affronted by such suggestions.

To make the first directly clinical point in this chapter, in considering whether someone may helpfully be referred for a mindfulness- or meditation-based intervention, it will be important to explore with them what their history of connection with meditation or mindfulness practices and the associated attitudes might be. It is important to approach this without too much in the way of preconceptions, as the reaction may occasionally be surprising.

Mindfulness for the Practitioner

> Use your five senses. Learn to see, learn to hear, learn to feel, learn to smell, and know that by practice alone you can become expert.
> Listen to your patient, he is telling you the diagnosis
> William Osler

Medical training includes the development of clinical skills such as visual observation, refined palpation, and auscultation. Hence, it involves refinement of attention control and, through training, some enhancement of discriminative abilities across multiple sensory modalities. The development and maintenance of these observational abilities may well be benefited from mindfulness and concentration training.

Not uncommonly, the situations of medical practice are associated with complex competing demands, with highly emotionally-charged contexts, and sometimes with unaccustomed hours, even occasionally extreme sleep deprivation. Despite being under these stresses, the physician is expected to maintain the ability to integrate findings from multiple sensory modalities, to relate these to clinical algorithms and other supports to decision-making, to make accurate and confident decisions while remaining empathic, tactful, and articulate in clinical and interprofessional relationships. So, medicine as a profession contains considerable stresses, and the phenomenon of clinical burnout as one of a range of possible adverse reactions to this has been well described. Research indicates that mindfulness-based trainings are among the interventions that can assist clinicians in avoiding burnout (Linzer et al. 2014; Van Gordon et al. 2014).

Mindfulness-based trainings may also be able to contribute to better empathic function in clinical and other contexts and to more positive and considerate behavior in workplaces. Again, the use of poetry can again be very helpful in such training, facilitating the development of a mindful presence in the physician (Connelly 1999; Shapiro 2001). Direct cultivation of compassion typically through loving-kindness meditation is likely also to be effective in this respect (Boellinghaus et al. 2014).

With these above considerations, a number of medical schools have introduced mindfulness training into their courses (Dobkin and Hutchinson 2013). In Australia, the one with strongest and most long-standing commitment to this has been Monash University. In the United States and Canada, programs can be found at least at Brown University Alpert Medical School, Duke University Medical School,

Georgetown University School of Medicine, McGill Faculty of Medicine, the University of Massachusetts, the University of Pennsylvania, the University of Rochester, and the University of Wisconsin. The last of these, for instance, has an approachable website supporting clinicians in engaging in mindfulness practice in ways adapted to the demands of busy clinical roles (University of Wisconsin School of Medicine and Public Health 2010).

Mindfulness and Meditation for People at Risk

Introduction

Among significant modifiable risk factors for cardiovascular disorders (Yusuf et al. 2004), here will be considered, in sequence, smoking, elevated lipid levels, hypertension, diabetes, overweight or obesity, depression, and alcohol use. In each paragraph there will be consideration of: the rationale, the evidence, and then some suggested conclusions regarding clinical management.

Smoking

There are theoretical reasons why mindfulness- or meditation-based approaches might be effective in assisting smoking reduction or cessation or indeed promoting positive changes in other substance use patterns. Individuals with greater levels of mindfulness with its features of self-awareness, attention control, and self-monitoring might be more able consistently to apply suggested strategies to reduce or cease smoking. There is indeed evidence that trait mindfulness among people taking part in smoking cessation programs is associated with better results for those participants (Vidrine et al. 2009). Physical exercise often is advocated in smoking cessation. The mindfulness-based interventions that involve yoga may be beneficial on this basis. Although mindfulness of the breath typically does not directly advise participants to slow their breathing, this commonly occurs, and the parasympathetic activation with reduction in sympathetic nervous system (SNS) activation with this, may reduce craving.

In a systematic review of the applicability of these interventions to smoking cessation (Carim-Todd et al. 2013), the review process, when a fairly broad inclusion criterion was adopted, identified 14 eligible studies. Problems identified with the body of evidence included: variability in the intervention conditions, including widely varying duration; variability in sample definitions, for instance, in terms of demographics and level of motivation to quit; inconsistent measurement of smoking behaviors; and inconsistent use of active control conditions that might allow attribution of effects to other than nonspecific factors. Publication bias cannot definitively be excluded and no studies were found reporting negative results. Meta-analysis then was not possible; however, the studies suggested a positive benefit for a range of interventions. Several studies, including studies of TM, yoga, and

mindfulness-based meditation, reported 20–30 % absolute risk reduction in smoking prevalence at the end of treatment, though follow-up typically was not extended.

Given a range of reasons that make the introduction of mindfulness- and meditation-based approaches into smoking cessation essentially plausible and some supporting evidence albeit of low level, it seems reasonable to suggest to patients that such interventions might be helpful, especially if they have some prior familiarity with meditation practice or are drawn to this by inclination.

High Cholesterol and Otherwise Abnormal Lipid Metabolism

Many mindfulness-based interventions are intended to reduce the experience of stress for participants, and through a range of physiological responses to stress including cortisol response (Sibbritt et al. 2011), this might affect lipid metabolism. The effects on breathing and shifts in SNS and parasympathetic activity might have beneficial influences on lipid metabolism.

Pilot studies have shown some promise, but evidence in this area is at present very limited (De Armond 1996; Gokal et al. 2007; Toomey 2007).

In terms of evidence-based practice for the clinician, there is insufficient existence for any possible effect.

Hypertension

The changes introduced earlier in discussion of smoking cessation including changes in parasympathetic and SNS nervous system balance along with other possible associated effects on stress hormones including the hypothalamic–pituitary–adrenal (HPA) axis would seem to indicate some promise for meditation-based approaches to management of identified hypertension, and indeed this is borne out in the literature.

TM was the first intervention in this area to show promise (Orme-Johnson et al. 2011). This has effectiveness established based on meta-analyses of nine RCTs including three of high quality (Goyal et al. 2014b). The conclusion from this was that a course of TM typically "is associated with a significant reduction in systolic and diastolic blood pressure of ~5 and 3 mmHg, respectively." Publication bias cannot definitively be excluded from possible influence in these conclusions, however. In a recent systematic review of mindfulness-based interventions on hypertension, four good-quality studies were identified with a moderate to large effect size overall (Abbott et al. 2014).

As an element of a comprehensive approach to management of chronic hypertension and where it seems acceptable to the patient, taking up either a mantra-based meditation practice or a mindfulness-based meditation practice seems likely to be beneficial. It would seem sensible to explore with such patients whether such

an approach as part of a comprehensive program is of appeal, and if so, supporting them in exploring possibilities.

Diabetes

In the context of diabetes, the rationale for the use of such techniques would seem to be in areas of reduction of stress and perhaps assisting with lifestyle modifications. Proposed effects on physiological parameters such as stress hormones including cortisol would seem to provide a positive rational for expecting that there might be clinically significant effects. As an intervention working in part through physical exercise, yoga might reasonably be expected to have a role.

There is evidence that meditation-based approaches may be helpful for stress in the context of diabetes, but to date, the picture is not so clear for diabetic control or for impact on other associated physical problems (Alexander et al. 2012; Berghmans et al. 2012; Krolikowski 2013; Schroevers et al. 2013; Schuster 2012; van Son et al. 2014). Findings relating to stress hormones that might contribute to diabetic control are somewhat inconsistent (Chiesa and Serrettiti 2009). A recent systematic review concluded that there is presently not clear evidence that mindfulness training can improve diabetic control or investigated associated renal dysfunction. Yoga has been studied as possibly having a role in diabetes self-care; here, there are particular challenges in understanding whether effects are specific or nonspecific and how much they relate to associated lifestyle changes such as dietary modifications that are commonly advocated in yoga training and the potentially beneficial effects of exercise itself. There are studies with positive findings for improved diabetes control, but there is not as yet a body of high-quality studies on which to base firm conclusions (Alexander et al. 2008).

Mindfulness- and meditation-based approaches may assist management of stress in the context of diabetes – individual benefit from taking on such practices cannot readily be estimated at this point, but it seems credible that for some patients, it may prove helpful.

Overweight or Obesity

Overeating may be an emotional response (Pidgeon et al. 2013) that could be improved by increased metacognitive awareness through mindfulness-based interventions. Yoga practice involves physical activity and often is associated in instruction programs with dietary and lifestyle modification, so a contribution to weight loss and management seems plausible.

There is evidence that mindfulness moderates the relationship between psychological distress and eating behavior (Pidgeon et al. 2013). Mindfulness-based interventions show promise in assisting weight loss; there are a number of studies suggesting that yoga can be helpful for weight loss and maintenance (Rioux and

Ritenbaughgh, 2013). Some pilot studies suggest that mindfulness-based interventions can assist weight loss (Tapper et al. 2009), though superiority to conventional CBT approaches has not been demonstrated.

Yoga and mindfulness-based approaches show promise as aids in weight control regimes. Where the patient has a positive cultural disposition to such approaches, these may be worth considering in treatment planning.

Depression

MBCT as an intervention is intended to assist people who have suffered episodes of depression to avert relapse or recurrence (Segal et al. 2002, 2012). An important aspect of the theoretical background to MBCT is the idea that rumination, often around the negative thought relation to things that have happened or might happen, is a critical trigger for recurrence of depression, particularly where people have had several previous episodes. The program emphasizes reducing avoidance as a coping strategy and promoting an approach coping style as a response to difficulty or discomfort. A strong focus of MBCT also, is the development of a relapse signature and relapse drill.

There is now a substantial accumulation of randomized controlled trials regarding MBCT and multiple published meta-analyses. Meta-analytic work focusing on 12-month follow-up of people with at least three prior episodes of depression showed 32 % of these patients relapsed as compared with 60 % of patients in the control groups (Chiesa and Serrettiti 2011; Piet and Hougaardrd 2011). While questions remain regarding the active principle of this therapy (Kuyken et al. 2012), internationally, work on developing guidelines increasingly is tending to lead to outputs (Jorm et al. 2013; National Institute for Health and Clinical Excellence 2009) that include MBCT as an option for people who have had at least three prior major depressive episodes. Recent Australian work has demonstrated effectiveness in the context of co-prescribing of medication (Meadows et al. 2014).

Generally for people who have had multiple episodes of major depression, MBCT can be recommended. Acceptability will vary and is likely to be greater where there is stronger cultural congruence including familiarity, for instance, with yoga or meditation practices.

Alcohol

The rationale for mindfulness-based approaches to alcohol and other substance misuse is similar to that introduced earlier regarding smoking.

Some effective interventions for abuse or dependence (Bramm et al. 2013; Chiesa and Serrettiti 2009; Fernandez et al. 2010; Garland et al. 2010; Ostafin and Marlatttt 2008; Uhlig 2009) have been demonstrated.

Where mindfulness-based interventions of this kind are available and culturally acceptable, then they can be recommended.

Mindfulness and Meditation in the Context of Management of People with Established Cardiac Disorders

Introduction

In this section, consideration of applications where patients already have established cardiac disease will be followed by exploration of the relevance of the work already presented on management of risk factors. In the case of treatment of established disorders, the body of evidence is more limited than in relation to risk factors, so it will be briefly summarized across the range of cardiac problems.

Rationale

Possible effects of mindfulness- and meditation-based approaches have already been noted on emotional stress levels and on hypertension, smoking, and depression. In most cases, it seems likely that these findings would also apply to people who have already developed cardiac problems, though there may be exceptions. For people with severe disorders, some of the physical aspects of specific interventions might be problematic. Prolonged sitting or lying and postures involved in yoga practice may be challenging for some individuals. Concentration on the breath may be challenging if dyspnea is a feature of the disorder, but not necessarily so and on the basis of fostering approach rather than avoidant coping styles as in MBCT or MBSR, it might be beneficial.

Emotional stress may be related to myocardial ischemia, nonischemic left ventricular dysfunction, and ventricular arrhythmias at least (Ziegelstein 2007). In that context, the evidence that mindfulness- and meditation-based approaches can reduce stress levels and improve positive affect seems relevant.

Evidence

A Cochrane review of psychological interventions in coronary disease (Whalley et al. 2011) did include meditation practices in scope and found no studies of sufficient quality to include in the analyses. Two studies were excluded on the basis of too short follow-up periods (Paul-Labrador et al. 2006; Robert McComb et al. 2004).

Of these, a study of TM in people with stable and well-managed coronary disease (Paul-Labrador et al. 2006) found positive effects on cardiac autonomic tone, on blood pressure measurement, and on insulin resistance. A small study with a mixed group of patients with cardiovascular disease with MBSR as an intervention (Robert McComb et al. 2004) found changes in breathing patterns but did not clearly demonstrate other benefits.

Depression in people with coronary heart disease has been linked with poor prognosis. MBCT has been demonstrated as effective in reducing recurrence and

relapse rates of depression (Chiesa and Serrettiti 2011). There seems no particular reason why this funding among people with depression generally should not also apply to people with cardiac problems. A small quasi-experimental study provides support for this (O'Doherty et al. 2014).

Recently, a major meta-analysis of MBCT and MBSR studies in this area (Abbott et al. 2014) found that MBSR or MBCT participation led to small-to-moderate effects for stress and depression. Across studies in people having heart disease and diabetes, there was also a moderate effect size observed for anxiety. By way of example of a positive study, a brief MBSR intervention for people post percutaneous coronary intervention showed greater improvement in psychosocial and social quality of life than the self-help control condition though only for patients below 60 years of age (Nyklicek et al. 2014).

Conclusion

The evidence regarding management of risk factors with mindfulness- and meditation-based approaches may often generalize to the context of management of these same factors as they can influence the course of established disorders. Hence, such approaches may be useful where depression and hypertension are of concern, possibly also where obesity, hypertension, and poor diabetic control are causing problems. Where subjective experience of stress, anxiety, or depression seems to be a risk factor of concern, then a range of meditation-based approaches may be valuable. This will particularly be so if the patient already has a background in such practices and where it is culturally congruous.

References

Abbott, R. A., Whear, R., Rodgers, L. R., Bethel, A., Coon, J. T., Kuyken, W., . . . Dickens, C. (2014). Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. *Journal of Psychosomatic Research, 76*(5), 341–351.

Alexander, G. K., Taylor, A. G., Innes, K. E., Kulbok, P., & Selfe, T. K. (2008). Contextualizing the effects of yoga therapy on diabetes management: A review of the social determinants of physical activity. *Family & Community Health: The Journal of Health Promotion & Maintenance, 31*(3), 228–239.

Alexander, G., Innes, K. E., Bourguignon, C., Bovbjerg, V. E., Kulbok, P., & Taylor, A. G. (2012). Patterns of yoga practice and physical activity following a yoga intervention for adults with or at risk for type 2 diabetes. *Journal of Physical Activity & Health, 9*(1), 53–61.

Barks, C., & Moyne, J. (1997). *The Essential Rumi*. San Francisco: Harper.

Berghmans, C., Godard, R., Joly, J., Tarquinio, C., & Cuny, P. (2012). Effects of the mindfulness based stress reduction (MBSR) approach on psychic health (stress, anxiety, depression) and coping mode of diabetic patients: A controlled and randomized pilot study. *Annales Médico-Psychologiques, 170*(5), 312–317.

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., . . . Devins, G. (2004). Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice, 11*(3), 230–241.

Boellinghaus, I., Jones, F. W., & Hutton, J. (2014). The role of mindfulness and loving-kindness meditation in cultivating self-compassion and other-focused concern in health care professionals. *Mindfulness, 5*(2), 129–138.

Bramm, S. M., Cohn, A. M., & Hagman, B. T. (2013). Can preoccupation with alcohol override the protective properties of mindful awareness on problematic drinking? *Addictive Disorders & Their Treatment, 12*(1), 19–27.

Carim-Todd, L., Mitchell, S. H., & Oken, B. S. (2013). Mind-body practices: An alternative, drug-free treatment for smoking cessation? A systematic review of the literature. *Drug and Alcohol Dependence, 132*(3), 399–410.

Chiesa, A., & Serretti, A. (2009). Usefulness of mindfulness meditations for psychiatric disorders: A systematic review. *Psichiatria e Psicoterapia, 28*(2), 93–110.

Chiesa, A., & Serretti, A. (2011). Mindfulness based cognitive therapy for psychiatric disorders: A systematic review and meta-analysis. [Meta-analysis review]. *Psychiatry Research, 187*(3), 441–453.

De Armond, D. L. (1996). Effects of the transcendental meditation(rtm) program on psychological, physiological, behavioral and organizational consequences of stress in managers and executives. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 57*(6-B), 4068.

Dobkin, P. L., & Hutchinson, T. A. (2013). Teaching mindfulness in medical school: Where are we now and where are we going? *Medical Education, 47*(8), 768–779.

Fernandez, A. C., Wood, M. D., Stein, L., & Rossi, J. S. (2010). Measuring mindfulness and examining its relationship with alcohol use and negative consequences. *Psychology of Addictive Behaviors, 24*(4), 608–616.

Garland, E. L., Gaylord, S. A., Boettiger, C. A., & Howard, M. O. (2010). Mindfulness training modifies cognitive, affective, and physiological mechanisms implicated in alcohol dependence: Results of a randomized controlled pilot trial. *Journal of Psychoactive Drugs, 42*(2), 177–192.

Gokal, R., Shillito, L., & Maharaj, S. R. (2007). Positive impact of yoga and pranayam on obesity, hypertension, blood sugar, and cholesterol: A pilot assessment. *The Journal of Alternative and Complementary Medicine, 13*(10), 1056–1057.

Goyal, M., Singh, S., Sibinga, E. M. S., Gould, N. F., Rowland-Seymour, A., Sharma, R., . . . Haythornthwaite, J. A. (2014a). Meditation programs for psychological stress and well-being. *Comparative Effectiveness Review*. Rockville. *13*(14)-EHC116-EF.

Goyal, M., Singh, S., Sibinga, E. M. S., Gould, N. F., Rowland-Seymour, A., Sharma, R., . . . Haythornthwaite, J. A. (2014b). Meditation programs for psychological stress and well-being: A systematic review and meta-analysis. [Meta-analysis research support, U.S. Gov't, P.H.S. Review]. *JAMA Internal Medicine, 174*(3), 357–368. doi:10.1001/jamainternmed.2013.13018.

Jorm, A., Allen, N., Morgan, A., Ryan, S., & Purcell, R. (2013). *A guide to what works for depression* (2nd ed.). Melbourne: beyondblue.

Kabat-Zinn, J. (2005). Full catastrophe living: Using the wisdom of your body and mind to face stress, pain, and illness (15th anniversary ed.).

Krolikowski, A. M. (2013). The effectiveness of internet-based mindfulness interventions for physical and mental illnesses: A narrative review. *International Journal of Cyber Behavior, Psychology and Learning, 3*(4), 84–96.

Kuyken, W., Watkins, E., Holden, E., White, K., Taylor, R., Byford, S., . . . Dalgleish, T. (2010). How does mindfulness-based cognitive therapy work? *Behaviour Research and Therapy, 48*, 1105–1112.

Kuyken, W., Crane, R., & Dalgleish, T. (2012). Does mindfulness based cognitive therapy prevent relapse of depression? [Research Support, Non-U.S. Gov't]. *BMJ, 345*, e7194.

Linzer, M., Levine, R., Meltzer, D., Poplau, S., Warde, C., & West, C. P. (2014). 10 bold steps to prevent burnout in general internal medicine. *Journal of General Internal Medicine, 29*(1), 18–20.

Meadows, G. N., Shawyer, F., Enticott, J. C., Graham, A. L., Judd, F., Martin, P. R., & Piterman, L. (2014). Mindfulness-based cognitive therapy for recurrent depression: A translational research study with 2-year follow-up. *Australian and New Zealand Journal of Psychiatry*. doi:10.1177/0004867414525841.

National Institute for Health and Clinical Excellence. (2009). Depression in adults; The treatment and management of depression in adults *NICE clinical guidelines* (p. 34). National Institute for Health and Clinical Excellence. London, UK.

Nyklicek, I., Dijksman, S. C., Lenders, P. J., Fonteijn, W. A., & Koolen, J. J. (2014). A brief mindfulness based intervention for increase in emotional well-being and quality of life in percutaneous coronary intervention (PCI) patients: The mindfulheart randomized controlled trial. *Journal of Behavioral Medicine, 37*(1), 135–144.

Oliver, M. (1986). *Dream Work*. Boston: Grove/Atlantic.

Oliver, M. (1990). *House of Light*. Boston: Beacon Press.

O'Doherty, V., Carr, A., McGrann, A., O'Neill, J. O., Dinan, S., Graham, I., & Maher, V. (2014). A controlled evaluation of mindfulness-based cognitive therapy for patients with coronary heart disease and depression. *Mindfulness(Pagination)*. doi:10.1007/s12671-013-0272-0. On Line.

Orme-Johnson, D.W., Barnes, V.A., & Schneider, R.H. (2011). Transcendental Meditation for primary and secondary prevention of coronary heart diseases. In: Allan, Fisher (eds) (2nd ed.), Heart & Mind: the practice of cardiac psychology, 365–379.

Ospina, M. B., Bond, K., Karkhaneh, M., Buscemi, N., Dryden, D. M., Barnes, V., . . . Shannahoff-Khalsa, D. (2008). Clinical trials of meditation practices in health care: Characteristics and quality. *The Journal of Alternative and Complementary Medicine, 14*(10), 1199–1213.

Ostafin, B. D., & Marlatt, G. (2008). Surfing the urge: Experiential acceptance moderates the relation between automatic alcohol motivation and hazardous drinking. *Journal of Social and Clinical Psychology, 27*(4), 404–418.

Owens, D. K., Lohr, K. N., Atkins, D., Treadwell, J. R., Reston, J. T., Bass, E. B., . . . Helfand, M. (2010). AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions – Agency for healthcare research and quality and the effective health-care program. *Journal of Clinical Epidemiology, 63*(5), 513–523. doi:10.1016/j.jclinepi.2009.03.009.

Paul-Labrador, M., Polk, D., Dwyer, J. H., Velasquez, I., Nidich, S., Rainforth, M., . . . Merz, C. N. B. (2006). Effects of a randomized controlled trial of transcendental meditation on components of the metabolic syndrome in subjects with coronary heart disease. *Archives of Internal Medicine, 166*(11), 1218–1224.

Pickert, K. (2014). The mindful revolution. *Time, 183*, 1.

Pidgeon, A., Lacota, K., & Champion, J. (2013). The moderating effects of mindfulness on psychological distress and emotional eating behaviour. *Australian Psychologist, 48*(4), 262–269.

Piet, J., & Hougaard, E. (2011). The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: A systematic review and meta-analysis. [Meta-analysis review]. *Clinical Psychology Review, 31*(6), 1032–1040.

Rioux, J. G., & Ritenbaugh, C. (2013). Narrative review of yoga intervention clinical trials including weight-related outcomes. [Research Support, N.I.H., Extramural Review]. *Alternative Therapies in Health & Medicine, 19*(3), 32–46.

Robert McComb, J. J., Tacon, A., Randolph, P., & Caldera, Y. (2004). A pilot study to examine the effects of a mindfulness-based stress-reduction and relaxation program on levels of stress hormones, physical functioning, and submaximal exercise responses. *Journal of Alternative & Complementary Medicine, 10*(5), 819–827.

Rosengren, A., Hawken, S., Ounpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A., . . . investigators, I. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*(9438), 953–962.

Schroevers, M. J., Tovote, K., Keers, J. C., Links, T. P., Sanderman, R., & Fleer, J. (2013). Individual mindfulness-based cognitive therapy for people with diabetes: A pilot randomized controlled trial. *Mindfulness*. doi:10.1007/s12671-013-0235-5. (Pagination), No Pagination Specified.

Schuster, K. (2012). Effect of mindfulness meditation on A1C levels in African American females with type 2 diabetes. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 72*(7-B), 4308.

Segal, Z. V., Williams, J. M. G., & Teasdale, J. (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. New York: Guilford.

Segal, Z. V., Williams, J. M. G., & Teasdale, J. (2012). *Mindfulness-based cognitive therapy for depression* (2nd ed.). New York: Guilford.

Shapiro, S. L. (2001). Poetry, mindfulness, and medicine. *Family Medicine*, 33(7), 505–507.

Sibbritt, D., Adams, J., & van der Riet, P. (2011). The prevalence and characteristics of young and mid-age women who use yoga and meditation: Results of a nationally representative survey of 19,209 Australian women. [Research support, Non-U.S. Gov't]. *Complementary Therapies in Medicine, 19*(2), 71–77.

Tapper, K., Shaw, C., Ilsley, J., Hill, A. J., Bond, F. W., & Moore, L. (2009). Exploratory randomised controlled trial of a mindfulness-based weight loss intervention for women. [Randomized controlled trial research support, Non-U.S. Gov't]. *Appetite, 52*(2), 396–404.

Thera, S. (2010). Satipatthana Sutta: The discourse on the arousing of mindfulness translated from the Pali. *Access to Insight Legacy Edition*. Retrieved 19 July 2014, from http://www.accesstoinsight.org/tipitaka/mn/mn.010.soma.html.

Toomey, M. (2007). The effects of the transcendental meditation program on carotid atherosclerosis and cardiovascular disease risk factors in Native Hawaiians. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 68*(6-B), 4169.

Uhlig, D. J. (2009). *Mindfulness based relapse prevention and the matrix model in substance abuse relapse prevention* (vol. 70). Walden University, Minnesota, USA.

University of Wisconsin School of Medicine and Public Health. (2010). Mindfulness in medicine. Retrieved 19 July 2014, from http://www.fammed.wisc.edu/mindfulness.

Van Gordon, W., Shonin, E., Zangeneh, M., & Griffiths, M. D. (2014). Work-related mental health and job performance: Can mindfulness help? *International Journal of Mental Health and Addiction, 12*(2), 129–137.

van Son, J., Nyklicek, I., Pop, V. J., Blonk, M. C., Erdtsieck, R. J., & Pouwer, F. (2014). Mindfulness-based cognitive therapy for people with diabetes and emotional problems: Long-term follow-up findings from the diamind randomized controlled trial. *Journal of Psychosomatic Research, 77*(1), 81–84.

Vidrine, J. I., Businelle, M. S., Cinciripini, P., Li, Y., Marcus, M. T., Waters, A. J., . . . Wetter, D. W. (2009). Associations of mindfulness with nicotine dependence, withdrawal, and agency. *Substance Abuse, 30*(4), 318–327.

Whalley, B., Rees, K., Davies, P., Bennett, P., Ebrahim, S., Liu, Z., . . . Taylor, R. (2011). Psychological interventions for coronary heart disease (Review). *Cochrane Database of Systematic Reviews,* (8), Art. No.: CD002902. doi:10.1002/14651858.CD002902.pub3.

World Medical Association. (2013). *WMA declaration of Helsinki – Ethical principles for medical research involving human subjects*. Ferney-Voltaire: World Medical Association.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., . . . Investigators, I. S. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet, 364*(9438), 937–952.

Ziegelstein, R. C. (2007). Acute emotional stress and cardiac arrhythmias. *JAMA: Journal of the American Medical Association, 298*(3), 324–329.

Psychopharmacology in the Treatment of Patients with Cardiovascular Disease

Scott R. Beach, Christopher M. Celano, Jeff C. Huffman, and Theodore A. Stern

Contents

S.R. Beach (✉) • C.M. Celano • J.C. Huffman
Department of Psychiatry, Massachusetts General Hospital/Warren 605, Boston, MA, USA

Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
e-mail: sbeach1@partners.org

T.A. Stern
Department of Psychiatry, Massachusetts General Hospital/Warren 605, Boston, MA, USA
e-mail: tstern@partners.org

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_53

Abstract

Cardiac illness is frequently comorbid with psychiatric disorders, and patients with heart disease are often prescribed psychotropic medications. Although psychotropics are in general well tolerated and efficacious in patients with cardiac disease, physicians need to be aware of key concerns related to side effects and safety. Among the antidepressants, selective serotonin reuptake inhibitors (SSRIs) have the most established track record for safety in cardiac patients, although atypical antidepressants, such as mirtazapine and bupropion, are also largely considered safe for use in these patients. Mood stabilizers, such as lithium and carbamazepine, have been associated with arrhythmias. Typical antipsychotics, such as haloperidol and chlorpromazine, increase the risk of QTc prolongation; however, the degree of such prolongation varies significantly among agents. Atypical antipsychotics, with the exception of ziprasidone, are considered safer in this regard, but some are associated with metabolic side effects that can increase the risk for coronary artery disease. The use of benzodiazepines is generally safe in patients with cardiac disease, and these agents may mitigate symptoms of acute coronary syndrome (ACS) by reducing catecholamine surges. Finally, stimulants, though relatively contraindicated in those with various heart conditions, may be used cautiously to rapidly treat depression and anergia in cardiac patients.

Keywords

Antidepressants • Selective serotonin reuptake inhibitors (SSRIs) • Mood stabilizers • Antipsychotics • Stimulants • Benzodiazepines

Introduction

Cardiac illness is frequently comorbid with psychiatric disorders, and patients with heart disease are often prescribed psychotropic medications. Although psychotropics are in general well tolerated and efficacious in patients with cardiac disease, physicians need to be aware of key concerns related to side effects and safety. This chapter examines various classes of psychiatric medications and their effects on the cardiovascular system.

Antidepressants

Tricyclic Antidepressants

Although tricyclic antidepressants (TCAs) were the mainstay of treatment for depression and anxiety in the late 1980s, selective serotonin reuptake inhibitors (SSRIs) have become the most commonly prescribed class of antidepressant medications. TCAs, because of their side effects and safety concerns, are no longer used

as first-line agents for depression and anxiety; however, they remain in common use for the treatment of insomnia and neuropathic pain.

TCAs cause a predictable increase in heart rate (of approximately nine beats per minute) as a result of their anticholinergic effects; they can also induce orthostatic hypotension due to blockade of alpha$_1$ receptors on blood vessels (Dec and Stern 1990). Orthostasis is more common with tertiary amine TCAs (e.g., amitriptyline, doxepin, clomipramine, imipramine) than with secondary amine TCAs (e.g., nortriptyline, desipramine, protriptyline).

TCAs also predispose to more serious but uncommon cardiac side effects. Since these agents are structurally similar to class I antiarrhythmics, they are pro-arrhythmic in roughly 10 % of the population in a dose-related fashion. In addition, approximately 20 % of patients with preexisting conduction disturbances have cardiac complications while taking TCAs (Roose et al. 1998). Moreover, the TCAs can contribute to prolongation of the PR, QRS, and QT intervals on the electrocardiogram (ECG), and TCAs have been associated with all manner of heart block. Some have suggested that the effects on cardiac conduction are most severe with desipramine, while other studies have found that amitriptyline and maprotiline are most often associated with torsades de pointes (Vieweg and Wood 2004). Case reports have also associated amoxapine with atrial flutter and atrial fibrillation. After overdoses on TCAs, potentially lethal ventricular arrhythmias can arise.

Due to the increased risk of ventricular arrhythmias and myocardial infarction (MI) following the use of TCAs, they are not recommended in patients with coronary artery disease (CAD). In fact, a study that controlled for medical and demographic factors found that depressed individuals receiving TCAs had more than a twofold risk of MI (Cohen et al. 2000).

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) are an older class of antidepressants that is now rarely used due to concerns about their tolerability and safety. While MAOIs were frequently prescribed for depression with atypical features, for anxiety disorders, and for mood episodes in the context of borderline personality disorder, it is uncommon for practitioners to prescribe these agents when other (better tolerated) agents are available.

While MAOIs are commonly associated with orthostasis, it is their potential to cause a severe hypertensive crisis (characterized by occipital headache, nausea, vomiting, diaphoresis, tachycardia, and severe hypertension) that limits their use (Lipson and Stern 1991). These crises typically occur when tyramine-containing foods (such as aged meats or cheeses, some wines and beers) are consumed or when indirect vasopressors (such as stimulants and many over-the-counter cough and cold preparations) are coadministered with MAOIs. MAOIs have also been implicated in cases of serotonin syndrome when used in combination with other serotonergic agents. Both hyperadrenergic/hypertensive crisis and serotonin syndrome carry a significant risk of adverse cardiac outcomes due to their increased cardiac

demand from rising heart rates and blood pressures. When a hypertensive crisis arises in the setting of MAOI use, phentolamine is the recommended treatment. A newer transdermal form of the MAOI, selegiline, carries a minimal risk of hypertensive crisis when used at low doses, though higher dosages continue to require adherence to a strict diet. Moclobemide, a reversible MAOI, is relatively safe (as it does not tend to cause QTc prolongation or increase the risk of arrhythmias at normal doses); moreover, it is not subject to the strict dietary requirements of other MAOIs (Lofuto-Neto et al. 1999).

Selective Serotonin Reuptake Inhibitors

SSRIs have become the mainstay of treatment for depression and anxiety disorders since their introduction in the late 1980s. Five SSRIs are in common use (fluoxetine, paroxetine, sertraline, citalopram, and escitalopram), with a sixth (fluvoxamine) prescribed less often (to treat obsessive-compulsive disorder).

SSRIs are generally considered to have a benign cardiovascular side effect profile. SSRIs are associated with fewer anticholinergic side effects than TCAs; they typically increase the heart rate by seven to eight beats per minute. Among the SSRIs, paroxetine has the greatest anticholinergic load and is therefore most likely to increase the heart rate. Orthostatic hypotension is an uncommon common side effect of SSRI treatment.

SSRIs are generally considered as safe for use in those with CAD and in post-MI patients; a small study of fluoxetine established the safety of SSRIs in this setting (Strik et al. 2000), and the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial found that citalopram was safe and effective in treating depression in patients with CAD (Lesperance et al. 2007). At least one study suggested that SSRI-treated depressed patients had lower rates of MI than nondepressed controls (Cohen et al. 2000). In the multicenter, double-blind, placebo-controlled SADHART trial (Glassman et al. 2002), investigators found that sertraline significantly improved depressive symptoms compared to placebo and was not associated with changes in ejection fraction, cardiac conduction, or adverse cardiac events, 6 months following its initiation after MI. Importantly, study subjects were not started on sertraline until 1 month after MI, and the safety of SSRIs in the immediate (first month) post-MI period has not been established, though most experts consider them safe for use in this context. Another study found that sertraline was safe for use in patients with congestive heart failure (CHF), though the use of sertraline did not improve depression or cardiac outcomes as compared to placebo (Jiang et al. 2008). More recently, several studies have linked SSRI treatment to lower rates of mortality and other adverse cardiac events in both post-MI patients and healthy controls (Carney et al. 2004; Kimmel et al. 2011; Tiihonen et al. 2006).

Recently, concern has arisen regarding the possibility that SSRIs lead to prolongation of the QTc interval and increase the risk of torsades de pointes. In fact, all SSRIs except paroxetine have been associated (in case reports) with QTc prolongation at therapeutic doses and in overdose (Beach et al. 2013). In particular, citalopram has been shown to have a modest QT-prolonging effect, which resulted in a Food and Drug Administration (FDA) recommendation in August 2011 to limit the maximum daily dose of citalopram to 40 mg per day (20 mg in patients with hepatic impairment or those older than 60 years) because of the increased risk of QTc prolongation at higher doses and to declare its use contraindicated in those with a congenital long QT syndrome. Less stringent revisions were issued in March 2012; however, citalopram remains not recommended for use at doses greater than 40 mg per day. No QTc-related recommendations have been issued for other SSRIs, although escitalopram appears to have a more modest, dose-dependent effect on prolongation of the QTc interval (Castro et al. 2013). A meta-analysis (of 16 studies) of the impact of SSRIs on the QTc interval found that SSRIs as a class prolonged the QTc by an average of 6 ms, suggesting that these agents convey a very low risk when used cautiously, even in patients with a history of cardiac disease (Beach et al. 2014).

Serotonin-Norepinephrine Reuptake Inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, desvenlafaxine, and duloxetine) are a newer class of antidepressants commonly used to treat depression.

Increased blood pressure, thought to be caused by noradrenergic effects, can occur with the use of immediate-release venlafaxine; roughly 7 % of patients taking $\leq$300 mg per day and 13 % taking >300 mg per day had elevations of blood pressure, which resolved spontaneously in half of the cases (Thase 1998). The extended-release formulation of venlafaxine appears to be associated with lower rates of hypertension. Desvenlafaxine has also been associated with elevations in diastolic blood pressure, though to a lesser extent than venlafaxine (Perry and Cassagnol 2009), whereas duloxetine has not been linked with significant alterations in blood pressure.

Several case reports have linked large overdoses of venlafaxine with acute heart failure and with cardiac death (Batista et al. 2013). In addition, a single case of takotsubo cardiomyopathy thought to have been caused by noradrenergic surge has also been reported in the setting of therapeutic venlafaxine use. Takotsubo cardiomyopathy has also been reported in cases of overdose of duloxetine and desvenlafaxine (Neil et al. 2012).

At least one study has suggested the possibility that QTc prolongation might occur with the use of venlafaxine, and overdose has been linked to ventricular arrhythmias. Desvenlafaxine and duloxetine have not been linked to QTc prolongation (Waring et al. 2010).

Other Antidepressants

Bupropion is a norepinephrine-dopamine reuptake inhibitor that is commonly used to treat depression, either as monotherapy or as an adjunctive agent with an SSRI. Bupropion is also indicated to facilitate smoking cessation.

Bupropion, at therapeutic doses, does not have adverse effects on blood pressure, heart rate, or other cardiovascular parameters (Kiev et al. 1994). An early study of bupropion in depressed patients with CAD found this agent to have a favorable cardiovascular side effect profile (Roose et al. 1991). The smoking cessation literature has demonstrated that bupropion (at doses up to 300 mg daily) is safe in the immediate post-MI period and not linked to adverse cardiac events (Rigotti et al. 2006). Even in overdose, bupropion does not appear to induce adverse cardiovascular events, though hypertension and tachycardia may develop (Balit et al. 2003), and some cases of wide-complex tachycardia and cardiac arrest have been noted (Tracey et al. 2002).

Mirtazapine, another atypical antidepressant, has a favorable cardiovascular side effect profile. It has few effects on cardiac conduction or vital signs, even in overdose (Velazquez et al. 2001). Recently, the Myocardial Infarction and Depression-Intervention Trial (MIND-IT), a 24-week randomized, placebo-controlled study, found that mirtazapine was safe in 209 post-MI patients diagnosed with depression within the first year after their MI (van den Brink et al. 2002). One potential drawback of its use in cardiac patients is its propensity to cause weight gain associated with its antihistaminergic potency.

Trazodone, developed as an antidepressant, is primarily used to treat insomnia in the USA, though it continues to be used as an antidepressant in other countries. Related compounds (nefazodone and the new agent, vilazodone) are occasionally used as antidepressants. Trazodone has, very infrequently, been associated with cardiac arrhythmias and QTc prolongation (Service and Waring 2008), possibly due to its effects on potassium channels; as a result, it should be used with caution in those with a propensity for, or a history of, arrhythmias. Orthostasis is much more common with the use oftrazodone than with the use of nefazodone, with reports of syncope associated with the former (Nambudiri et al. 1989). Vilazodone has not been shown to have adverse cardiac effects.

Recommendations for Using Antidepressants in Patients with Cardiac Disease

In general, for patients with cardiac disease that requires pharmacologic treatment of depression or anxiety, SSRIs (due to their efficacy and their established record of safety) are the first-line treatment. Bupropion is a reasonable augmentation strategy for patients achieving only partial remission on monotherapy, keeping in mind that it is sometimes associated with worsening panic. Mirtazapine, although safe for use in cardiac patients, is not a first-line agent due to its propensity to cause weight gain. SNRIs have less well-established safety records in cardiac patients, and venlafaxine is strongly associated with increases in blood pressure. According to many practitioners, TCAs and MAOIs (with the possible exception of moclobemide) should generally be avoided in patients with cardiac disease.

Mood Stabilizers

Lithium remains the "gold standard" treatment for bipolar disorder, and it is sometimes used as augmentation in patients with unipolar depression. Lithium has been reported to cause sinus bradycardia, sinus node dysfunction, atrioventricular (AV) block, T-wave changes, and ventricular irritability (Freeman and Freeman 2006). However, it has not been commonly associated with other effects on the cardiovascular system; sick sinus syndrome is considered to be the only cardiac contraindication to lithium use.

Valproic acid is an anticonvulsant that is frequently used in the treatment of bipolar disorder, particularly for the treatment of manic episodes. Valproic acid has been associated with thrombocytopenia, abnormal platelet function, and an increased risk for bleeding following medical interventions or surgery. Otherwise, no cardiac side effects have been linked with valproic acid use.

Carbamazepine and oxcarbazepine are other anticonvulsants used in the treatment of bipolar disorder. Carbamazepine can slow cardiac conduction and should be avoided in patients with high-grade AV block and sick sinus syndrome. Overdose of carbamazepine may cause high-grade AV block. Oxcarbazepine has not been associated with adverse cardiac side effects.

Lamotrigine is an anticonvulsant that is commonly used to treat depressive episodes in the setting of bipolar disorder. Cardiovascular effects of lamotrigine have not been described, and it is considered safe for use in patients with cardiac disease.

Recommendations for Using Mood Stabilizers in Patients with Cardiac Disease

There have been no randomized trials of mood stabilizers in patients with cardiac disease. Nonetheless, mood stabilizers are generally considered as being safe in this population in the absence of a conduction delay. In cases of AV block and sick sinus syndrome, lithium and carbamazepine should be avoided.

Antipsychotics

Conventional Antipsychotics

First-generation or "typical" antipsychotic medications have a long history of use for the treatment of psychotic symptoms in the setting of schizophrenia, schizoaffective disorder, affective illnesses (depression or bipolar disorder), or delirium. While effective at treating these symptoms, their propensity to cause motor (i.e., extrapyramidal) side effects, such as dystonic reactions, akathisia, and tardive dyskinesia, has led to a decline in their use for chronic mental illnesses.

However, these medications can still be used for cardiac patients, most commonly for the management of delirium.

Antipsychotic medications are the first-line treatment for the management of agitation associated with delirium; haloperidol is the antipsychotic agent most frequently used for this purpose (American Psychiatric Association 1999). Though this medication can be administered orally or intramuscularly, its intravenous form is preferred for several reasons: it is easy and painless to administer, it works quickly (onset of action is ~15–30 min), and it is less likely to induce motor side effects compared to its other formulations. From a cardiac perspective, its effects on heart rate, blood pressure, or respiratory status are minimal; it has no active metabolites and essentially no anticholinergic effects.

Though less commonly used, chlorpromazine, a low-potency typical antipsychotic medication, also serves as a treatment for delirium, in large part because it can be administered intravenously (allowing it to be fast-acting and sedating) in the medically ill. Unlike haloperidol, chlorpromazine and other low-potency antipsychotics (e.g., thioridazine) can have significant cardiovascular effects. Specifically, their anticholinergic properties can cause tachycardia, and their alpha-$_1$ blockade can induce significant hypotension. As a result, these medications are commonly avoided in cardiac patients, especially those with hemodynamic instability.

Additionally, all typical antipsychotic medications are linked with torsades de pointes (TDP), a malignant polymorphic ventricular arrhythmia that can occur with agents that lengthen the QTc interval (Beach et al. 2013; Wenzel-Seifert et al. 2011). All typical antipsychotic medications can cause QTc prolongation, and many have been associated with TDP. In general, there is a dose-response relationship between antipsychotic dose and QTc prolongation (Reilly et al. 2000), and lower-potency antipsychotics tend to cause more QTc prolongation than higher-potency medications (Mehtonen et al. 1991). For example, thioridazine, a low-potency antipsychotic medication, has consistently been shown to cause the greatest degree of QTc prolongation of the antipsychotics (Beach et al. 2013; Harrigan et al. 2004; Wenzel-Seifert et al. 2011). However, higher-potency medications, such as haloperidol, also cause QTc prolongation (Harrigan et al. 2004; Ozeki et al. 2010). In general, haloperidol causes mild QTc prolongation (~5–7 ms when given orally at 15 mg/day) (Harrigan et al. 2004). However, the risk of QTc prolongation and TDP increases substantially when haloperidol is administered intravenously. When administered intravenously, and especially at higher doses (>35 mg daily), haloperidol has been associated with greater rates of QTc prolongation and TDP (Ozeki et al. 2010; Sharma et al. 1998; Vieweg et al. 2009). More than 70 cases of TDP have been reported in association with haloperidol (Wenzel-Seifert et al. 2011), and rates of TDP from haloperidol in the treatment of delirious patients have ranged from 0.36 % to 3.5 % (Sharma et al. 1998; Wilt et al. 1993). Several other factors (e.g., structural cardiac disease, congenital long QT syndrome, older age, female gender, electrolyte abnormalities (hypokalemia, hypomagnesemia), and endocrine and neurologic disorders) also contribute to QTc prolongation and the risk of TDP (Vieweg 2002). Therefore, extra care should be taken when using typical antipsychotics in these patients.

Atypical Antipsychotics

The use of second-generation, or "atypical," antipsychotics has increased since their introduction into clinical practice. In contrast to typical antipsychotics, atypical agents induce extrapyramidal side effects less often and therefore are often preferred over typical antipsychotics for the management of a number of psychiatric illnesses. They are considered as the first-line treatment for schizophrenia and can be used for the management of mania or depression in bipolar disorder, as augmenting agents to antidepressants for major depressive disorder or obsessive-compulsive disorder, or for the management of mood instability or irritability in the setting of certain personality disorders. Furthermore, like typical antipsychotics, these medications can be used for the management of agitation in patients with delirium.

Like typical antipsychotics, atypical antipsychotics have been associated with a number of cardiovascular side effects (including hypotension, orthostasis, tachycardia, QTc prolongation, and TDP). This class of medications has also been linked to the development of metabolic side effects (including weight gain, hyperlipidemia, and glucose dysregulation). Due to their unique receptor-binding profiles, cardiovascular side effects vary considerably among the atypical antipsychotics.

Dizziness and hypotension are the most common cardiovascular side effects of antipsychotic medications, with some studies finding that the majority of patients treated with these agents develop transient dizziness or hypotension after they are initiated (Mackin 2008). These side effects are typically mediated by the anticholinergic and anti-adrenergic potency of the atypical antipsychotics. Clozapine, quetiapine, and risperidone are frequently linked to orthostatic hypotension (Drici and Priori 2007; Khasawneh and Shankar 2014), while olanzapine and ziprasidone are less likely to have this side effect (given their less potent adrenergic blockade) (Khasawneh and Shankar 2014).

Tachycardia also is common with the use of atypical antipsychotics and may be related to the anticholinergic properties of these medications. All atypical antipsychotics can cause tachycardia, though this side effect is classically linked with clozapine use (Drici and Priori 2007; Mackin 2008). Clozapine, used primarily for refractory schizophrenia, also is unique in its propensity to cause myocarditis; it has received a black box warning as a result of this relatively rare but potentially life-threatening side effect (Drici and Priori 2007; Khasawneh and Shankar 2014; Mackin 2008).

Atypical antipsychotics have been associated with the onset of significant metabolic side effects (including weight gain, hyperglycemia, and dyslipidemia). Weight gain is thought to result from 5HT-$_{2C}$ and H_1 receptor antagonism and is characterized by rapid weight gain during the first few months of use, followed by a less rapid gain in weight for ~1 year, until a new steady-state weight is reached (American Diabetes Association and American Psychiatric Association 2004; Deng 2013). Glucose dysregulation appears to be primarily caused by an increase in insulin resistance and may be independent of weight gain (American Diabetes Association and American Psychiatric Association 2004; Deng 2013). Finally, the

dyslipidemia (primarily hypertriglyceridemia) associated with atypical antipsychotics may be caused by direct effects on triglyceride metabolism or related to the weight gain and insulin resistance noted above (Yan et al. 2013). Regardless, in all of these areas, certain antipsychotics are more prone to cause metabolic side effects. Specifically, the risk of metabolic side effects is highest with clozapine and olanzapine, moderate with risperidone and quetiapine, and lowest with aripiprazole and ziprasidone (American Diabetes Association and American Psychiatric Association 2004; Deng 2013; Drici and Priori 2007; Yan et al. 2013).

Finally, like typical antipsychotics, atypical antipsychotic medications can cause QTc prolongation, and many have been associated in case reports with TDP. Of the atypical antipsychotics, ziprasidone is the medication most commonly associated with QTc prolongation (Beach et al. 2013; Harrigan et al. 2004). In a randomized trial evaluating the effects of six medications on QTc in patients with psychotic disorders, ziprasidone caused a greater increase in the QTc (15.9 ms) than olanzapine (1.7 ms), quetiapine (5.7 ms), and risperidone (3.9 ms) (Harrigan et al. 2004). There are fewer data available about newer antipsychotic medications, and most information is available only from package inserts. Of the newer antipsychotic medications, iloperidone and paliperidone carry the greatest risk of QTc prolongation (mean increases of 1–12 ms) (Citrome 2011; "Fanapt (Iloperidone) [package insert]," 2012; Hough et al. 2011; "Invega (paliperidone) [package insert]," 2011; Weiden et al. 2008), while asenapine and lurasidone are less likely to cause QTc prolongation (mean increases from 0.3 to 8 ms) (Citrome 2009; "Latuda (lurasidone) [package insert]," 2012; Potkin et al. 2011; "Saphris (asenapine) [package insert]," 2012). Aripiprazole is the only atypical antipsychotic medication that has not been associated with QTc prolongation (Belgamwar and El-Sayeh 2011; Muzyk et al. 2011). The links between atypical antipsychotics and TDP are less clear, with case reports and adverse event reports being the primary sources of more serious cardiovascular side effects. Two large retrospective studies have found atypical antipsychotics to be linked to sudden cardiac death, with TDP being one possible mechanism leading to mortality in these patients (Jolly et al. 2009; Ray et al. 2009). Ziprasidone has been linked to TDP in two case reports (Heinrich et al. 2006; Manini et al. 2007), and quetiapine has been implicated with a case of TDP in another report (Vieweg et al. 2005). Clozapine, asenapine, lurasidone, iloperidone, and paliperidone have never been associated with cases of TDP; however, given the low incidence of TDP, larger studies may be needed to detect an increased risk of TDP with these medications.

Recommendations for Using Antipsychotics in Patients with Cardiac Disease

Antipsychotic medications can be used safely in patients with cardiovascular disease. For most psychiatric conditions that require treatment with an antipsychotic medication, atypical antipsychotic medications are considered first line. For those with or at risk for the metabolic syndrome, care should be taken to choose a medication that has lower risks of metabolic side effects (e.g., aripiprazole). When

starting an atypical antipsychotic medication, patients should be monitored closely for metabolic side effects, especially over the first year. The American Diabetes Association and American Psychiatric Association recommend the following monitoring schedule: weight should be monitored monthly for the first and then quarterly thereafter; fasting blood glucose should be obtained at baseline and 3 months and then annually thereafter; and a fasting lipid panel should be obtained at baseline, 3 months, and then every 5 years thereafter (American Diabetes Association and American Psychiatric Association 2004).

For patients with delirium-associated agitation, antipsychotics are considered first line for the management of these symptoms, and in patients with hemodynamic instability, a high-potency typical antipsychotic (e.g., haloperidol) is optimal. However, as noted above, care should be taken to minimize the risk of QTc prolongation and TDP. When using intravenous haloperidol in particular, daily EKGs are recommended to ensure that the QTc remains below 500 ms throughout the treatment course. If a patient develops significant QTc prolongation, exposure to other risk factors should be minimized, and an antipsychotic medication with less propensity to cause QTc prolongation should be used.

Benzodiazepines

Benzodiazepines are commonly prescribed for anxiety disorders and for insomnia. Though now largely intended for short-term use until other medications (such as SSRIs) take effect, many patients are treated chronically with benzodiazepines. In the hospital setting, benzodiazepines are also used to manage alcohol withdrawal. One important caveat for the use of benzodiazepines is that they can exacerbate confusion and paradoxically worsen agitation in patients with delirium or dementia; therefore, other agents (e.g., antipsychotics) may be more appropriate for the treatment of anxiety, fear, and distress in the delirious or demented cardiac patient.

Benzodiazepines are generally well tolerated, with low rates of hypotension, virtually no anticholinergic effects, and very low rates of respiratory compromise when standard doses are used. Benzodiazepines reduce catecholamine levels both at baseline and during times of stress (Dixon et al. 1980; Melsom et al. 1976) and decrease coronary vascular resistance (Nitenberg et al. 1983). Benzodiazepines have also been linked to decreased left ventricular end diastolic pressure, decreased platelet aggregation, and decreased rates of ventricular dysrhythmias (Huffman and Stern 2003; Muenster et al. 1967; Van Loon 1968).

Benzodiazepines are frequently administered to patients with chest pain and are thought to be safe for use and effective in both cardiac and noncardiac chest pain. Wheatley found that the addition of benzodiazepines to standard cardiac medications in the post-MI period led to significantly lower rates of reinfarction in patients not taking β-blockers (Wheatley 1984). It should be noted that the patients in these studies, however, were not taking β-blockers.

Withdrawal from benzodiazepines leads to anxiety, tremor, diaphoresis, nausea, insomnia, and irritability; vital signs—especially blood pressure and heart rate—are

often elevated in untreated benzodiazepine withdrawal. Delirium from benzodiazepine withdrawal is associated with significant risk of congestive heart failure, aspiration, deep venous thrombosis, and other serious medical complications (e.g., falls).

Recommendations for Using Benzodiazepines in Patients with Cardiac Disease

Benzodiazepines are generally considered safe for use in patients with cardiac disease and may fulfill a role as an important anxiolytic adjunctive medication in patients presenting with cardiac chest pain. Benzodiazepines can worsen delirium and increase the risk for falls and should therefore be used cautiously in elderly patients and other populations at risk for such complications.

Stimulants

In addition to being prescribed for attention-deficit hyperactivity disorder, psychostimulants have also been shown to be rapidly acting, efficacious antidepressants in medically hospitalized patients (Masand et al. 1991; Woods et al. 1986). Though they may elevate blood pressure and heart rate, stimulants may be useful in cardiac patients whose depression requires rapid treatment (e.g., depression that is severe, is negatively affecting rehabilitation due to anergia or minimal oral intake, or is affecting the patient's capacity to make medical decisions). Stimulants are relatively contraindicated in those with a history of ventricular tachycardia, a recent MI, CHF, uncontrolled hypertension or tachycardia, or those who are concurrently taking MAOIs. However, in many cardiac patients, psychostimulants can be used safely with slow upward dosage titration. Modafinil, a stimulant-like medication used for narcolepsy, typically has fewer effects on blood pressure and heart rate and may be used as an alternative.

Conclusion

While many psychiatric medications are safe for use in patients with cardiac disease, physicians need to be aware of and monitor for potential side effects that may be specific to individual classes. The presence of heart disease should not preclude necessary treatment of psychiatric comorbidity given the links between cardiac disease and psychiatric illness, but may require thoughtfulness and careful evaluation of risk/benefit on the part of the prescriber.

Clinical Implications

Due to their efficacy and their established record of safety, SSRIs are the first-line treatment for depression and anxiety in patients with cardiac disease. Bupropion is a reasonable and safe augmentation strategy for depression. Mood stabilizers are considered safe in cardiac populations in the absence of conduction delay. Antipsychotics can be safely used in cardiac patients, with atypical agents considered first-line treatment. Efforts should be made to minimize metabolic side effects in patients with CAD or CHF. Antipsychotic agents also carry a risk of prolonged QTc intervals and caution should be exercised in this regard. Benzodiazepines are typically safe for use in cardiac patients and may alleviate anxiety associated with cardiac chest pain. Stimulants can also be used safely in this population with some basic precautions.

References

American Diabetes Association, & American Psychiatric Association. (2004). Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care, 27*(2), 596–601.

American Psychiatric Association. (1999). Practice guideline for the treatment of patients with delirium. *The American Journal of Psychiatry, 156*(5 Suppl), 1–20.

Balit, C. R., Lynch, C. N., & Isbister, G. K. (2003). Bupropion poisoning: A case series. *Medical Journal of Australia, 178*(2), 61–63.

Batista, M., Dugernier, T., Simon, M., Haufroid, V., Capron, A., Fonseca, S., … Hantson, P. (2013). The spectrum of acute heart failure after venlafaxine overdose. *Clinical Toxicology (Phila), 51*(2), 92–95. doi:10.3109/15563650.2012.763133.

Beach, S. R., Celano, C. M., Noseworthy, P. A., Januzzi, J. L., & Huffman, J. C. (2013). QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics, 54*(1), 1–13. doi:10.1016/j.psym.2012.11.001.

Beach, S. R., Kostis, W. J., Celano, C. M., Januzzi, J. L., Ruskin, J. N., Noseworthy, P. A., & Huffman, J. C. (2014). Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *Journal of Clinical Psychiatry, 75*(5), e441–e449. doi:10.4088/JCP.13r08672.

Belgamwar, R. B., & El-Sayeh, H. G. (2011). Aripiprazole versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews, 8*, CD006622. doi:10.1002/14651858.CD006622.pub2.

Carney, R. M., Blumenthal, J. A., Freedland, K. E., Youngblood, M., Veith, R. C., Burg, M. M., … Investigators, E. (2004). Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. *Psychosomatic Medicine, 66*(4), 466–474. doi:10.1097/01.psy.0000133362.75075.a6.

Castro, V. M., Clements, C. C., Murphy, S. N., Gainer, V. S., Fava, M., Weilburg, J. B., … Perlis, R. H. (2013). QT interval and antidepressant use: A cross sectional study of electronic health records. *BMJ, 346*, f288. doi:10.1136/bmj.f288.

Citrome, L. (2009). Asenapine for schizophrenia and bipolar disorder: A review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *International Journal of Clinical Practice, 63*(12), 1762–1784. doi:IJCP2228 [pii] 10.1111/j.1742-1241.2009.02228.x.

Citrome, L. (2011). Iloperidone: A clinical overview. *Journal of Clinical Psychiatry, 72*(Suppl 1), 19–23. doi:10.4088/JCP.10075su1.04.

Cohen, H. W., Gibson, G., & Alderman, M. H. (2000). Excess risk of myocardial infarction in patients treated with antidepressant medications: Association with use of tricyclic agents. *American Journal of Medicine, 108*(1), 2–8.

Dec, G. W., & Stern, T. A. (1990). Tricyclic antidepressants in the intensive care unit. *Journal of Intensive Care Medicine, 5*(2), 69–81.

Deng, C. (2013). Effects of antipsychotic medications on appetite, weight, and insulin resistance. *Endocrinology and Metabolism Clinics of North America, 42*(3), 545–563. doi:10.1016/j.ecl.2013.05.006. S0889-8529(13)00041-8 [pii].

Dixon, R. A., Edwards, I. R., & Pilcher, J. (1980). Diazepam in immediate post-myocardial infarct period. A double blind trial. *British Heart Journal, 43*(5), 535–540.

Drici, M. D., & Priori, S. (2007). Cardiovascular risks of atypical antipsychotic drug treatment. *Pharmacoepidemiology and Drug Safety, 16*(8), 882–890. doi:10.1002/pds.1424.

Fanapt (Iloperidone). (2012) *Novartis Pharmaceuticals Corporation*. East Hanover.

Freeman, M. P., & Freeman, S. A. (2006). Lithium: Clinical considerations in internal medicine. *American Journal of Medicine, 119*(6), 478–481. doi:10.1016/j.amjmed.2005.11.003.

Glassman, A. H., O'Connor, C. M., Califf, R. M., Swedberg, K., Schwartz, P., Bigger, J. T., Jr., … Sertraline antidepressant heart attack randomized trial, G. (2002). Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA, 288*(6), 701–709.

Harrigan, E. P., Miceli, J. J., Anziano, R., Watsky, E., Reeves, K. R., Cutler, N. R., … Middle, M. (2004). A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *Journal of Clinical Psychopharmacology, 24*(1), 62–69. doi:10.1097/01.jcp.0000104913.75206.62.

Heinrich, T. W., Biblo, L. A., & Schneider, J. (2006). Torsades de pointes associated with ziprasidone. *Psychosomatics, 47*(3), 264–268. doi:10.1176/appi.psy.47.3.264. S0033-3182(06)71161-6 [pii].

Hough, D. W., Natarajan, J., Vandebosch, A., Rossenu, S., Kramer, M., & Eerdekens, M. (2011). Evaluation of the effect of paliperidone extended release and quetiapine on corrected QT intervals: A randomized, double-blind, placebo-controlled study. *International Clinical Psychopharmacology, 26*(1), 25–34. doi:10.1097/YIC.0b013e3283400d58.

Huffman, J. C., & Stern, T. A. (2003). The use of benzodiazepines in the treatment of chest pain: A review of the literature. *Journal of Emergency Medicine, 25*(4), 427–437.

Invega (paliperidone). (2011). *Titusville*. Titusville: Janssen Pharmaceuticals.

Jiang, W., O'Connor, C., Silva, S. G., Kuchibhatla, M., Cuffe, M. S., Callwood, D. D., … Investigators, S. C. (2008). Safety and efficacy of sertraline for depression in patients with CHF (SADHART-CHF): A randomized, double-blind, placebo-controlled trial of sertraline for major depression with congestive heart failure. *American Heart Journal, 156*(3), 437–444. doi:10.1016/j.ahj.2008.05.003.

Jolly, K., Gammage, M. D., Cheng, K. K., Bradburn, P., Banting, M. V., & Langman, M. J. (2009). Sudden death in patients receiving drugs tending to prolong the QT interval. *British Journal of Clinical Pharmacology, 68*(5), 743–751. doi:10.1111/j.1365-2125.2009.03496.x.

Khasawneh, F. T., & Shankar, G. S. (2014). Minimizing cardiovascular adverse effects of atypical antipsychotic drugs in patients with schizophrenia. *Cardiology Research and Practice, 2014*, 273060. doi:10.1155/2014/273060.

Kiev, A., Masco, H. L., Wenger, T. L., Johnston, J. A., Batey, S. R., & Holloman, L. C. (1994). The cardiovascular effects of bupropion and nortriptyline in depressed outpatients. *Annals of Clinical Psychiatry, 6*(2), 107–115.

Kimmel, S. E., Schelleman, H., Berlin, J. A., Oslin, D. W., Weinstein, R. B., Kinman, J. L., … Lewis, J. D. (2011). The effect of selective serotonin re-uptake inhibitors on the risk of myocardial infarction in a cohort of patients with depression. *British Journal of Clinical Pharmacology, 72*(3), 514–517. doi:10.1111/j.1365-2125.2011.04008.x.

Latuda (lurasidone) [package insert]. (2012). *Marlborough*. MA: Sunovion Pharmaceuticals.

Lesperance, F., Frasure-Smith, N., Koszycki, D., Laliberte, M. A., van Zyl, L. T., Baker, B., … Investigators, C. (2007). Effects of citalopram and interpersonal psychotherapy on depression

in patients with coronary artery disease: The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA, 297*(4), 367–379. doi: 10.1001/jama.297.4.367.

Lipson, R. E., & Stern, T. A. (1991). Management of monoamine oxidase inhibitor-treated patients in the emergency and critical care setting. *Journal of Intensive Care Medicine, 6*, 117–125.

Lotufo-Neto, F., Trivedi, M., & Thase, M. (1999). Meta-analysis of the reversible inhibitors of monoamine oxidase A moclobemide and brofaromine for the treatment of depression. *Neuropsychopharmacology, 20*(3), 226–247. doi:10.1016/S0893-133X(98)00075-X.

Mackin, P. (2008). Cardiac side effects of psychiatric drugs. *Human Psychopharmacology, 23* (Suppl 1), 3–14. doi:10.1002/hup.915.

Manini, A. F., Raspberry, D., Hoffman, R. S., & Nelson, L. S. (2007). Delayed torsade de pointes (TdP) associated with ziprasidone overdose [abstract]. *Clinical Toxicology (Philadelphia, Pa.), 45*, 366.

Masand, P., Pickett, P., & Murray, G. B. (1991). Psychostimulants for secondary depression in medical illness. *Psychosomatics, 32*(2), 203–208. doi:10.1016/S0033-3182(91)72093-8.

Mehtonen, O. P., Aranko, K., Malkonen, L., & Vapaatalo, H. (1991). A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. *Acta Psychiatrica Scandinavica, 84*(1), 58–64.

Melsom, M., Andreassen, P., Melsom, H., Hansen, T., Grendahl, H., & Hillestad, L. K. (1976). Diazepam in acute myocardial infarction. Clinical effects and effects on catecholamines, free fatty acids, and cortisol. *British Heart Journal, 38*(8), 804–810.

Muenster, J. J., Rosenberg, M. S., Carleton, R. A., & Graettinger, J. S. (1967). Comparison between diazepam and sodium thiopental during DC countershock. *JAMA, 199*(10), 758–760.

Muzyk, A. J., Rivelli, S. K., Gagliardi, J. P., Revollo, J. Y., & Jiang, W. (2011). A retrospective study exploring the effects of intramuscular aripiprazole on QTc change in agitated medically ill patients. *Journal of Clinical Psychopharmacology, 31*(4), 532–534. doi:10.1097/JCP.0b013e318221e63b. 00004714-201108000-00024 [pii].

Nambudiri, D. E., Mirchandani, I. C., & Young, R. C. (1989). Two more cases of trazodone-related syncope in the elderly. *Journal of Geriatric Psychiatry and Neurology, 2*(4), 225.

Neil, C. J., Chong, C. R., Nguyen, T. H., & Horowitz, J. D. (2012). Occurrence of Tako-Tsubo cardiomyopathy in association with ingestion of serotonin/noradrenaline reuptake inhibitors. *Heart, Lung & Circulation, 21*(4), 203–205. doi:10.1016/j.hlc.2011.12.004.

Nitenberg, A., Marty, J., Blanchet, F., Zouioueche, S., Baury, A., & Desmonts, J. M. (1983). Effects of flunitrazepam on left ventricular performance, coronary haemodynamics and myocardial metabolism in patients with coronary artery disease. *British Journal of Anaesthesia, 55* (12), 1179–1184.

Ozeki, Y., Fujii, K., Kurimoto, N., Yamada, N., Okawa, M., Aoki, T., . . . Kunugi, H. (2010). QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia. *Progress in Neuropsychopharmacology and Biological Psychiatry, 34*(2), 401–405. doi: S0278-5846(10)00016-3 [pii].10.1016/j.pnpbp.2010.01.008.

Perry, R., & Cassagnol, M. (2009). Desvenlafaxine: A new serotonin-norepinephrine reuptake inhibitor for the treatment of adults with major depressive disorder. *Clinical Therapeutics, 31* (Pt 1), 1374–1404. doi:10.1016/j.clinthera.2009.07.012.

Potkin, S. G., Ogasa, M., Cucchiaro, J., & Loebel, A. (2011). Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. *Schizophrenia Research, 132*(2–3), 101–107. doi:10.1016/j.schres.2011.04.008: S0920-9964(11)00214-3 [pii].

Ray, W. A., Chung, C. P., Murray, K. T., Hall, K., & Stein, C. M. (2009). Atypical antipsychotic drugs and the risk of sudden cardiac death. *New England Journal of Medicine, 360*(3), 225–235. doi:10.1056/NEJMoa0806994. 360/3/225 [pii].

Reilly, J. G., Ayis, S. A., Ferrier, I. N., Jones, S. J., & Thomas, S. H. (2000). QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet, 355*(9209), 1048–1052. doi: S0140673600020353 [pii].

Rigotti, N. A., Thorndike, A. N., Regan, S., McKool, K., Pasternak, R. C., Chang, Y., ... Singer, D. E. (2006). Bupropion for smokers hospitalized with acute cardiovascular disease. *American Journal of Medicine, 119*(12), 1080–1087. doi: 10.1016/j.amjmed.2006.04.024.

Roose, S. P., Dalack, G. W., Glassman, A. H., Woodring, S., Walsh, B. T., & Giardina, E. G. (1991). Cardiovascular effects of bupropion in depressed patients with heart disease. *The American Journal of Psychiatry, 148*(4), 512–516.

Roose, S. P., Laghrissi-Thode, F., Kennedy, J. S., Nelson, J. C., Bigger, J. T., Jr., Pollock, B. G., ... Gergel, I. (1998). Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA, 279*(4), 287–291.

Saphris (asenapine). (2012). *Whitehouse station*. NJ: Merck Sharpe & Dohme Corp.

Service, J. A., & Waring, W. S. (2008). QT Prolongation and delayed atrioventricular conduction caused by acute ingestion of trazodone. *Clinical Toxicology (Philadelphia, Pa.), 46*(1), 71–73. doi:10.1080/15563650701275322.

Sharma, N. D., Rosman, H. S., Padhi, I. D., & Tisdale, J. E. (1998). Torsades de Pointes associated with intravenous haloperidol in critically ill patients. *American Journal of Cardiology, 81*(2), 238–240. doi: S0002-9149(97)00888-6 [pii].

Strik, J. J., Honig, A., Lousberg, R., Lousberg, A. H., Cheriex, E. C., Tuynman-Qua, H. G., ... Van Praag, H. M. (2000). Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: Findings from a double-blind, placebo-controlled trial. *Psychosomatic Medicine, 62*(6), 783–789.

Thase, M. E. (1998). Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. *Journal of Clinical Psychiatry, 59*(10), 502–508.

Tiihonen, J., Lonnqvist, J., Wahlbeck, K., Klaukka, T., Tanskanen, A., & Haukka, J. (2006). Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. *Archives of General Psychiatry, 63*(12), 1358–1367. doi:10.1001/archpsyc.63.12.1358.

Tracey, J. A., Cassidy, N., Casey, P. B., & Ali, I. (2002). Bupropion (Zyban) toxicity. *Irish Medical Journal, 95*(1), 23–24.

van den Brink, R. H., van Melle, J. P., Honig, A., Schene, A. H., Crijns, H. J., Lambert, F. P., & Ormel, J. (2002). Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: Rationale and outline of the myocardial INfarction and depression-intervention trial (MIND-IT). *American Heart Journal, 144*(2), 219–225.

Van Loon, G. R. (1968). Ventricular arrhythmias treated by diazepam. *Canadian Medical Association Journal, 98*(16), 785–787.

Velazquez, C., Carlson, A., Stokes, K. A., & Leikin, J. B. (2001). Relative safety of mirtazapine overdose. *Veterinary and Human Toxicology, 43*(6), 342–344.

Vieweg, W. V. (2002). Mechanisms and risks of electrocardiographic QT interval prolongation when using antipsychotic drugs. *Journal of Clinical Psychiatry, 63*(Suppl 9), 18–24.

Vieweg, W. V., & Wood, M. A. (2004). Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. *Psychosomatics, 45*(5), 371–377. doi:10.1176/appi.psy.45.5.371.

Vieweg, W. V., Schneider, R. K., & Wood, M. A. (2005). Torsade de pointes in a patient with complex medical and psychiatric conditions receiving low-dose quetiapine. *Acta Psychiatrica Scandinavica, 112*(4), 318–322. doi:10.1111/j.1600-0447.2005.00592.x. author reply 322doi: ACP592 [pii].

Vieweg, W. V., Wood, M. A., Fernandez, A., Beatty-Brooks, M., Hasnain, M., & Pandurangi, A. K. (2009). Proarrhythmic risk with antipsychotic and antidepressant drugs: Implications in the elderly. *Drugs and Aging, 26*(12), 997–1012. doi:10.2165/11318880-000000000-000002 [pii].

Waring, W. S., Graham, A., Gray, J., Wilson, A. D., Howell, C., & Bateman, D. N. (2010). Evaluation of a QT nomogram for risk assessment after antidepressant overdose. *British Journal of Clinical Pharmacology, 70*(6), 881–885. doi:10.1111/j.1365-2125.2010.03728.x.

Weiden, P. J., Cutler, A. J., Polymeropoulos, M. H., & Wolfgang, C. D. (2008). Safety profile of iloperidone: A pooled analysis of 6-week acute-phase pivotal trials. *Journal of Clinical Psychopharmacology, 28*(2 Suppl 1), S12–S19. doi:10.1097/JCP.0b013e3181694f5a.

Wenzel-Seifert, K., Wittmann, M., & Haen, E. (2011). QTc prolongation by psychotropic drugs and the risk of Torsade de Pointes. *Deutsches Ärzteblatt International, 108*(41), 687–693. doi:10.3238/arztebl.2011.0687.

Wheatley, D. (1984). Anxiolytic drug use in cardiovascular disease: An overview. *Psychopharmacology Bulletin, 20*(4), 649–659.

Wilt, J. L., Minnema, A. M., Johnson, R. F., & Rosenblum, A. M. (1993). Torsade de pointes associated with the use of intravenous haloperidol. *Annals of Internal Medicine, 119*(5), 391–394.

Woods, S. W., Tesar, G. E., Murray, G. B., & Cassem, N. H. (1986). Psychostimulant treatment of depressive disorders secondary to medical illness. *Journal of Clinical Psychiatry, 47*(1), 12–15.

Yan, H., Chen, J. D., & Zheng, X. Y. (2013). Potential mechanisms of atypical antipsychotic-induced hypertriglyceridemia. *Psychopharmacology, 229*(1), 1–7. doi:10.1007/s00213-013-3193-7.

Impact of Cardiac Medications on Mood

Geoffrey A. Head

Contents

Abstract

Cardiac medications including β-blockers, cardiac glycosides, and antiarrhythmics have long been known to have CNS effects including alterations in mood, emotion state anxiety, and depression. While the predominant effects come from those with higher lipophilicity and when used at high doses, the evidence is actually quite mixed. At cardiac therapeutic doses, lipophilic β-blockers like propranolol have actually few CNS effects on mood. The effectiveness of β-blockers is established for relieving performance anxiety, but the actions involve more a peripheral relief of somatic symptoms rather than a central effect. By contrast the reduction in consolidation of aversive and stressful memory by propranolol appears to involve altering the functioning of the amygdala and hippocampus directly. While evidence suggests that β-blockers

G.A. Head (✉)
Neuropharmacology Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia
e-mail: geoff.head@bakeridi.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_65

reduce aggressive behaviors associated with various psychological conditions such as schizophrenia, they are now used relatively rarely. Cardiac glycosides such as digoxin have been implicated in causing a variety of mental dysfunctions including depression, yet quality prospective trials are lacking and evidence is largely anecdotal. The difficulty is that the patients likely to receive either β-blockers or digoxin are often suffering heart failure which in itself causes mood alterations such as depression. The current review analyzes the evidence of mood-altering side effects for the various pharmacological agents used to treat cardiac disease.

Keywords

Anti-arrhythmic effects • Arrhythmias • Beta-adrenoceptor antagonist • Adverse CNS effects • Aggression treatment • Depression • Anxiety treatment • Mechanism • Post-traumatic stress disorder treatment • Cardiac arrhythmias • Cardiac glycosides • Digoxin • Mood • Antiarrhythmic agents • Digoxin • Post-traumatic stress disorder • Propranolol

Introduction

The concept that drugs prescribed to treat heart conditions may have central side effects affecting mood has been around for a very long time (Celano et al. 2011). The issue was highlighted by the very early suggestion of Waal who reported in a letter to the British Medical Journal in 1967 that patients taking propranolol, the prototype β-adrenoceptor antagonist developed by Sir James Black in the early 1960s, showed a high incidence of depression (Waal 1967). This observation was treated with some skepticism that same year by Fitzgerald who stated that the adverse reactions among the 60,000 patients receiving propranolol were low and the incidence of depression was 0.1 % (Fitzgerald 1967). Fitzgerald was working for ICI at the time who manufactured propranolol as sold as Inderil. Thus, the debate began and over the last 47 years, there has been great interest in not only this specific issue but also the wider area of whether and how cardiac drugs affect mood and other CNS processes. Such side effects can undoubtedly affect the usage of drugs like propranolol and the newer more selective β-blockers and is counterproductive to the appropriate use of these valuable agents if these side effects have not been properly and scientifically validated. The confounding issue is that behavioral and psychological symptoms including changes in mood are very common in patients with cardiovascular disease (Pozuelo et al. 2009). Depression and anxiety are associated with heart failure (Glassman et al. 1983), and its prevalence can range from 15 % to 36 % (Konstam et al. 2005). Patients who have undergone coronary artery bypass surgery or experienced a recent myocardial infarction are well known to suffer more major depressive episodes and anxiety which is also linked to subsequent events including death (Frasure-Smith et al. 1993; van Melle et al. 2006). Thus, with anecdotal and case reports and even with small uncontrolled studies, it is easy to see why particular medications that are cardiac specific might

be inappropriately thought to produce neuropsychiatric disorders such as depression. The purpose of the chapter is to comprehensively review the current views relating to this important issue, not only with respect to β-blockers but also other agents prescribed by cardiologists to control cardiac function.

Beta-Adrenoceptor Antagonists and Depression

The early suggestions by Waal of mood-altering side effects of β-adrenoceptor antagonists (Waal 1967) was not an isolated report. Petri and colleagues reported three patients given propranolol had severe depressive episodes which were dose dependent and quickly resolved when propranolol was stopped (Petrie et al. 1982). A small study of 34 patients receiving propranolol found that there was no relationship between dosage and depressive symptoms for the group as a whole; there was a positive correlation in those with a negative history of depression between propranolol dosage and depression scores (Griffin and Friedman 1986). Propranolol is highly lipophilic and rapidly crosses the blood-brain barrier (Fodor et al. 1987). There has been the suggestion that substitution of a less lipophilic drug like atenolol might reduce depressive and mood symptoms (Fraser and Carr 1976), and this was confirmed in case reports where this proved to be highly successful (McNeil et al. 1982; Oppenheim 1983). A small cohort of 20 healthy volunteers were treated for only 4 days with either propranolol or metoprolol or placebo and recorded a slightly higher state of tension and depression at an 80 mg dose level of propranolol compared to placebo (Head et al. 1996).

Other early evidence for depression-causing side effects of β-blockers came from epidemiological studies that found a greater rate of prescription of antidepressants in patients given β-blockers (Avorn et al. 1986; Thiessen et al. 1990). However, these findings have been questioned as being rather indirect and not definitive (Patten and Love 1993). Bright and Everett explained the possible association in an analysis of a large Medicaid database which indicated that associated cofounders such as benzodiazepine use, illness, and willingness to see a health-care provider when used in the analysis as cofactors eliminated the association of antidepressant prescriptions with β-blocker use (Bright and Everitt 1992).

The evidence supporting an effect of β-blockers on mood is anecdotal and not strongly supported by the scientific evidence (Stoudemire et al. 1984). Indeed the strongest evidence is actually against this being a major effect of β-blockers like propranolol. In a randomized controlled trial, patients suffering from anxiety neurosis were randomized to various treatment regimes including propranolol. Various measures of mood and depression were measured weekly for 3 weeks, but the study found no evidence that propranolol exacerbates or promotes depression (Binstok et al. 1984). In a relatively small study of patients undergoing cardiac catheterization, similar proportions of patients receiving beta-blockers compared to other medications had symptoms for major depressive disorder (Carney et al. 1987). A prospective study of the prevalence of depression 3 or 4 months post-myocardial

infarction did not find that β-blockers reach significance as a predictor (Schleifer et al. 1991). These findings were confirmed in a multicenter prospective trial of nearly 400 post-myocardial infarction patients prescribed either beta-blockers or other drugs and followed for 12 months (van Melle et al. 2006). A study from the Harvard community health plan population who followed a large number of patients starting a range of pharmaceutical treatments for at least 6 months found that the rates of depression (major and minor) in those prescribed beta-blockers after adjustment for age and sex were similar to those who were prescribed other drugs (Gerstman et al. 1996). However, this study lacked any assessment of baseline levels of depression. A Department of Veterans Affairs study of treating hypertension in the elderly (older than 60) with hydrochlorothiazide found no significant difference in the prevalence of depression for those additionally prescribed β1 selective antagonist metoprolol compared to other antihypertensive agents (Goldstein et al. 1990). A major multicenter double-blind randomized controlled prospective trial of atenolol in the elderly did not find any deterioration in measures of cognition, emotional state, physical function, or leisure activities (Applegate et al. 1994). Also in a double-blind placebo-controlled study of the nonselective β-blocker nadolol to treat chronic aggression, there was no difference between control and treatment groups for symptoms of depression (Sorgi et al. 1992). A large retrospective analysis of Odense University Pharmacoepidemiological Database was used to determine the association between β-blocker and antidepressant combined therapy whereby a depression-causing effect would result in an excess of patients starting the drug first (Hallas 1996). This was not the case for β-blockers. A major review of several clinical studies of a range of β-blocker usage in nearly 6000 patients found that depression was rarely associated with propranolol and only after long-term treatment at high doses (Stoudemire et al. 1984). A review of the literature in 1996 cast further doubt on the depression hypothesis and suggested that β-blockers may have been unjustly blamed and that their use has been avoided for that reason (Ried et al. 1998). A more recent meta-analysis of the association of β-blockers with CNS symptoms using 15 trials from 1966 to 2001 involving 35,000 subjects found no relationship with depression (Ko et al. 2002). Chronic treatment with the newer third generation β1 selective antagonist nebivolol in combination with other antihypertensive agents did not result in listing of depression in the adverse side effects (Papademetriou 2009). However, as pointed out in a commentary, there is little evidence to suggest that depression is caused by β-blockers in any case (van Melle and de Jonge 2009). Thus, while patients with cardiovascular disease are at greater risk of developing major depressive illness, there is little convincing evidence that prescribing β-blockers will add to that risk.

Mechanism

There is no question that some β-blockers penetrate the CNS effectively at dose used to treat hypertension and other cardiac-related disorders (Middlemiss

et al. 1981). The level of CNS β-adrenoceptor antagonists is closely related to the lipid solubility of the compound, but the issue is somewhat complicated by protein binding in plasma and the uptake into lipophilic tissues (Taylor et al. 1981). A single oral dose of 80 mg propranolol leads to concentrations in cerebrospinal fluid likely to produce a high level of receptor blockade (Taylor et al. 1981). Interestingly a 100 mg dose of atenolol leads to about five times higher cerebrospinal fluid concentrations as it is not protein bound like propranolol which might be considered sufficient for central β-adrenoceptor blockade (Taylor et al. 1981). However, another study that same year measured brain concentration after 5–11 days of treatment in patients and showed that propranolol had 250 times greater brain to plasma rations that atenolol which would very much explain the low level of CNS side effects with atenolol (Glaubiger and Lefkowitz 1977). Myers and colleagues suggested the brain/plasma ratio in rabbit was ~15:1 and similar to that in post-mortem human samples (Myers et al. 1975). In theory greater lipophilicity would be expected to produce more CNS effects although the evidence supporting this is practice is conflicting (Keller and Frishman 2003).

The mechanism by which these drugs could induce depression has been suggested to involve an upregulation of β-adrenoceptors or compensatory postsynaptic noradrenergic receptor hypersensitivity in the CNS (Charney et al. 1981; Oppenheim 1983). Animal studies have confirmed that there is up regulation of β-adrenoceptors in tissue with chronic treatment with propranolol (Glaubiger and Lefkowitz 1977). Long-term treatment with antidepressants reduces β-adrenergic sensitivity and increases responsiveness to serotonergic and α-adrenergic agonists (Lerer et al. 1981), while treatment with β-adrenoceptor agonists decreases receptor sensitivity (Neil-Dwyer et al. 1981). Further, chronic treatment agonists such as salbutamol have been shown to be as effective as clomipramine in relieving symptoms in depressed patients (Middlemiss et al. 1981).

Beta-Adrenoceptor Antagonists and Other Adverse CNS Effects

While β-blockers have been incorrectly in most cases associated with depression, there are other CNS effects worthy of note, including sedation, fatigue, reduced cognition, anxiolysis, and reduction in aggressive behavior as well as being an effective treatment for migraine. A placebo-controlled study in a small number of volunteers using a range of acute doses of propranolol and a number of psychological and psychomotor tests found that propranolol at doses between 40 and 320 mg decreased alertness, prolonged reaction time, reduced response to digital copying test, and increased detachment (Salem and McDevitt 1984). Thus, while the study is well controlled and indicates CNS effect of propranolol, the effects were seen at some doses, and there was not a clear dose-response relationship which is unusual. A placebo-controlled comparison of a number of antihypertensive agents found that propranolol was associated with drowsiness and impaired reaction time, symbol copying, and memory (Frcka and Lader 1988). A later randomized double-blind parallel study compared the effects on cognitive function of atenolol, captopril,

enalapril, and propranolol in hypertensive men and found that propranolol showed worsening of or less improvement in distressing psychological symptoms compared to the other drugs (Steiner et al. 1990). As this large trial included another less lipophilic drug atenolol, these effects are not a class effect but are drug specific. An analysis of 55 studies on the effect of β-blockers on cognitive function revealed that perceptual motor cognitive was frequently affected by these drugs but there was no trend for lipophilic drugs to be more indicated than lipophobic drugs (Dimsdale et al. 1989). Further, this study found that while some positive effect on complex task performance was observed, beta-antagonists are associated with increased sedation (Dimsdale et al. 1989). Other trials have found that atenolol used as an antihypertensive actually improved surveyed psychological well-being to a degree similar to that observed following captopril (Fletcher et al. 1990). The meta-analysis by Ko and colleagues that did not find any evidence for depressive effects of β-blockers did reveal a greater risk of fatigue and sexual dysfunction although the incidence was low (Ko et al. 2002).

Occasionally but very rarely are β-antagonists associated with psychosis (Love and Handler 1995). In one case the symptoms associated with lower doses of propranolol and other cases by changing to atenolol from propranolol (McGahan et al. 1984; Parker 1985). An isolated case has also been reported for atenolol (Viadero et al. 1983) and in an elderly patient given metoprolol (Fisher et al. 2002). However, given the huge number of patients taking these agents, such reports are extremely rare.

Beta-Adrenoceptor Antagonists and CNS Indications

β-Antagonists have indications and contraindications in a number of neuropsychological conditions, many of which are beyond the scope of this review. For example, they may be used as an adjunct therapy to reduce akinesia in schizophrenia patients receiving neuroleptics (Keller and Frishman 2003). This section will concentrate on the impact of the use of β-blockers on mood, memory, and behavior.

Treatment of Aggression

There is an appreciable long-standing literature that suggests that β-blockers are effective in decreasing the intensity and also the frequency of aggressive behaviors associated with a wide variety of situations such as dementia, posttraumatic stress disorder, schizophrenia, forensic psychiatry settings, attention-deficit disorder, personality disorders, as well as mental retardation, autism, and brain injury (Haspel 1995; Brieden et al. 2002; Fleminger et al. 2006; Ward et al. 2013). While the successful treatment of aggression with any agent without sedation is actually quite difficult to achieve, in this regard, β-blockers are quite successful although at the higher doses used, the side effect of hypotension and bradycardia may be an issue and limit their use (Fava 1997). The use of

propranolol in the very elderly to limit aggressive or agitated behaviors associated with dementia is effective but is limited by the high frequency of contraindications of using β-blockers in this population (Peskind et al. 2005). A recent systematic review of the efficacy of β-blockers in the treatment of aggressive behaviors in individuals with intellectual disabilities found that the evidence is supportive but lacking in quality randomized controlled and blinded studies (Ward et al. 2013). Nevertheless, a double-blind, placebo-controlled crossover study, albeit only in thirty subjects, found that pindolol (a dual β-adrenoceptor and 5HT1A receptor antagonist) was effective in reducing the intensity and frequency of aggressive episodes. In reality, β-blockers are now rarely used to treat aggression in clinical practice (Volavka et al. 2006).

Treatment of Anxiety

There is a body of evidence that suggests that β-antagonists can be useful in the treatment of anxiety, particularly related to performances and taken about an hour before hand (Brantigan et al. 1982; Hartley et al. 1983; Liebowitz et al. 1985; Schneier 2006). Propranolol has also been shown to improve test scores during exams presumably by reducing the stress-induced impairment of cognitive functioning (Faigel 1991). However, early placebo-controlled studies failed to find any effect of propranolol on subjective anxiety ratings, while diazepam in the same test was effective (Ashton et al. 1976). Also anxiety state before and after exercise was not affected by propranolol or metoprolol at normal doses used to treat hypertension (Head et al. 1996). Nevertheless, the prevailing view backed by numerous studies is that the antianxiety effects of β-antagonists are not central effects but somatic due to the reduction of the stress-induced tachycardia caused by peripheral β-blockade (Granville-Grossman and Turner 1966; Kelly 1985; Hayes and Schulz 1987). However, comparison between the non-lipophilic atenolol and propranolol in a double-blind crossover study of a limited number of subjects showed clear effectiveness of propranolol but not atenolol in formal psychological tests of mood, motivation, and anxiety (Conant et al. 1989). The authors suggest that a direct CNS action of propranolol is the likely explanation. Indeed in rats propranolol dose dependently decreases anxiety in an open field test (Angrini et al. 1998) and also during a startle in a bright light environment (Walker and Davis 2002).

β-Blockers have also been indicated in other situations as an adjunct to regular therapy. Early studies suggested that propranolol is effective in suppressing panic attacks and reducing avoidance behavior in patients (Ravaris et al. 1991). Pindolol has been used in combination with selective serotonin uptake inhibitors to reduce the time of onset of clinical efficacy in depressive and anxiety disorders. Also pindolol has an augmenting effect on fluoxetine in treatment of resistant panic disorder (Hirschmann et al. 2000). Studies in rats using an elevated T-maze test indicate that pindolol combined with paroxetine (but not alone) had panicolytic effects (Sela et al. 2010) which is supportive of the effectiveness of the combination.

Treatment of Posttraumatic Stress Memories

It has been well established that during trauma, the excessive levels of emotion and distress that are experienced can augment memory processes that are readily reactivated during a contextual stimulus. It is becoming increasingly recognized that such traumas particularly early in life can dramatically increase the risk of psychiatric disorders such as depression, panic attack, phobias, addiction, and phobias (Carr et al. 2013; Lonergan et al. 2013). One can reduce the long-term influence of emotional memory events associated with trauma by preventing memory consolidation. In the seminal study published in Nature in 1994, the effectiveness of propranolol compared to placebo in reducing the memories of a set of emotionally disturbing pictures was demonstrated (Cahill et al. 1994). The mechanism may involve reducing memory consolidation (Garakani et al. 2006) as propranolol can reduce the consolidation and recall of negative emotional experiences from pictures and words in normal subjects (for overview, see Lonergan et al. 2013). The process affected may involve protein synthesis inhibition (Nader et al. 2000) in specific nuclei within the amygdala and hippocampus which has been demonstrated using functional magnetic resonance imaging of subjects (Schwabe et al. 2009, 2012). Administration of propranolol within a few hours of the event and continuing for several days has a long-term benefit (Pitman et al. 2002; Vaiva et al. 2003). Oral administration of propranolol disrupted memory consolidation and produced diminished fear (Kindt et al. 2009). Also it appears that such blockade may prevent the rebuilding of the emotional memory. An important consideration is the dose used and the sex of the patient as men are less sensitive to the effects of propranolol and may need higher doses (Cahill and van Stegeren 2003; Lonergan et al. 2013). Interestingly Soeter and Kindt noticed that the declarative memory of the event was intact after propranolol which might result in the recovery of a fear response. Importantly the effect of propranolol persisted for 1 month suggesting that this does not occur suggesting that β-blockade may also disrupt memory reconsolidation (Soeter and Kindt 2010). In addition to the effects of propranolol on consolidation of fear, studies in animals have shown that the drug can reduce expression and extinction conditioned fear in rats (Rodriguez-Romaguera et al. 2009). This effect was not observed with sotalol even though both drugs produced similar bradycardia. This suggests a clear centrally mediated mechanism.

It is not surprising then that lipophilic β-antagonists like propranolol are effective at treating posttraumatic stress disorder (Haspel 1995; Cukor et al. 2009; de Kleine et al. 2013; Tawa and Murphy 2013). A recent review of the treatment of the military for posttraumatic stress does support the use of propranolol as an effective treatment (Tawa and Murphy 2013). However, there are some negative studies as well which failed to find effects such as in the trauma associated with burns although this was a retrospective study of limited quality (McGhee et al. 2009). A placebo-controlled trial in posttraumatic stress disorder patients and controls recalling an emotionally arousing story found that a very low dose of propranolol was effective in reducing recall but there was no difference between groups (Reist et al. 2001). Clearly there is good evidence of effectiveness of lipophilic β-blockers

on reducing the impact of negative emotional experiences provided it is given within the memory consolidation period and at sufficient doses.

Digoxin and Mood

Cardiac glycosides originally discovered by William Withering who extracted the active compound digoxin from foxglove (Withering 1785) have been used since to treat heart failure. Digoxin is a potent inhibitor of cardiac sodium potassium adenosine triphosphatase (ATPase) but is about ten times more potent on neuronal equivalents. Thus, it might be expected to have CNS effects at high doses. Indeed one of the complications of therapy, noticed very early on, has been delirium and depression (Smith 1938; Patten and Love 1993). A comprehensive review by Keller and Frishman of the neuropsychiatric effects of a number of cardiovascular drugs listed the effects of digoxin to include hallucinations, amnesia, confusion, disorientation, apathy, belligerence, delusions, delirium, cognitive changes, mania/euphoria, depression/lethargy, encephalopathy, and psychosis (Keller and Frishman 2003). The difficulty in determining the correctness of these associations is that patients with heart failure as mentioned above are often elderly and have greater prevalence of many of these conditions (Glassman et al. 1983; Patten and Love 1993). The studies are mainly case reports and there have been few properly designed controlled trials in this area. A prospective study that adjusted for a number of obvious cofounders using logistic regression found that the use of digoxin was an independent predictor of depressive episodes (Schleifer et al. 1991). A randomized parallel design comparison of digoxin, non-pharmacological treatment and placebo in 20 heart failure patients was designed to assess functional capacity and mood (Kostis et al. 1994). While the exercise non-pharmacological approach improved mood the most, digoxin was better than placebo and had the added effect over the other treatments of improving ejection fraction (Kostis et al. 1994). However, one cannot rule out a mood effect secondary to the improved cardiac function as the patients become more active.

Antiarrhythmic Agents and Mood

Patients with arrhythmias have higher states of mood disorder than those without arrhythmias (Dunbar et al. 1999). There are a variety of agents effective in treating cardiac arrhythmias, some of which have been associated with delirium. Class I agents that block sodium channels such as procainamide have not been tested for psychological effects in randomized controlled prospective studies although there are some case reports of delirium and mania (Keller and Frishman 2003). Class III agents like amiodarone block sodium channels as well as influence calcium and potassium currents. Its antiarrhythmic effects may be due to its perturbation of the membrane lipids and may also have CNS effects as suggested by reports of

depression, delirium, and sexual dysfunction (Keller and Frishman 2003). Like Class I agents there are few dedicated trials of these agents involving mood.

References

Angrini, M., Leslie, J. C., & Shephard, R. A. (1998). Effects of propranolol, buspirone, pcpa, reserpine, and chlordiazepoxide on open-field behavior. *Pharmacology Biochemistry and Behavior, 59*(2), 387–397.

Applegate, W. B., Pressel, S., Wittes, J., Luhr, J., Shekelle, R. B., Camel, G. H., et al. (1994). Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. *Archives of Internal Medicine, 154*(19), 2154–2160.

Ashton, H., Millman, J., Telford, R., & Thompson, J. W. (1976). A comparison of some physiological and psychological effects of propranolol and diazepam in normal subjects. *British Journal of Clinical Pharmacology, 3*, 551–559.

Avorn, J., Everitt, D. E., & Weiss, S. (1986). Increased antidepressant use in patients prescribed beta-blockers. *JAMA, 255*(3), 357–360.

Binstok, G., Foster, L. G., & Mullane, J. F. (1984). Propranolol and the depression component of anxiety neurosis. *Current Therapeutic Research, 35*(3), 423–432.

Brantigan, C. O., Brantigan, T. A., & Joseph, N. (1982). Effect of beta blockade and beta stimulation on stage fright. *American Journal of Medicine, 72*(1), 88–94.

Brieden, T., Ujeyl, M., & Naber, D. (2002). Psychopharmacological treatment of aggression in schizophrenic patients. *Pharmacopsychiatry, 35*(3), 83–89.

Bright, R. A., & Everitt, D. E. (1992). Beta-blockers and depression. Evidence against an association. *JAMA, 267*(13), 1783–1787.

Cahill, L., & van Stegeren, A. (2003). Sex-related impairment of memory for emotional events with beta-adrenergic blockade. *Neurobiology of Learning and Memory, 79*(1), 81–88.

Cahill, L., Prins, B., Weber, M., & McGaugh, J. L. (1994). Beta-adrenergic activation and memory for emotional events. *Nature, 371*(6499), 702–704.

Carney, R. M., Rich, M. W., teVelde, A., Saini, J., Clark, K., & Freedland, K. E. (1987). Prevalence of major depressive disorder in patients receiving beta-blocker therapy versus other medications. *American Journal of Medicine, 83*(2), 223–226.

Carr, C. P., Martins, C. M., Stingel, A. M., Lemgruber, V. B., & Juruena, M. F. (2013). The role of early life stress in adult psychiatric disorders: A systematic review according to childhood trauma subtypes. *Journal of Nervous and Mental Disease, 201*(12), 1007–1020.

Celano, C. M., Freudenreich, O., Fernandez-Robles, C., Stern, T. A., Caro, M. A., & Huffman, J. C. (2011). Depressogenic effects of medications: A review. *Dialogues in Clinical Neuroscience, 13*(1), 109–125.

Charney, D. S., Menkes, D. B., & Heninger, G. R. (1981). Receptor sensitivity and the mechanism of action of antidepressant treatment. Implications for the etiology and therapy of depression. *Archives of General Psychiatry, 38*(10), 1160–1180.

Conant, J., Engler, R., Janowsky, D., Maisel, A., Gilpin, E., & LeWinter, M. (1989). Central nervous system side effects of [beta]-adrenergic blocking agents with high and low lipid solubility. *Journal of Cardiovascular Pharmacology, 13*(4), 656–661.

Cukor, J., Spitalnick, J., Difede, J., Rizzo, A., & Rothbaum, B. O. (2009). Emerging treatments for ptsd. *Clinical Psychology Review, 29*(8), 715–726.

de Kleine, R. A., Rothbaum, B. O., & van Minnen, A. (2013). Pharmacological enhancement of exposure-based treatment in ptsd: A qualitative review. *European Journal Psychotraumatology*, 4, 21626.

Dimsdale, J. E., Newton, R. P., & Joist, T. (1989). Neuropsychological side effects of beta-blockers. *Archives of Internal Medicine, 149*(3), 514–525.

Dunbar, S. B., Kimble, L. P., Jenkins, L. S., Hawthorne, M., Dudley, W., Slemmons, M., et al. (1999). Association of mood disturbance and arrhythmia events in patients after cardioverter defibrillator implantation. *Depression and Anxiety, 9*(4), 163–168.

Faigel, H. C. (1991). The effect of beta blockade on stress-induced cognitive dysfunction in adolescents. *Clinical Pediatrics (Phila), 30*(7), 441–445.

Fava, M. (1997). Psychopharmacologic treatment of pathologic aggression. *The Psychiatric Clinics of North America, 20*(2), 427–451.

Fisher, A. A., Davis, M., & Jeffery, I. (2002). Acute delirium induced by metoprolol. *Cardiovascular Drugs and Therapy, 16*(2), 161–165.

Fitzgerald, J. D. (1967). Propranolol-induced depression. *British Medical Journal, 2*(5548), 372–373.

Fleminger, S., Greenwood, R. J., & Oliver, D. L. (2006). Pharmacological management for agitation and aggression in people with acquired brain injury. *Cochrane Database of Systematic Reviews, 4*, CD003299.

Fletcher, A. E., Bulpitt, C. J., Hawkins, C. M., Havinga, T. K., ten Berge, B. S., May, J. F., et al. (1990). Quality of life on antihypertensive therapy: A randomized double-blind controlled trial of captopril and atenolol. *Journal of Hypertension, 8*(5), 463–466.

Fodor, J. G., Chockalingam, A., Drover, A., Fifield, F., & Pauls, C. J. (1987). A comparison of the side effects of atenolol and propranolol in the treatment of patients with hypertension. *The Journal of Clinical Pharmacology, 27*(11), 892–901.

Fraser, H. S., & Carr, A. C. (1976). Propranolol psychosis. *British Journal of Psychiatry, 129*, 508–509.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1993). Depression following myocardial infarction. Impact on 6-month survival. *JAMA, 270*(15), 1819–1825.

Frcka, G., & Lader, M. (1988). Psychotropic effects of repeated doses of enalapril, propranolol and atenolol in normal subjects. *British Journal of Clinical Pharmacology, 25*(1), 67–73.

Garakani, A., Mathew, S. J., & Charney, D. S. (2006). Neurobiology of anxiety disorders and implications for treatment. *Mount Sinai Journal of Medicine, 73*(7), 941–949.

Gerstman, B. B., Jolson, H. M., Bauer, M., Cho, P., Livingston, J. M., & Platt, R. (1996). The incidence of depression in new users of beta-blockers and selected antihypertensives. *Journal of Clinical Epidemiology, 49*(7), 809–815.

Glassman, A. H., Johnson, L. L., Giardina, E. G., Walsh, B. T., Roose, S. P., Cooper, T. B., et al. (1983). The use of imipramine in depressed patients with congestive heart failure. *JAMA, 250*(15), 1997–2001.

Glaubiger, G., & Lefkowitz, R. J. (1977). Elevated beta-adrenergic receptor number after chronic propranolol treatment. *Biochemical and Biophysical Research Communications, 78*(2), 720–725.

Goldstein, G., Materson, B. J., Cushman, W. C., Reda, D. J., Freis, E. D., Ramirez, E. A., et al. (1990). Treatment of hypertension in the elderly: Ii. Cognitive and behavioral function. Results of a department of veterans affairs cooperative study. *Hypertension, 15*(4), 361–369.

Granville-Grossman, K. L., & Turner, P. (1966). The effect of propranolol on anxiety. *Lancet, 1*(7441), 788–790.

Griffin, S. J., & Friedman, M. J. (1986). Depressive symptoms in propranolol users. *Journal of Clinical Psychiatry, 47*(9), 453–457.

Hallas, J. (1996). Evidence of depression provoked by cardiovascular medication: A prescription sequence symmetry analysis. *Epidemiology, 7*(5), 478–484.

Hartley, L. R., Ungapen, S., Davie, I., & Spencer, D. J. (1983). The effect of beta adrenergic blocking drugs on speakers' performance and memory. *British Journal of Psychiatry, 142*, 512–517.

Haspel, T. (1995). Beta-blockers and the treatment of aggression. *Harvard Review Psychiatry, 2*(5), 274–281.

Hayes, P., & Schulz, S. (1987). Beta-blockers in anxiety disorders. *Journal of Affective Disorders, 13*(2), 119–130.

Head, A., Kendall, M. J., Ferner, R., & Eagles, C. (1996). Acute effects of beta blockade and exercise on mood and anxiety. *British Journal of Sports Medicine, 30*(3), 238–242.

Hirschmann, S., Dannon, P. N., Iancu, I., Dolberg, O. T., Zohar, J., & Grunhaus, L. (2000). Pindolol augmentation in patients with treatment-resistant panic disorder: A double-blind, placebo-controlled trial. *Journal of Clinical Psychopharmacology, 20*(5), 556–559.

Keller, S., & Frishman, W. H. (2003). Neuropsychiatric effects of cardiovascular drug therapy. *Cardiology in Review, 11*(2), 73–93.

Kelly, D. (1985). Beta-blockers in anxiety. *Stress Medicine, 1*(2), 143–152.

Kindt, M., Soeter, M., & Vervliet, B. (2009). Beyond extinction: Erasing human fear responses and preventing the return of fear. *Nature Neuroscience, 12*(3), 256–258.

Ko, D. T., Hebert, P. R., Coffey, C. S., Sedrakyan, A., Curtis, J. P., & Krumholz, H. M. (2002). Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA, 288*(3), 351–357.

Konstam, V., Moser, D. K., & De Jong, M. J. (2005). Depression and anxiety in heart failure. *Journal of Cardiac Failure, 11*(6), 455–463.

Kostis, J. B., Rosen, R. C., Cosgrove, N. M., Shindler, D. M., & Wilson, A. C. (1994). Nonpharmacologic therapy improves functional and emotional status in congestive heart failure. *Chest, 106*(4), 996–1001.

Lerer, B., Ebstein, R. P., & Belmaker, R. H. (1981). Subsensitivity of human beta-adrenergic adenylate cyclase after salbutamol treatment of depression. *Psychopharmacology, 75*(2), 169–172.

Liebowitz, M. R., Gorman, J. M., Fyer, A. J., & Klein, D. F. (1985). Social phobia. Review of a neglected anxiety disorder. *Archives of General Psychiatry, 42*(7), 729–736.

Lonergan, M. H., Olivera-Figueroa, L. A., Pitman, R. K., & Brunet, A. (2013). Propranolol's effects on the consolidation and reconsolidation of long-term emotional memory in healthy participants: A meta-analysis. *Journal of Psychiatry and Neuroscience, 38*(4), 222–231.

Love, J. N., & Handler, J. A. (1995). Toxic psychosis: An unusual presentation of propranolol intoxication. *American Journal of Emergency Medicine, 13*(5), 536–537.

McGahan, D. J., Wojslaw, A., Prasad, V., & Blankenship, S. (1984). Propranolol-induced psychosis. *Drug Intelligence & Clinical Pharmacy, 18*(7–8), 601–603.

McGhee, L. L., Maani, C. V., Garza, T. H., Desocio, P. A., Gaylord, K. M., & Black, I. H. (2009). The effect of propranolol on posttraumatic stress disorder in burned service members. *Journal of Burn Care & Research, 30*(1), 92–97.

McNeil, G. N., Shaw, P. K., & Dock, D. S. (1982). Substitution of atenolol for propranolol in a case of propranolol-related depression. *The American Journal of Psychiatry, 139*(9), 1187–1188.

Middlemiss, D. N., Buxton, D. A., & Greenwood, D. T. (1981). Beta-adrenoceptor antagonists in psychiatry and neurology. *Pharmacology and Therapeutics, 12*(2), 419–437.

Myers, M. G., Lewis, P. J., Reid, J. L., & Dollery, C. T. (1975). Brain concentration of propranolol in relation to hypotensive effect in the rabbit with observations on brain propranolol levels in man. *Journal of Pharmacol and Experimental Therapeutics, 192*(2), 327–335.

Nader, K., Schafe, G. E., & Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406*(6797), 722–726.

Neil-Dwyer, G., Bartlett, J., McAinsh, J., & Cruickshank, J. M. (1981). Beta-adrenoceptor blockers and the blood-brain barrier. *British Journal of Clinical Pharmacology, 11*(6), 549–553.

Oppenheim, G. (1983). Propranolol-induced depression: Mechanism and management. *The Australian and New Zealand Journal of Psychiatry, 17*(4), 400–402.

Papademetriou, V. (2009). Comparison of nebivolol monotherapy versus nebivolol in combination with other antihypertensive therapies for the treatment of hypertension. *American Journal of Cardiology, 103*(2), 273–278.

Parker, W. A. (1985). Propranolol-induced depression and psychosis. *Clinical Pharmacy, 4*(2), 214–218.

Patten, S. B., & Love, E. J. (1993). Can drugs cause depression? A review of the evidence. *Journal of Psychiatry and Neuroscience, 18*(3), 92–102.

Peskind, E. R., Tsuang, D. W., Bonner, L. T., Pascualy, M., Riekse, R. G., Snowden, M. B., et al. (2005). Propranolol for disruptive behaviors in nursing home residents with probable or possible alzheimer disease: A placebo-controlled study. *Alzheimer Disease and Associated Disorders, 19*(1), 23–28.

Petrie, W. M., Maffucci, R. J., & Woosley, R. L. (1982). Propranolol and depression. *The American Journal of Psychiatry, 139*(1), 92–94.

Pitman, R. K., Sanders, K. M., Zusman, R. M., Healy, A. R., Cheema, F., Lasko, N. B., et al. (2002). Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biological Psychiatry, 51*(2), 189–192.

Pozuelo, L., Tesar, G., Zhang, J., Penn, M., Franco, K., & Jiang, W. (2009). Depression and heart disease: What do we know, and where are we headed? *Cleveland Clinic Journal of Medicine, 76*(1), 59–70.

Ravaris, C. L., Friedman, M. J., Hauri, P. J., & McHugo, G. J. (1991). A controlled study of alprazolam and propranolol in panic-disordered and agoraphobic outpatients. *Journal of Clinical Psychopharmacology, 11*(6), 344–350.

Reist, C., Duffy, J. G., Fujimoto, K., & Cahill, L. (2001). Beta-adrenergic blockade and emotional memory in ptsd. *International Journal of Neuropsychopharmacology, 4*(4), 377–383.

Ried, L. D., McFarland, B. H., Johnson, R. E., & Brody, K. K. (1998). B-blockers and depression: The more the murkier? *Annals of Pharmacotherapy, 32*(6), 699–708.

Rodriguez-Romaguera, J., Sotres-Bayon, F., Mueller, D., & Quirk, G. J. (2009). Systemic propranolol acts centrally to reduce conditioned fear in rats without impairing extinction. *Biological Psychiatry, 35*, 887–892.

Salem, S. A. M., & McDevitt, D. G. (1984). Central effects of single oral doses of propranolol in man. *British Journal of Clinical Pharmacology, 17*, 31–36.

Schleifer, S. J., Slater, W. R., Macari-Hinson, M. M., Coyle, D. A., Kahn, M., Zucker, H. D., et al. (1991). Digitalis and beta-blocking agents: Effects on depression following myocardial infarction. *American Heart Journal, 121*(5), 1397–1402.

Schneier, F. R. (2006). Clinical practice. Social anxiety disorder. *New England Journal of Medicine, 355*(10), 1029–1036.

Schwabe, L., Romer, S., Richter, S., Dockendorf, S., Bilak, B., & Schachinger, H. (2009). Stress effects on declarative memory retrieval are blocked by a beta-adrenoceptor antagonist in humans. *Psychoneuroendocrinology, 34*(3), 446–454.

Schwabe, L., Nader, K., Wolf, O. T., Beaudry, T., & Pruessner, J. C. (2012). Neural signature of reconsolidation impairments by propranolol in humans. *Biological Psychiatry, 71*(4), 380–386.

Sela, V. R., Roncon, C. M., Zangrossi, H., Jr., Graeff, F. G., & Audi, E. A. (2010). Pindolol potentiates the panicolytic effect of paroxetine in the elevated t-maze. *Life Sciences, 87* (13–14), 445–450.

Smith, H. (1938). Cerebral manifestations of digitalis intoxication. *Mayo Clinic Proceedings, 13*, 574–575.

Soeter, M., & Kindt, M. (2010). Dissociating response systems: Erasing fear from memory. *Neurobiology of Learning and Memory, 94*(1), 30–41.

Sorgi, P., Ratey, J., Knoedler, D., Arnold, W., & Cole, L. (1992). Depression during treatment with beta-blockers: Results from a double-blind placebo-controlled study. *Journal of Neuropsychiatry and Clinical Neurosciences, 4*(2), 187–189.

Steiner, S. S., Friedhoff, A. J., Wilson, B. L., Wecker, J. R., & Santo, J. P. (1990). Antihypertensive therapy and quality of life: A comparison of atenolol, captopril, enalapril and propranolol. *Journal of Human Hypertension, 4*(3), 217–225.

Stoudemire, A., Brown, J. T., Harris, R. T., Blessing-Feussner, C., Roberts, J. H., Nichols, J. C., et al. (1984). Propranolol and depression: A reevaluation based on a pilot clinical trial. *Psychiatric Medicine, 2*(2), 211–218.

Tawa, J., & Murphy, S. (2013). Psychopharmacological treatment for military posttraumatic stress disorder: An integrative review. *Journal American Association Nurse Practitioner, 25*(8), 419–423.

Taylor, E. A., Jefferson, D., Carroll, J. D., & Turner, P. (1981). Cerebrospinal fluid concentrations of propranolol, pindolol and atenolol in man: Evidence for central actions of beta-adrenoceptor antagonists. *British Journal of Clinical Pharmacology, 12*(4), 549–559.

Thiessen, B. Q., Wallace, S. M., Blackburn, J. L., Wilson, T. W., & Bergman, U. (1990). Increased prescribing of antidepressants subsequent to beta-blocker therapy. *Archives of Internal Medicine, 150*(11), 2286–2290.

Vaiva, G., Ducrocq, F., Jezequel, K., Averland, B., Lestavel, P., Brunet, A., et al. (2003). Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. *Biological Psychiatry, 54*(9), 947–949.

van Melle, J. P., & de Jonge, P. (2009). Beta-blocker use and the development of depression. *American Journal of Cardiology, 103*(9), 1331–1332.

van Melle, J. P., Verbeek, D. E. P., van den Berg, M. P., Ormel, J., van der Linde, M. R., & de Jonge, P. (2006). Beta-blockers and depression after myocardial infarction a multicenter prospective study. *Journal of the American College of Cardiology, 48*(11), 2209–2214.

Viadero, J. J., Wong, S. H., & White, W. B. (1983). Acute psychotic behavior associated with atenolol. *The American Journal of Psychiatry, 140*(10), 1382.

Volavka, J., Citrome, L., & Huertas, D. (2006). Update on the biological treatment of aggression. *Actas Españolas de Psiquiatría, 34*(2), 123–135.

Waal, H. J. (1967). Propranolol-induced depression. *British Medical Journal, 2*(5543), 50.

Walker, D. L., & Davis, M. (2002). Light-enhanced startle: Further pharmacological and behavioral characterization. *Psychopharmacology, 159*(3), 304–310.

Ward, F., Tharian, P., Roy, M., Deb, S., & Unwin, G. L. (2013). Efficacy of beta blockers in the management of problem behaviours in people with intellectual disabilities: A systematic review. *Research in Developmental Disabilities, 34*(12), 4293–4303.

Withering, W. (1785). *An account of the foxglove and some of its medical uses; with practical remarks on the dropsy, and some other diseases*. Birmingham: Swinney.

Part VI

Lifestyle Management in Cardiovascular Disease: Prevention and Secondary Intervention

Changing Lifestyle Behaviors to Improve the Prevention and Management of Cardiovascular Disease

Brian Oldenburg, Shaira Baptista, Fiona Cocker, and Adrienne O'Neil

Contents

B. Oldenburg (✉) • S. Baptista • F. Cocker
Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia
e-mail: brian.oldenburg@monash.edu; brian.oldenburg@unimelb.edu.au; bolderburg@unimelb.edu.au; sbaptista@unimelb.edu.au; fcocker@unimbelb.edu.au

A. O'Neil
Melbourne School of Population and Global Health, The University of Melbourne, Parkville, VIC, USA

School of Public Health and Preventive Medicine, Monash University, Clayton, VIC, USA

IMPACT Strategic Research Centre, Deakin University, Geelong, VIC, USA
e-mail: Adrienne.oneil@unimelb.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_54

Abstract

Up to 80 % of the risk for cardiovascular disease (CVD) in the general population is attributable to lifestyle factors. Hence, the modification of lifestyle behaviors is important for reducing cardiovascular risk in the context of primary and secondary CVD prevention. However, initiating and sustaining changes in lifestyle behaviors remains challenging, particularly for patients who have experienced a potentially life-threatening CVD event. This chapter reviews the evidence base for changing lifestyle behaviors that contribute most to the etiology, progression, and outcomes of CVD, that is, nutrition and dietary behaviors, physical activity, and smoking. Furthermore, the evidence in relation to the effectiveness of behavioral interventions and key factors to consider in the implementation of effective behavior and lifestyle change programs in clinical and non-clinical settings are discussed. Finally, the implications of these findings for future research and practice in the field are considered.

Keywords

Cardiovascular disease • Lifestyle • Behavior interventions • Risk factors

The Importance of Lifestyle Change

Introduction

The Importance of Behavior and Lifestyle to Cardiovascular Risk

Cardiovascular disease (CVD) is the leading cause of death and disability in both men and women in most countries around the world (Alwan 2011). Over the last 60 years, an extensive body of evidence has demonstrated the impact of key lifestyle behaviors on the pathophysiology, course, and short- and long-term outcomes of CVD (Fisher et al. 2011). Further, social and behavioral epidemiologic research has demonstrated the complex interplay between behavioral, psychological, social, and environmental factors, and how these factors – individually and collectively – influence lifestyle and, subsequently, disease progression, and quality of life and health outcomes (Begg et al. 2007; Fisher et al. 2011; World Health Organization 2003). Therefore, it is essential that any program designed to reduce the risk and/or progression of CVD addresses changes in key lifestyle behaviors, while keeping in mind important environmental and contextual factors that influence behavior and behavior change (Marrero et al. 2013). Indeed, most guidelines for the prevention and management of CVD in general practice, primary care, cardiac rehabilitation, and community and allied health services emphasize the importance of addressing lifestyle behaviors, specifically smoking, nutrition, healthy weight, physical activity, and alcohol use, and helping patients to address these (D'Agostino et al. 2008; Grundy et al. 1999; National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand 2012; Perk et al. 2012).

The seminal INTERHEART study identified 9 modifiable risk factors (smoking, lipid profile, hypertension, diabetes, obesity, diet, physical activity, alcohol consumption, and psychosocial factors) that account for over 90 % of the risk for acute myocardial infarction (MI) and CVD, with people's behavior and lifestyle being related to all of these (Yusuf et al. 2004). These risk factors are variously important in every geographic region and every racial and ethnic group worldwide and are apparent in men and women (Rosengren et al. 2004; Yusuf et al. 2004). While these are independent risk factors for CVD, many are interconnected with one another. For example, a sedentary lifestyle and poor nutrition are both major risk factors for overweight and obesity which in turn, lead to increased blood pressure, increased insulin resistance, and unfavorable lipid levels and thus to an elevated risk of CVD (World Health Organization 2002).

Despite the amount of evidence regarding CVD risk factors and the importance of lifestyle and behavior, there is a considerable evidence demonstrating the complexities and difficulties associated with implementing and maintaining lifestyle-related changes at the individual and population level. Indeed, behavior is shaped in positive and negative ways at an individual level (knowledge, cognitions, and attitudes) and an interpersonal or social level (including the influence of cultural and societal norms for different behaviors) and at the broader community level, as a result of people's living situations and their role/s at work and in the broader community. Traditionally, behavioral and social scientists assumed an individual's decision to make and maintain health behavior changes resulted from a rational decision-making process. However, it is now well known that one's lifestyle and associated behaviors, and any attempts to change these, are heavily influenced by the highly contextualized nature of behavior (Marrero et al. 2013). An individual's socioeconomic and social situation (Brofenbrenner 1977; Riley et al. 2011; Ryan and Deci 2000), cultural environment (Glanz et al. 2008; Riley et al. 2011), and the influence of advertising and marketing (Anderson et al. 2009; Lovato et al. 2003) can all have a substantial influence on an individual's health behaviors, motivation to change behavior, and relative success in being able to do so.

Principles of Lifestyle and Behavior Change

As already stated, health behaviors can be very difficult to change and to sustain in the longer term. For example, following a heart event, many individuals will make initial changes to their lifestyle, but maintenance is often poor, and relapse is common within 6–12 months of the event (Mendis et al. 2005; Rosamond et al. 2008). Key theories and models of health behavior, the change process, and of health more broadly, can contribute to a better understanding of the development of lifestyle behaviors the determinants of behavior change, and the change process itself (Glanz et al. 2008; Lippke and Ziegelmann 2008). The following section overviews key constructs from some of the most commonly used theoretical models and frameworks.

From the 1970s to the 1980s, on the intrapersonal factors that influence behavior such as a person's beliefs, knowledge, and skills. Such theories assume that lifestyle behaviors and behavior change are largely determined by cognitive and psychosocial factors at the individual level, with change being a result of rational, individualized decision-making. Examples of intrapersonal theories are the Health Belief Model, Theory of Planned Behavior, and the Transtheoretical Model of Behavior Change (Glanz et al. 2008). The Health Belief Model focuses on individual beliefs concerning their perceived susceptibility to the severity of a health issue and the perceived benefits and barriers that may result from taking action (Becker 1974; Janz and Becker 1984). The Transtheoretical Model proposes key steps that are involved in behavior change, including pre-contemplation, contemplation, preparation, action, and maintenance. The importance of identifying readiness to change is a key construct in this model (Prochaska and Velicer 1997). Consequently, proponents of this model argue that intervention strategies and programs be tailored according to a group or an individual's "stage of readiness." Accordingly, different intervention strategies are likely to be effective for one's specific stage of change. The Transtheoretical Model has been usefully applied to explain and predict changes in behaviors such as smoking, diet, physical activity, as well as alcohol and illicit drug use (Glanz et al. 2008). In contrast, interpersonal theories use the premise that a person's behavior is heavily influenced by one's personal, family, social relationships and context. Therefore, according to this level of theories, a person's social environment plays a very important role in determining his/her health behaviors. Attention to these influences can also assist an individual in changing health behaviors such as smoking, nutrition, and sedentariness.

The most popular interpersonal health behavior theory is Social Cognitive Theory (Bandura 2001; Stokols et al. 2003; Yusuf et al. 2004), and over the past 30 years, this model has influenced the development of many other theories and models. Social Cognitive Theory postulates one's attitudes, cognitions, and beliefs, environmental influences and behavior interact in a dynamic, reciprocal manner to influence behavior and behavior change (Bandura 2001). Intervention strategies based on this model are often derived from principles of learning that include observational learning, positive and negative reinforcement, and strategies that aim to improve self-control and self-efficacy. Socio-ecological models of health explain behavior by considering multi-level and diverse influences in people's lives, including individual, interpersonal, organizational, and broader environmental level influences and how all of these can interact to determine and influence lifestyle behaviors and the behavior change process. Indeed, there is now good evidence that health interventions are likely to be more successful when they are based on such a socio-ecological perspective (Brofenbrenner 1977; Glanz et al. 2008).

Much of the early research concerning the determinants of health behaviors was based on individual and intrapersonal theories of behavior. Hence, many of the intervention strategies incorporated into the lifestyle change counseling and intervention programs of the 1970s and 1980s focused on influencing individual factors such as knowledge, attitudes, self-efficacy, and skills. However, as multi-level and

socio-ecological models have gained momentum in more recent years, lifestyle change programs have increasingly adopted broader strategies that can help address individual, social, and environmental level factors, recognizing that these can influence the change process and the long-term sustainability of behavior change. For example, individuals wishing to increase their level of physical activity may have more success if intervention strategies are aimed not only at enhancing self-efficacy at the individual level but also at increasing social support from the family and work colleagues at the interpersonal level, combined with broader community-wide strategies that are likely to make increased levels of physical activity more achievable and sustainable.

Health Behavior Change to Reduce CVD Risk: What Works?

In the following section, we consider the evidence base concerning the effectiveness of behavioral interventions and lifestyle change programs in relation to the prevention and management of CVD and related chronic conditions. While a substantial evidence base has established the effectiveness of lifestyle change approaches as an important component of smoking cessation over more than 30 years (e.g., Barth et al. 2008; DiClemente et al. 1991), CVD prevention and lifestyle change programs related to diet and physical activity are not nearly as well established (Yach et al. 2005).

Smoking Cessation

Extensive research has been undertaken in general populations, as well as clinical populations, including individuals with CVD, and demonstrates that, when compared with interventions targeting other health behaviors, interventions targeting smoking have been relatively successful. For example, smoking cessation interventions have increased the likelihood of quitting from 28 to 66 %, when compared with usual care (Oldenburg et al. 2010). Group delivery of programs has been shown to be quite effective, although this mode of delivery is not as convenient or well received by many. Group-based programs incorporating standardized socio-behavioral intervention strategies have also been shown to be more effective when combined with pharmacological interventions such as nicotine replacement therapy (Pearson et al. 2000). The key elements of successful programs are typically related to program intensity and duration and the inclusion of components that address cognitive and behavioral skills and the prevention of relapse (Oldenburg et al. 2010). Although standardized self-help formats have some benefit, tailored self-help programs have been found to be even more successful. Programs delivered by various modes have been demonstrated to be effective, including via the telephone and, more recently, the Internet (Stokols et al. 2003). There are several reasons for the relative success of smoking cessation programs, especially when compared to other lifestyle risk factors (Oldenburg et al. 2010). First, the evidence

linking ongoing tobacco use to poor health outcomes is very well established, and programs can be delivered in a variety of modes and by a range of health professionals. However, it is important to note that although such interventions can significantly increase initial quit rates, absolute abstinence still remains very low, regardless of the type of intervention used. Indeed, the evidence shows that the majority of smokers will relapse several times before finally succeeding in quitting. Hence, persistence is the key to long-term success with smoking interventions (Rosengren et al. 2004).

Nutrition and Dietary Interventions

Although various aspects of nutrition and diet such as low intake of fruit and vegetables; high intake of (saturated) fat, sugar, and salt (World Health Organization 2002); and the consumption of a proinflammatory diet high in sugar, highly processed foods, and trans fats (O'Neil et al. 2015) have been consistently implicated as important risk factors for CVD, the effects of lifestyle-related interventions targeting these have been modest. Nonadherence is also much higher for nutritional advice when compared to other risk factor such as smoking and medication taking. One possible reason is that instigating and maintaining such changes can be complex in clinical populations, especially in combination with other components of a complex treatment plan (Burke et al. 1997). Group-based educational and lifestyle change programs have been somewhat successful in reducing total calories, total and saturated fat, and cholesterol levels when used in primary prevention (Burke et al. 1997). Individual counseling with a dietician has also shown positive results, with significant reduction in dietary fat and cholesterol consumption that was maintained after 7 years (Burke et al. 1997). Furthermore, dietary advice from a health professional has been linked to patients reaching their target LDL-cholesterol levels (Pearson et al. 2000). Another key to success is social and family involvement, with greater success attributed to their involvement, and community-based programs (as distinct to those conducted in more clinical settings) tend to be more successful, especially when they incorporate specific and practical dietary advice (Hooper et al. 2012).

Despite a substantial focus on dietary interventions that reduce dietary fat intake, the clinical outcomes of these studies remain mixed. In a recent systematic review, nutritional interventions aimed at influencing dietary fat – that is, reducing and/or modifying total fat intake – did demonstrate a significant reduction in the incidence of combined cardiovascular events but no clear effect on total mortality, despite reductions in weight, body mass index, total cholesterol, and LDL cholesterol (Hooper et al. 2012). Further, these effects were only reported for trials where participants were involved for more than 2 years, and overall, there was very little evidence to support a direct link between dietary intervention that focuses on modifying dietary fats and reductions in total mortality (Hooper et al. 2012).

Increasing Physical Activity

Increasing physical activity is associated with many health-related benefits including improvements in CVD risk markers as well as reducing many CVD risk factors. While the optimal amount of exercise required to achieve such benefits remains unclear, population-based interventions which encourage modest increases in physical activity among largely sedentary individuals have been shown to be effective. In more clinical populations, attrition from cardiac rehabilitation programs, and other kinds of programs, is usually very high (Burke et al. 1997). There is some evidence that adherence to an exercise regimen can be improved by incorporating strategies such as self-monitoring, regular prompting and verbal persuasion and by also having support from key family members and others (Burke et al. 1997). A recent review of the available evidence has demonstrated that good compliance with exercise training can improve objectively measured physiological and anthropometric factors including lipid profile among patients in comprehensive cardiac rehabilitation (Oldenburg et al. 2010). Although no reduction was found in body mass index, body composition changed significantly, with an increase in lean body mass and a reduction in adipose tissue. In studies with longer follow-up of exercise training and cardiac rehabilitation programs, and also with an emphasis on other lifestyle changes related to CVD risk, they have been able to demonstrate significant benefits in terms of both survival and quality of life (Oldenburg et al. 2010).

When composite diet and exercise interventions have been evaluated, similar small improvements have also been found in weight, BMI, and waist circumference. These findings have been corroborated by a recent review which systematically identified, synthesized, and graded a wide range of evidence about the relationship of intervention content to effectiveness in individual-level interventions for promoting changes in diet and/or physical activity in adults (Greaves et al. 2011). In summary, greater effectiveness of interventions was causally linked with targeting diet and physical activity, mobilizing social support, and the use of well-described and/or established behavior change techniques. Further, greater effectiveness was also associated with using multiple self-regulatory techniques such as goal-setting, prompting self-monitoring, providing feedback on performance, goal review, and providing a higher contact time or frequency of contacts.

Reducing Sedentariness

Recently, sedentary behavior has gained increasing attention as a another risk factor for CVD, independent of physical activity. Key indicators of sedentariness include the amount of sitting time and the time spent watching TV and using a computer, talking on the phone, and driving. All of these have increased markedly in recent years, due to changing lifestyles and the significant increase in use of new technologies in most countries. Sedentariness has been linked to poor lipid

profiles, increased BMI, increased blood pressure, and other negative risk factors associated with an increased risk of CVD (León-Latre et al. 2014). As the deleterious effects of sedentary behavior are not necessarily negated by an overall increase in physical activity, this presents a novel challenge and opportunity within the context of disease prevention and control. Indeed, preliminary studies have linked reductions in sedentary behavior to positive changes to triglyceride levels, waist circumference, and inflammation (Ekblom-Bak et al. 2014; Ford and Caspersen 2012). As a relatively new concept, sedentary behavior is a potential modifiable risk factor for CVD that presents a promising avenue for future research and interventions, particularly through the use of more environmental interventions.

Multiple Risk Factor Interventions

The majority of adults engage in two or more lifestyle behaviors that increase their risk of CVD and related chronic conditions (King et al. 2015). More specifically, prevalence rates of multiple risk behaviors in adult populations worldwide have been reported as 68 % in England (Poortinga 2007) and 52 % in the United States (USA) (Coups et al. 2004). Further, interventions targeting multiple lifestyle behaviors can be more effective in terms of reducing disease risk compared to those focusing on a single risk factor (King et al. 2015). Such an approach also helps to address the complex interplay between lifestyle behaviors and risk factors for CVD. Indeed, a recent meta-analysis of multifactorial interventions in patients showed a reduction of 18 % in fatal cardiovascular events as well as a small but nonsignificant reduction in overall mortality and hospital readmissions (de Waure et al. 2013). Multiple risk factor interventions typically comprise multiple socio-behavioral strategies that variously target combinations of diet, exercise, weight loss, smoking cessation, and medication adherence.

Considerations for Intervention Success

Settings for Program Delivery

Lifestyle change programs can be delivered in a variety of settings, including health-care settings, workplaces, schools, and settings within the community. Some settings can be more conducive to recruitment of a large number of participants, for example, large numbers of working adults can be potentially reached in workplace settings (Hutchinson and Wilson 2012). However, the level of reach of an intervention does not necessarily translate to effectiveness. Indeed, there are well-established benefits in targeting "defined" populations for more intensive interventions with a specific focus on key lifestyle behaviors (Anderson et al. 2009a).

Level of Intervention

Primary prevention aims to prevent disease prior to clinical manifestation by minimizing exposure to the risks that contribute to disease risk. Secondary prevention aims to reduce the impact of a disease that has already occurred by detecting and treating disease as soon as possible to halt or slow its progress. Finally, tertiary prevention aims to reduce the impact of an ongoing and persistent illness by helping people manage long-term, often-complex health problems, thereby aiming to maximize quality of life and life expectancy. Lifestyle and behavior change programs can be designed and implemented to address each of these levels. Over the past 40 years, primary prevention efforts have been quite effective in substantially reducing death rates due to coronary heart disease (CHD) in many developed countries (de Waure et al. 2013; Ebrahim et al. 2011). Secondary prevention programs, for people at risk for coronary heart disease, have tended to have a focus on multiple risk factors, and there has been a trend for a modest reduction in the frequency of cardiac events and overall mortality (Angermayr 2010; de Waure et al. 2013; Lin et al. 2014) and modest measurable improvements in diet, exercise, and medication adherence (Cole et al. 2010). Finally, cardiac rehabilitation programs that address low physical activity and other lifestyle behaviors by incorporating counseling and education have demonstrated some significant health outcomes (de Waure et al. 2013; Oldridge 2012).

Features of Intervention and Program Delivery

In a recent review of behavioral interventions to improve the prevention and management of CVD, Oldenburg et al. (2010) reported that longer, more intensive interventions were generally more effective than brief interventions. However, longer, more intense programs tend to be more expensive, require more resources, and can have greater attrition rates. In their systematic review of intervention components promoting dietary and physical activity, Greaves et al. (Greaves et al. 2011) noted several important program factors, likely to affect the outcomes by moderating the relationship between program exposure, intensity, and effectiveness. For example, lower quality, lower intensity interventions are likely to result in higher rates of attrition. Hence, it is important to strike a balance between intensity, duration, and cost-effectiveness in order to maximize the efficacy of an intervention and its broader reach and scalability.

The delivery mode of a lifestyle intervention is also important to consider. For example, while physicians have the ability to provide advice and deliver programs for behavior change, most do not do this very well, other than to give generalized advice about what to do. This is despite the fact that physicians often have a "window of opportunity" within which to provide tailored advice and suggestions relevant to lifestyle change. Hence, it is important to consider alternative modes of program delivery. For example, some interventions may be better suited to being

delivered through technology-based platforms, whereas others may be better delivered by lay leaders or peers (Dale et al. 2008; Foster et al. 2007; Fisher et al. 2009). Of course, individuals will also have their own preferences in relation to different modes of delivery as well.

Potential of New Technologies

Rapid advances in interactive digital technologies have changed the way in which communication and social interaction occurs worldwide, and these advances have the potential to profoundly influence the design and delivery of lifestyle change programs. Recent years have seen the rapid uptake and use of the Internet, Facebook, Twitter, Wiki, and technology platforms using smartphones, tablets, and other devices. For example, while Facebook had approximately 1 million users at the end of its first year in existence in 2004, it now has well over 1 billion monthly active users (eMarketer Inc 2013). Technology also provides the flexibility of various modes of communication, including photos, videos, three-dimensional images, visual simulations, and even virtual reality. Hence, use of the Internet and mHealth interventions now offer opportunities to reach and engage with individuals worldwide and beyond traditional "communities" (Smith et al. 2014).

Wantland et al. (2004) pooled studies of web-based interventions containing nearly 12,000 participants, including cross-sectional, self-managed, and longitudinal intervention studies ranging from 3 to 78 weeks. When compared to interventions, utilizing more traditional means of delivery web-based interventions reported reaching an equal proportion of men and women and having lower than usual rates of attrition (21 %). However, although the average drop-out rate was relatively low, measures of program exposure and intensity were also modest. For example, participants showed significant variation in time spent per session and the number of times the intervention site was visited. Despite wide variation in intensity, nearly all of the studies showed an improvement in knowledge and/or behavioral outcomes. Some examples of improved outcomes were increase in exercise duration, 18-month weight loss maintenance, and increased utilization of health care (Wantland et al. 2004). In addition to improvements in knowledge and health behaviors, interactive health communication applications have also been shown to improve social support, self-efficacy, and clinical outcomes (Murray 2006).

The telephone provides another channel to promote participant access due to freedom from spatial and temporal restrictions, and positive behavioral outcomes observed in such programs have been linked to duration and intensity (number of calls) of the intervention (Eakin et al. 2007). Other key factors that may impact on the success of such programs may be targeting selected clinical samples and the use of theory-based models including the transtheoretical model, social cognitive theory, and motivational interviewing.

The use of new technologies, such as smartphones and apps, to deliver program content and messages often demonstrate a high degree of fidelity, standardization, and replicability, reducing the variability in content and delivery that is possible

when such programs are delivered by health professionals. For example, Mobile Health (mHealth) platforms are now using smartphones and computer tablets to deliver health behavior change programs to improve prevention and management of lifestyle-related chronic conditions such as CVD, with high reach, fidelity, and a good user experience (Oldenburg et al. 2015). Further, user engagement of Internet-based behavioral interventions for chronic disease is improved by addressing health concerns important to the individual and is further enhanced by incorporating personally tailored advice and feedback (Kelders et al. 2011; Schubart et al. 2011).

The emergence of computer software and the development of "expert systems" (originally developed in the 1990s) have also increased the sophistication of tailoring of programs (Kong et al. 2012; Latimer et al. 2010) and led to algorithm-driven approaches which combine the benefits of traditional mass media campaigns with individually tailored interventions to reach a very large number of individuals. By remembering preferences for content and mode of delivery, an algorithm-driven approach combined with new technologies that "crowd-source" feedback and "data" from thousands of participants in real time allows the delivery of program content to be adapted to multiple circumstances, contexts, and situations while remaining unique to individual users. Hence, while traditionally delivered health education and health promotion programs can be tailored for small numbers of individuals, new technologies can deliver highly personalized, standardized, and tailored messages to whole populations (Oldenburg et al. 2015) This is one of the reasons why the use of new technology for program delivery may be particularly advantageous in developing countries (Peiris et al. 2014).

The rapid evolution and uptake of smartphones and handheld computers will inevitably lead to increased uptake and use of social media for health programs, allowing individuals to interact with, shape, and even disseminate their own intervention messages through their social networks. However, it is vital that programs delivered using such platforms are designed and delivered with an understanding of the user experience, predicting how individuals will respond to, shape and share program content and the ramifications of this (Chou et al. 2013; Coley et al. 2013). For example, positive and derisive viewer comments could shape other users' evaluations of the credibility of certain health messages delivered via new technologies (Walther et al. 2010).

Peer Support Interventions

Peer support delivery of lifestyle change programs incorporates appraisal, informational, and emotional support being provided by a peer who may live with the same condition as the recipient of the intervention (Peer support delivery of lifestyle change programs incorporates appraisal, informational, and emotional support being provided by a peer who may live with the same condition as the recipient of the intervention (Boothroyd and Fisher 2010)). Informational support can increase knowledge, understanding, and coping skills (Campbell et al. 2004).

Emotional support is based on empathic communications between individuals and their peer, designed to enhance self-confidence and self-esteem, reduce negative feelings, and improve relationships (Gray et al. 1997; Helgeson and Cohen 1996). Peer support delivery has been shown to be effective for a variety of clinical populations, with beneficial effects across a wide spectrum of health outcomes (Fisher et al. Dennis et al. 2002; Morrow et al. 1999), enhancing mental health (Repper and Carter 2011), and increasing health-related quality of life (Ashbury et al. 1998; Hibbard et al. 2002; Whalley et al. 2014). Verheijden et al. (2002) propose that the support derived from natural support networks, as distinct from the nonreciprocal relationship provided by health professionals, may help explain the beneficial effects.

Results from a recent systematic review suggested that peer support may improve self-efficacy in individuals with heart disease and may also have a beneficial effect on the health and well-being of those recovering from an MI (Parry and Watt-Watson 2010). Key determinants of the success of peer support interventions are the standardization of peer training, the mode of delivery, and the dose of the intervention as well as the peer to participant ratio.

Worthy of note is the increased delivery of peer support via mobile and web-based technologies and online communities. These involve peer support groups that connect using web chat and text messaging and target clinical outcomes and healthy behavior modifications (Wei et al. 2011). Online peer support may also be delivered via live chats and forums which allow users to talk to each other in real time or post topics for discussion. Although the evidence is not yet conclusive, Cotter et al. (2014) suggest that providing support via text or web provides participants with opportunities to discuss problems with others experiencing the same issues and receive immediate feedback, significantly improving engagement as well as behavioral and clinical outcomes.

Achieving Sustainability and Maintenance of Lifestyle Change

With some notable exceptions, the majority of published lifestyle change intervention trials have still only achieved modest outcomes, even when evaluated under controlled conditions. Further, the implementation and dissemination of such programs under more "real-world" settings is often poorly evaluated (Glanz et al. 2008), diluting already modest effects. The Diabetes Initiative of the Robert Wood Johnson Foundation in the United States evaluated the resources and supports for self-management of diabetes in various community settings. The program identified six key supports for program success: individualized assessment and tailored measurement; collaborative goal-setting; enhancement of key skills for disease management, health behaviors, and problem solving; continuity of high-quality, safe clinical care; ongoing follow-up and support; and a very important role for supportive community resources (Fisher et al. 2011). The authors concluded that the concept of "equifinality" is especially helpful for thinking about the way in which such programs can work for individuals in community settings. In other

words, different procedures, strategies, or programs can work in complementary ways to achieve similar ends or effects.

While no formal economic evaluation was conducted as part of most of these reviews, a number of authors note that interventions evaluated under very controlled conditions tend to be being too resource intensive for broader uptake (Ebrahim et al. 2006). Further investigation of the cost-effectiveness of lifestyle interventions is very important in order to allow for priority setting and for governments and major donors to justify spending resources on modifying behavioral risk factors and lifestyle change programs. The World Health Organization has recognized the importance of reducing lifestyle risk factors in cost-effective ways, stating in their 2002 World Health Report that their ultimate goal is to help governments of all countries to raise the healthy life expectancy of their populations. However, the cost-effectiveness of lifestyle interventions to improve quality of life and life expectancy from preventable chronic diseases should also be established in resource poor countries before recommending their widespread uptake.

Conclusions and Practical Implications

With a few notable exceptions, most published lifestyle intervention trials have achieved only modest outcomes. Further, even when evaluated under controlled conditions, their wider implementation and dissemination is seldom evaluated (Glanz et al. 2008; Oldenburg and Glanz 2008). Moreover, intensive lifestyle change interventions for people with minimal risk might not be particularly cost-effective. Therefore, more population-based or upstream social and economic interventions to reduce cardiovascular risk are likely to be more cost-effective. Given the increasing pressures on limited resources for health care and prevention in most countries, and the increasing burden of chronic diseases, it is important that resources are prioritized for populations where the interventions will be most effective and with the greatest reach.

If properly designed and implemented, lifestyle change interventions have excellent potential to reduce CVD risk and to improve the quality of life and health outcomes of those who already have CVD. Despite requiring more rigorous research, early evidence points to the likely cost-effectiveness of some lifestyle change interventions, even when compared to more traditional medical interventions. The use of new technologies is an especially exciting recent development, especially when combined with more traditional delivery approaches used by health professionals, peer leaders, and others in health-care and community settings. Given the very rapid increase of disease burden attributable to chronic noncommunicable disease as a result of lifestyle behaviors in developing regions of the world, these kinds of approaches urgently need further development and adaptation to the growing health needs and challenges of the 80 % of the world's population living in these regions of the world (Beaglehole and Bonita 2008).

In conclusion, lifestyle interventions and programs have been shown to have positive effects on many different health behaviors, thereby also having a substantial effect on ameliorating cardiovascular risk. Future research on interventions and their delivery will inform how to better combine the various intervention components, their intensity, and duration in order to strengthen program delivery and maximize long-term outcomes.

References

Alwan, A., & MacLean, D. R. (2009). A review of non-communicable disease in low-and middle-income countries. *International Health, 1*(1), 3–9.

Alwan, A. (2011). *Global status report on noncommunicable diseases 2010*. World Health Organization.

Anderson, L., Quinn, T., Glanz, K., Ramirez, G., Kahwati, L., Johnson, D., … & Task Force on Community Preventive Services. (2009a). The effectiveness of worksite nutrition and physical activity interventions for controlling employee overweight and obesity. *American Journal of Preventive Medicine, 37*, 340–357.

Anderson, P., De Bruijn, A., Angus, K., Gordon, R., & Hastings, G. (2009b). Impact of alcohol advertising and media exposure on adolescent alcohol use: A systematic review of longitudinal studies. *Alcohol and Alcoholism, 44*, 229–243.

Angermayr, L. D. K. (2010). Multifactorial lifestyle interventions in the primary and secondary prevention of cardiovascular disease and type 2 diabetes mellitus—a systematic review of randomized controlled trials. *Annals of Behavioral Medicine, 40*, 49–64.

Ashbury, F. D., Cameron, C., Mercer, S. L., Fitch, M., & Nielsen, E. (1998). One-on-one peer support and quality of life for breast cancer patients. *Patient Education and Counselling, 35*, 89–100.

Bandura, A. (2001). Social cognitive theory: An agentic perspective. *Annual Review of Psychology, 52*, 1.

Barth, J., Critchley, J. A., & Bengel, J. (2008). Psychosocial interventions for smoking cessation in patients with coronary heart disease. *The Cochrane Library*.

Becker, M. H. (1974). *The health belief model and personal health behavior*. Thorofare: Slack.

Begg, S., Vos, T., Barker, B., Stevenson, C., Stanley, L., & Lopez, A. (2007). *Burden of disease and injury in Australia 2003*. Canberra: Australian Institute of Health and Welfare (AIHW).

Beaglehole, R., & Bonita, R. (2008). Global public health: A scorecard. *The Lancet, 372*(9654), 1988–1996.

Brofenbrenner, U. (1977). Toward an experimental ecology of human development. *American Psychologist, 32*, 513–531.

Burke, L., Dunbar-Jacob, J., & Hill, M. (1997). Compliance with cardiovascular disease prevention strategies: A review of the research. *Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine, 19*, 239–263.

Campbell, H. S., Phaneuf, M. R., & Deane, K. (2004). Cancer peer support programs—do they work? *Patient Education and Counseling, 55*, 3–15.

Chou, W. S., Prestin, A., Lyons, C., & Wen, K. (2013). Web 2.0 for health promotion: Reviewing the current evidence. *American Journal of Public Health, 103*, 9–18.

Cole, J. A., Smith, S. M., Hart, N., & Cupples, M. E. (2010). Systematic review of the effect of diet and exercise lifestyle interventions in the secondary prevention of coronary heart disease. *Cardiology Research & Practice, 2011*, 1–25.

Coley, H. L., Sadasivam, R. S., Williams, J. H., Volkman, J. E., Schoenberger, Y.-M., Kohler, C. L., … & Ford, D. E. (2013). Crowdsourced peer-versus expert-written smoking-cessation messages. *American Journal of Preventive Medicine, 45*, 543–550.

Cotter, A. P., Durant, N., Agne, A. A., & Cherrington, A. L. (2014). Internet interventions to support lifestyle modification for diabetes management: A systematic review of the evidence. *Journal of Diabetes and its Complications, 28*, 243–251.

Coups, E. J., Gaba, A., & Orleans, C. T. (2004). Physician screening for multiple behavioral health risk factors. *American Journal of Preventive Medicine, 27*, 34–41.

Dale, J., Caramlau, I. O., Lindenmeyer, A., & Williams, S. M. (2008). Peer support telephone calls for improving health. *The Cochrane Library*.

D'Agostino, R. B., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care the Framingham Heart Study. *Circulation, 117*, 743–753.

de Waure, C., Lauret, G. J., Ricciardi, W., Ferket, B., Teijink, J., Spronk, S., & Myriam Hunink, M. G. (2013). Lifestyle interventions in patients with coronary heart disease: A systematic review. *American Journal of Preventive Medicine, 45*, 207–216.

DiClemente, C. C., Prochaska, J. O., Fairhurst, S. K., Velicer, W. F., Velasquez, M. M., & Rossi, J. S. (1991). The process of smoking cessation: An analysis of precontemplation, contemplation, and preparation stages of change. *Journal of Consulting and Clinical Psychology, 59*(2), 295.

Dennis, C. L., Hodnett, E., Gallop, R., & Chalmers, B. (2002). The effect of peer support on breastfeeding duration among primiparous women: A randomized controlled trial. *Canadian Medical Association Journal, 166*, 21–28.

Eakin, E. G., Lawler, S. P., Vandelanotte, C., & Owen, N. (2007). Telephone interventions for physical activity and dietary behavior change: A systematic review. *American Journal of Preventive Medicine, 32*, 419–434.

Ebrahim, S., Beswick, A., Burke, M., & Davey, S. G. (2006). Multiplerisk factor interventions for primary prevention of coronaryheart disease. *Cochrane Database of Systematic Reviews, 4*, CD001561.

Ebrahim, S., Taylor, F., Ward, K., Beswick, A., Burke, M., & Davey Smith, G. (2011). Multiple risk factor interventions for primary prevention of coronary heart disease. *The Cochrane Library, 1*.

Ekblom-Bak, E., Ekblom, B., Vikström, M., de Faire, U., & Hellénius, M.-L. (2014). The importance of non-exercise physical activity for cardiovascular health and longevity. *British Journal of Sports Medicine, 48*, 233–238.

eMarketer Inc. (2013). *Social networking reaches nearly one in four around the world*. Social Media. Available via e Marketer. http://www.emarketer.com/Article/Social-Networking-Reaches-Nearly-One-Four-Around-World/1009976. Accessed 19 Feb 2015.

Fisher, E. B., Strunk, R. C., Highstein, G. R., Kelley-Sykes, R., Tarr, K. L., Trinkaus, K., & Musick, J. (2009). A randomized controlled evaluation of the effect of community health workers on hospitalization for asthma: The asthma coach. *Archives of Pediatrics & Adolescent Medicine, 163*(3), 225–232.

Fisher, E. B., Fitzgibbon, M. L., Glasgow, R. E., Haire-Joshu, D., Hayman, L. L., Kaplan, R. M., ... & Ockene, J. K. (2011). Review and special article: Behavior matters. *American Journal of Preventive Medicine, 40*, 15–30.

Fisher, E. B., Ayala, G. X., Ibarra, L., Cherrington, A. L., Elder, J. P., Tang, T. S., … & Simmons, D. (2015). Contributions of peer support to health, health care, and prevention: papers from peers for progress. *The Annals of Family Medicine, 13*(Suppl. 1), S2–S8.

Ford, E. S., & Caspersen, C. J. (2012). Sedentary behaviour and cardiovascular disease: A review of prospective studies. *International Journal of Epidemiology, 41*, 1338–1353.

Foster, G., Taylor, S. J., Eldridge, S. E., Ramsay, J., & Griffiths, C. J. (2007). Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database of Systematic Reviews, 4*(4).

Glanz, K., Rimer, B. K., & Viswanath, K. (2008). *Health behavior and health education: Theory, research, and practice* (4th ed.). San Francisco: Wiley.

Gray, R., Fitch, M., Davis, C., & Phillips, C. (1997). A qualitative study of breast cancer self-help groups. *Psycho-Oncology, 6*, 279–289.

Greaves, C. J., Sheppard, K. E., Abraham, C., Hardeman, W., Roden, M., Evans, P. H., & Schwarz, P. (2011). Systematic review of reviews of intervention components associated with increased effectiveness in dietary and physical activity interventions. *BMC Public Health, 11*, 119–130.

Grundy, S. M., Pasternak, R., Greenland, P., Smith, S., & Fuster, V. (1999). Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Journal of the American College of Cardiology, 34*, 1348–1359.

Helgeson, V. S., & Cohen, S. (1996). Social support and adjustment to cancer: Reconciling descriptive, correlational, and intervention research. *Health Psychology, 15*, 135.

Hibbard, M. R., Cantor, J., Charatz, H., Rosenthal, R., Ashman, T., Gundersen, N., . . . & Gartner, A.(2002). Peer support in the community: Initial findings of a mentoring program for individuals with traumatic brain injury and their families. *The Journal of head trauma rehabilitation, 17*, 112–131.

Hooper, L., Summerbell, C. D., Thompson, R., Sills, D., Roberts, F. G., Moore, H. J., & Davey, S. G. (2012). Reduced or modified dietary fat for preventing cardiovascular disease. *The Cochrane Database of Systematic Reviews, 5*, CD002137.

Hutchinson, A. D., & Wilson, C. (2012). Improving nutrition and physical activity in the workplace: A meta-analysis of intervention studies. *Health Promotion International, 27*, 238–249.

Janz, N., & Becker, M. H. (1984). The health belief model: A decade later. *Health Education Quarterly, 11*, 1–47.

Kelders, S. M., Van Gemert-Pijnen, J. E., Werkman, A., Nijland, N., & Seydel, E. R. (2011). Effectiveness of a Web-based intervention aimed at healthy dietary and physical activity behavior: A randomized controlled trial about users and usage. *Journal of Medical Internet Research, 13*.

King, K., Meader, N., Wright, K., Graham, H., Power, C., Petticrew, M., . . . & Sowden, A. J. (2015). Characteristics of interventions targeting multiple lifestyle risk behaviours in adult populations: A systematic scoping review. *PLoS ONE, 10*, 1–13.

Kong, G., Singh, N., & Krishnan-Sarin, S. (2012). A review of culturally targeted/tailored tobacco prevention and cessation interventions for minority adolescents. *Nicotine & Tobacco Research, 14*, 1394–1406.

Latimer, A. E., Brawley, L. R., & Bassett, R. L. (2010). A systematic review of three approaches for constructing physical activity messages: What messages work and what improvements are needed? *International Journal of Behavioral Nutrition and Physical Activity, 7*, 36.

León-Latre, M., Moreno-Franco, B., Andrés-Esteban, E. M., Ledesma, M., Laclaustra, M., Alcalde, V., . . . & Casasnovas, J. A. (2014). Sedentary lifestyle and its relation to cardiovascular risk factors, insulin resistance and inflammatory profile. *Revista Española de Cardiología (English Edition), 67*, 449–455.

Lin, J. S., O'Connor, E., Evans, C. V., Senger, C. A., Rowland, M. G., & Groom, H. C. (2014). Behavioral counseling to promote a healthy lifestyle in persons with cardiovascular risk factors: A systematic review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine, 161*, 568–578.

Lippke, S., & Ziegelmann, J. P. (2008). Theory-based health behavior change: Developing, testing, and applying theories for evidence-based interventions. *Applied Psychology, 57*, 698–716.

Lovato, C., Linn, G., Stead, L. F., & Best, A. (2003). Impact of tobacco advertising and promotion on increasing adolescent smoking behaviours. *The Cochrane Database of Systematic Reviews,* CD003439.

Marrero, D. G., Ard, J., Delamater, A. M., Peragallo-Dittko, V., Mayer-Davis, E. J., Nwankwo, R., & Fisher, E. B. (2013). Twenty-first century behavioral medicine: A context for empowering clinicians and patients with diabetes: a consensus report. *Diabetes Care, 36*, 463–470.

Mendis, S., Abegunde, D., Yusuf, S., Ebrahim, S., Shaper, G., Ghannem, H., & Shengelia, B. (2005). WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). *Bulletin of the World Health Organization, 83*, 820–829.

Morrow, A. L., Guerrero, M. L., Shults, J., Calva, J. J., Lutter, C., Bravo, J., ... & Butterfoss, F. D. (1999). Efficacy of home-based peer counselling to promote exclusive breastfeeding: A randomised controlled trial. *The Lancet, 353*, 1226–1231.

Murray, S. (2006). Doubling the burden: Chronic disease. *Canadian Medical Association Journal, 174*, 771–772.

National Heart Foundation of Australia, & Cardiac Society of Australia and New Zealand. (2012). *Reducing risk in heart disease: An expert guide to clinical practice for secondary prevention of coronary heart disease*. Melbourne: National Heart Foundation of Australia.

O'Neil, A., et al. (2015). Pro-inflammatory dietary intake as a risk factor for CVD in men: A 5-year longitudinal study. *British Journal of Nutrition, 114*(12), 2074–2082.

Oldenburg, B., & Glanz, K. (2008). Diffusion of innovations. In C. T. Orleans (Ed.), *Health behavior and health education theory, research and practice* (Vol. 14, pp. 313–333). San Fransciso: Wiley.

Oldenburg, B., Absetz, P., & Chan, C. K. Y. (2010). Behavioral interventions for prevention and management of chronic disease. In A. Steptoe (Ed.), *Handbook of behavioral medicine* (pp. 969–988). New York: Springer.

Oldridge, N. (2012). Exercise-based cardiac rehabilitation in patients with coronary heart disease: Meta-analysis outcomes revisited. *Future Cardiology, 8*, 729–751.

Oldenburg, B., Taylor, C. B., O'Neil, A., Cocker, F., & Cameron, L. D. (2015). Using new technologies to improve the prevention and management of chronic conditions in populations. *Annual Review of Public Health, 36*, 483–505.

Parry, M., & Watt-Watson, J. (2010). Peer support intervention trials for individuals with heart disease: A systematic review. *European Journal of Cardiovascular Nursing, 9*, 57–67.

Pearson, T. A., Osorio, D., & Brown, K. (2000). Nutritional interventions in cardiovascular disease: New challenges and opportunities. *Current Atherosclerosis Reports, 2*, 515–521.

Peiris, D., Praveen, D., Johnson, C., & Mogulluru, K. (2014). Use of mhealth systems and tools for non-communicable diseases in low-and middle-income countries: A systematic review. *Journal of Cardiovascular Translational Research, 7*, 677–692.

Perk, J., De Backer, G., Gohlke, H., Graham, I., Reiner, Ž., Verschuren, M., ... & Cifkova, R. (2012). European guidelines on cardiovascular disease prevention in clinical practice (version 2012). *European Heart Journal, 19*, 403–488.

Poortinga, W. (2007). The prevalence and clustering of four major lifestyle risk factors in an English adult population. *Preventive Medicine, 44*, 124–128.

Prochaska, J. O., & Velicer, W. F. (1997). The transtheoretical model of health behavior change. *American Journal of Health Promotion, 12*, 38–48.

Repper, J., & Carter, T. (2011). A review of the literature on peer support in mental health services. *Journal of Mental Health, 20*, 392–411.

Riley, W. T., Rivera, D. E., Atienza, A. A., Nilsen, W., Allison, S. M., & Mermelstein, R. (2011). Health behavior models in the age of mobile interventions: Are our theories up to the task? *Translational Behavioral Medicine, 1*, 53–71.

Rosamond, W., Flegal, K., Furie, K., Go, A., Greenlund, K., Haase, N., ... & Stroke Statistics Subcommittee. (2008). Heart disease and stroke statistics—2008 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation, 117*, 25–146.

Rosengren, A., Hawken, S., Ôunpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A. ... & Yusuf, S. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): Case-control study. *The Lancet, 364*, 953–962.

Ryan, R. M., & Deci, E. L. (2000). Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *The American Psychologist, 55*, 68–79.

Schubart, J. R., Stuckey, H. L., Ganeshamoorthy, A., & Sciamanna, C. N. (2011). Chronic health conditions and internet behavioral interventions: A review of factors to enhance user engagement. *Computers, Informatics, Nursing, 29*, 81–92.

Smith, M. A., Rainie, L., Shneiderman, B., & Himelboim, I. (2014). *Mapping Twitter topic networks: From polarized crowds to community clusters Pew Research Internet Project*. Washington, DC: Pew Research Center.

Stokols, D., Grzywacz, J. G., McMahan, S., & Phillips, K. (2003). Increasing the health promotive capacity of human environments. *American Journal of Health Promotion, 18*, 4–13.

van Gemert-Pijnen, J. E., Nijland, N., van Limburg, M., Ossebaard, H. C., Kelders, S. M., Eysenbach, G., & Seydel, E. R. (2011). A holistic framework to improve the uptake and impact of eHealth technologies. *Journal of Medical Internet Research, 13*(4), e111.

Verheijden, M. W., Bakx, J. C., van Weel, C., Koelen, M. A., & van Staveren, W. A. (2002). Role of social support in lifestyle-focused weight management interventions. *European Journal of Clinical Nutrition, 59*, 179–186.

Walther, J. B., DeAndrea, D., Kim, J., & Anthony, J. C. (2010). The influence of online comments on perceptions of antimarijuana public service announcements on YouTube. *Human Communication Research, 36*, 469–492.

Wantland, D. J., Portillo, C. J., Holzemer, W. L., Slaughter, R., & McGhee, E. M. (2004). The effectiveness of web-based vs. non-web-based interventions: A meta-analysis of behavioral change outcomes. *Journal of Medical Internet Research*. Available via e Marketer. Accessed 10 Nov.

Wei, J., Hollin, I., & Kachnowski, S. (2011). A review of the use of mobile phone text messaging in clinical and healthy behaviour interventions. *Journal of Telemedicine and Telecare, 17*, 41–48.

Whalley, B., Thompson, D., & Taylor, R. (2014). Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. *International Journal of Behavioral Medicine, 21*, 109–121.

World Health Organization. (2002). *The world health report 2002. Reducing risks, promoting health life*. Geneva: The World Health Organization.

World Health Organization. (2003). *The world health report 2003: Shaping the future*. Switzerland: World Health Organization.

Yach, D., McKee, M., Lopez, A. D., & Novotny, T. (2005). Improving diet and physical activity: 12 lessons from controlling tobacco smoking. *BMJ [British Medical Journal], 330*(7496), 898.

Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., ... & Varigos, J. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *The Lancet, 364*, 937–952.

Physical Activity and Recovery from Cardiovascular Disease: A Psychological Perspective

Vicki Myers and Yariv Gerber

Contents

Abstract

Lack of physical activity is a key risk factor for the development of coronary heart disease, yet activity is decreasing in the modern world. Once cardiovascular disease is present, physical activity is an essential ingredient of recovery and rehabilitation. Heart patients who are regularly active have a much smaller risk of dying compared with inactive patients. Several factors have been found to be associated with the uptake and maintenance of physical inactivity in cardiovascular patients, including psychological, social, and socioeconomic factors. This chapter will first describe the effects of physical activity on post-MI survival and will subsequently examine issues which act as barriers to exercise in this population.

V. Myers (✉) • Y. Gerber
School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
e-mail: vickim@post.tau.ac.il; vicki_myers@hotmail.com; yarivg@post.tau.ac.il

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_55

Modern lifestyles are increasingly sedentary yet lack of physical activity is a key risk factor for cardiovascular disease. Moderate to high activity levels offer significant protection against developing CHD via multiple pathways. Furthermore physical activity is an essential ingredient of recovery and rehabilitation after myocardial infarction (MI), with heart patients who participate in cardiac rehabilitation having far greater odds of survival. However, less than 50% of post-MI patients engage in cardiac rehabilitation. Maintaining an active lifestyle is often challenging with many factors involved, and around half of people who begin an exercise program will not continue. Several barriers to physical activity in heart patients are discussed here, including depression, low socioeconomic status, poor sense of coherence, anxiety and social support.

Keywords
Physical activity • Myocardial infarction • Cardiac rehabilitation • Survival • Depression • Anxiety • Socioeconomic status • Social support

Introduction

Physical fitness quantifies the ability of the lungs, heart, blood, and vascular system to transport oxygen and the ability of the tissues and organs to extract and use oxygen. Lack of physical activity is a key risk factor for many chronic illnesses, and reams of evidence have accumulated over the years showing that a sedentary lifestyle is a risk factor for CHD, yet physical activity is on the wane as Western society becomes more urbanized, more automated, and less active. According to the WHO's European Health Report, 20 % of Europeans take little or no physical exercise (WHO 2009). Physical inactivity has been estimated to cause approximately 600,000 deaths a year in Europe or 5–10 % of total mortality.

The twin burdens of inactivity and obesity are constantly on the increase leading to higher risk of chronic illness. Healthcare professionals and government try to encourage and incentivize physical activity as a primary prevention strategy. Moderate to high activity levels offer significant protection against developing CHD, as demonstrated by numerous studies and meta-analyses; for example, a review of 26 studies covering half a million people reported a 27 % reduced risk of CHD associated with the highest category of activity (Sofi et al. 2008). Physical activity lowers CHD risk via several pathways including lowering blood pressure, improving lipid profile, decreasing obesity, and reducing levels of inflammatory markers.

What about secondary prevention? For patients who have already developed heart disease and have suffered a myocardial infarction (MI), how does exercise fit into the picture? In the past, the prevailing wisdom prescribed bed rest after MI and instilled in heart patients a fear of exercise, with the suggestion that exercise could cause overexertion and reinfarction. In recent years, the evidence has dispelled this myth, and it is now widely understood – at least among healthcare professionals – that physical activity is an essential ingredient of recovery and rehabilitation after MI. In fact, the major component of most cardiac rehabilitation programs is exercise.

Cardiac Rehabilitation

Cardiac rehabilitation comprises three phases: phase 1, during acute inpatient hospitalization; phase 2, a supervised outpatient program lasting 3–6 months following hospitalization; and phase 3, the maintenance phase with minimal or no supervision (Gonzalez et al. 2004).

While exercise is generally associated with improved recovery, it should be noted that different levels of physical activity are advised for heart patients depending on disease severity. Cardiac function is categorized according to the New York Heart Association scale from I (least severe) to IV (most severe). Patients in class I can perform any physical activity without limitation, including contact sports and weight lifting. Class II patients have slight limitation and are recommended to limit their activity to <7 METS, allowing for brisk walking, gardening, and tennis but excluding jogging. Class III patients are limited to light activity <5 METS, such as golf or bowling, walking, and light cleaning, while class IV patients are unable to perform any physical activity >2 METS (Goldman et al. 1981). Aerobic exercise is generally recommended for rehabilitation and cardiovascular fitness. Clinically stable patients are also encouraged to engage in resistance training; however this is not recommended for patients with heart failure, uncontrolled arrhythmia, or very high blood pressure (Gonzalez et al. 2004).

Numerous studies have shown that heart patients who participate in cardiac rehabilitation have far greater odds of survival and lower risk of subsequent ischemic events (Heran et al. 2011; Lawler et al. 2011; Oldridge 2012; Coll-Fernandez et al. 2014). While the true effects on all-cause survival have been debated (West and Jones 2013), reductions in the risk of cardiovascular mortality have been reported as particularly striking (Heran et al. 2011). In addition to reducing mortality risk, exercise-based rehabilitation has been shown to have favorable effects on cardiovascular risk factors such as smoking and body weight (Lawler et al. 2011) as well as on mental health (NACR 2013).

However, patients' perceptions may not have changed in line with research developments. Multinational surveys show that <50 % of post-MI patients engage in cardiac rehabilitation and reap the benefits of this important strategy for recovery (Bjarnason-Wehrens et al. 2010; NACR 2013).

Physical Activity and Post-MI Survival

Beyond state-sponsored rehabilitation, what happens when patients are left to their own devices? Do they continue to be active or fall back into old habits? With improved cardiac care, patients now live longer after MI; therefore maintenance of healthy lifestyle habits is essential, including maintaining an active lifestyle. Physical activity outside the framework of formal rehabilitation is also keenly associated with improved prognosis in heart patients (Blumenthal et al. 2004; Al-Khalili et al. 2007; Apullan et al. 2008). For example, a weekly session of exercise was associated with lower all-cause mortality in CHD patients (Moholdt et al. 2008),

while cardiac patients who engaged in exercise at least four times per week reduced their risk of death and recurrent CHD by 30 % (Booth et al. 2014).

Results from a prospective cohort study: Since physical activity is an ongoing lifestyle behavior with cumulative effects, prospective studies are useful for assessing its relationship with health outcomes. The Israel Study of First Acute Myocardial Infarction investigated the benefits of leisure-time physical activity (LTPA) in an Israeli cohort of post-MI patients and the barriers to participation, in an attempt to understand why so few heart patients are physically active (Gerber et al. 2011). This longitudinal study followed patients aged $\leq$65 years from initial hospitalization for first acute MI over 10–13 years, collecting data on socioeconomic, clinical, psychological, and cardiovascular risk factors, including leisure-time physical activity (LTPA), on five separate occasions. Participants self-reported their activity levels including frequency, duration, and type of activity, including walking, cycling, swimming, gardening, going to the gym, and team sports. These responses were summarized into three groups: inactive, irregularly active, and regularly active patients. Regular physical activity was defined as at least three 30-min sessions per week, according to published guidelines at the time (Pate et al. 1995), although these guidelines have since been updated and increased to 30 min of moderate activity five times a week or 20 min of vigorous activity three times a week. The study found a point prevalence rate of 40 % for regular LTPA among MI survivors and a continuous rate of 18 % at 10 years post-MI.

Individuals who were regularly active had about half the risk of dying compared with inactive patients, irrespective of pre-MI habits. Just three short sessions of activity per week – which could be walking, cycling, gardening, or organized sports – were associated with doubled odds of survival. And importantly, this survival benefit occurred in both individuals who were previously active and in those who had been previously inactive. Although we may imagine the effects of physical activity as being cumulative and therefore change in mid-or later life to be pointless, these results show this not to be the case. Similar to smoking cessation after MI, taking up exercise has a real effect on prognosis, demonstrating that it is never too late to get active. This message should be made clear to patients who have suffered a heart attack or who have developed CHD. If the true influence of activity levels on survival was more widely understood, people might be more inclined to take part.

Of course, motivation is not the only resource required for getting active.

Barriers to Physical Activity in Post-MI Survivors

Evidence has clearly shown that a sedentary lifestyle is a risk factor for developing CHD. Previous research has further suggested that physical activity may be equally vital in secondary prevention, for those who have already suffered an MI. However, exercise participation is low in this population. Furthermore, typically only 50 % or less of individuals who start an exercise program will continue. Several factors have been identified which act as barriers to exercise participation in CHD patients.

Research in CHD patients has focused on links between physical activity and mental health, for example, depression, or has examined psychological constructs which predict initiation and maintenance of physical activity, including perceived control and sense of coherence (Allan et al. 2007; Petter et al. 2009). A recent cohort study of all patients hospitalized with first MI within a year in central Denmark reported a significant increase in death and reinfarction associated with decreasing mental health status (measured via the SF-12 (Short-Form Health Survey)) (Nielsen et al. 2013). Patients with the poorest mental health had almost 50 % higher risk of new cardiovascular events or death.

Depression

Depression is generally more prevalent in CHD patients and up to three times more common in MI patients compared to the general population (Thombs et al. 2006). Literature consistently puts the incidence of depressive symptoms in post-MI populations at around 30 %, as assessed by the Beck Depression Inventory (BDI) (Frasure-Smith et al. 1999; Lane et al. 2002a; Strik et al. 2004; Thombs et al. 2006; Leung et al. 2007), while the presence of major depression, diagnosed by clinical interview, has been reported in 15–20 % during hospitalization (Schleifer et al. 1989; Lichtman et al. 2008). Depressive symptoms may persist several months after MI (Schleifer et al. 1989; Strik et al. 2004).

Prognostic Role of Depression in CHD

Numerous studies have reported post-MI depression to be a significant predictor of cardiac mortality (Frasure-Smith et al. 1995; Welin et al. 2000; Ziegelstein et al. 2000; Lesperance et al. 2002; Blumenthal et al. 2004; Jaffe et al. 2006; Leung et al. 2007), a finding confirmed by meta-analyses (Barth et al. 2004; van Melle et al. 2004), although not supported unanimously (Lane et al. 2002; Lauzon et al. 2003). The American Academy of Family Physicians reviewed the literature in 2009 and found that the association between depression and mortality post-MI was both statistically and clinically significant (AAFP 2009).

Meta-analyses examining the prognostic role of depression in patients with existing CHD reported effect sizes of 1.6–2.6. Van Melle et al. (2004) reviewed 22 studies investigating the role of depression in post-MI outcome. Post-MI depression, measured within 3 months of MI, was significantly associated with all-cause mortality (OR, 2.38; 95 % CI, 1.76–3.22) and cardiac mortality (OR, 2.59; 95 % CI, 1.77–3.77) within 2 years of MI. Depression was assessed via self-report or clinical interview. A second meta-analysis by Barth et al. (2004) investigated mortality in CHD patients and concluded that the risk of death in depressed patients was more than twice as high as that of nondepressed patients (OR, 2.24; 1.37–3.60).

Post-MI Depression and Exercise

Health behaviors have been shown to influence CV outcomes in MI patients; both factors related to post-MI care – adherence to medication and participation in

cardiac rehabilitation – and lifestyle factors including diet, exercise and smoking have a clear influence on prognosis. Research has shown that depressed patients are less likely to engage in these behaviors. For example, depressed acute coronary syndrome patients (BDI >10) were less adherent to aspirin than nondepressed patients, and improvements in depression were associated with improvements in adherence (Rieckmann et al. 2006).

Post-MI patients with depressive symptoms are less likely to be physically active than nondepressed patients. Depression is also linked to increased risk of mortality post-MI as well as increased hospital admissions during follow-up and lack of exercise factors into the equation. A prospective cohort study of MI survivors found that depressed patients were less likely to be physically active (OR, 0.80, CI, 0.69–0.94) than nondepressed patients, alongside reduced likelihood of stopping smoking (OR, 0.75, CI, 0.60–0.94) and participating in cardiac rehabilitation (OR, 0.74, CI, 0.59–0.92) (Myers et al. 2011a). Moreover, depressed patients had a 50 % higher risk of hospitalization for unspecified chest pain compared to nondepressed, which was attenuated to 16 % on adjustment for sociodemographic and clinical factors, and a 30 % (crude) increased risk of hospitalization for cardiac events, reduced to 13 % when fully adjusted for covariates. Since depression is common following MI, with reported prevalence of around 30 %, including 15–20 % who are diagnosed with major depression, this is a sizeable problem (Strik et al. 2004).

Exercise as Therapy for Post-MI Depression

Exercise is an integral part of cardiac rehabilitation, and regular physical activity is vital in both increasing chances of survival and in maintaining quality of life. Several studies investigated exercise as a treatment for post-MI depression and found it to be as effective as antidepressant medication (Blumenthal et al. 2004); however there is no evidence that treating depression with exercise improves cardiac prognosis.

Socioeconomic Background and Neighborhood Socioeconomic Status (SES)

Socioeconomic factors have also been implicated as a barrier to physical activity in patients with CHD (Stewart et al. 2013). A social gradient in health exists, and studies have shown that low SES (represented by low income, unemployment, and fewer years of education) is a risk factor for developing CVD (Yen and Kaplan 1998). Recent investigations have additionally looked at neighborhood SES, finding that beyond personal characteristics, the socioeconomic nature of one's residential area may also influence health outcomes.

In the Israel Study of First Acute Myocardial Infarction, neighborhood SES was predictive of poorer LTPA throughout follow-up (Gerber et al. 2011). Participants from disadvantaged neighborhoods were less likely to be engaged in LTPA in the decade following MI than participants from wealthier neighborhoods, regardless of their personal SES (see Fig. 1). Generalized estimating equation (GEE)-derived

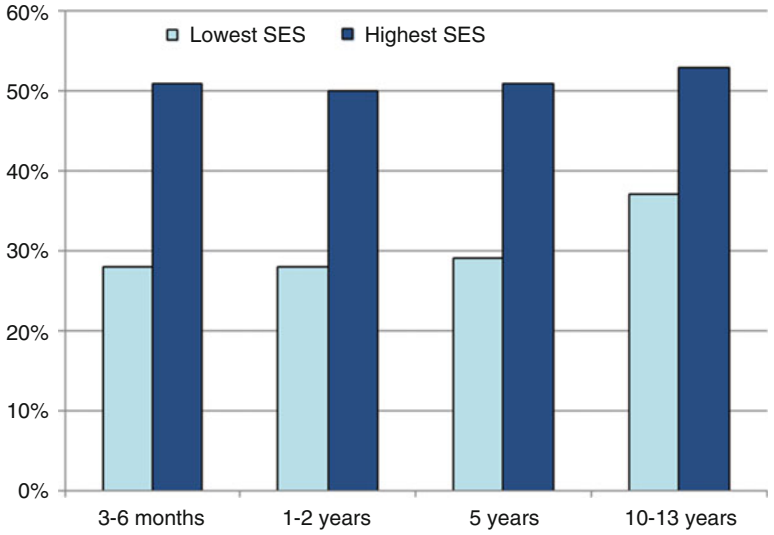


Fig. 1 Point prevalence of LTPA according to neighborhood SES tertiles in a post-MI cohort

odds ratios (95 % CI) for decreased LTPA level in the lower and middle vs. upper neighborhood SES tertiles were 2.49 (2.05–3.02) and 1.60 (1.33–1.92) after age and sex adjustment and 1.55 (1.26–1.90) and 1.23 (1.02–1.49).

Neighborhood wealth or deprivation affects the amount of physical activity people do for a number of reasons which generally fall into physical and social elements. Physical characteristics such as access to facilities, lighting, and accommodation for pedestrians may present physical barriers to exercise, while social norms of the neighborhood or perceptions of safety or lack thereof may present psychological barriers.

Recommendations for physical activity should be supported by appropriate infrastructure and the provision of free or low-cost sports facilities in areas of deprivation. Exercise-based rehabilitation should be available to all MI survivors, with special efforts made to encourage participation in patients from deprived neighborhoods.

Sense of Coherence

Additional psychosocial constructs have been investigated in relation to physical activity in CVD patients. Sense of coherence (SOC) is a central construct of the salutogenic model developed by Antonovsky and represents a person's confidence that they have the resources to cope with problems and challenges (Antonovsky 1987). The sense of coherence scale, a 29-item questionnaire, measures personality resources for coping with stress and comprises the three constructs of

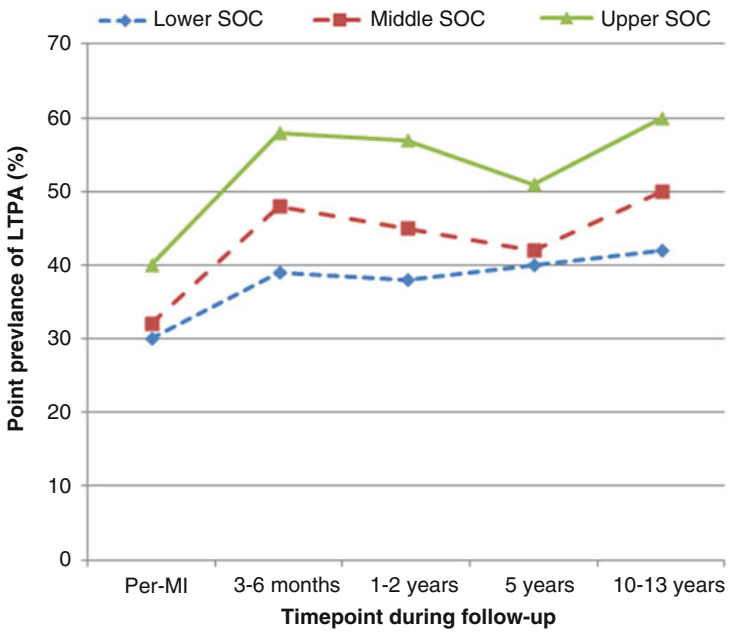


Fig. 2 Percentage of post-MI patients regularly engaged in leisure-time physical activity at different time points across sense of coherence tertiles

comprehensibility, manageability, and meaningfulness (Antonovsky 1993). SOC has been shown to be related to health outcomes, as well as to health behaviors.

In a prospective study of MI patients, after controlling for disease severity, depression, and sociodemographic and clinical factors, SOC was consistently associated with engagement in LTPA throughout 13 years of follow-up (Fig. 2). Individuals in the lowest SOC category had significantly higher odds of decreasing their engagement in LTPA during follow-up compared to those in the highest tertile (OR, 1.38; 95 % CI 1.02–1.85 after multivariable adjustment) (Myers et al. 2011b).

The significant association between SOC and LTPA suggests that a strong SOC may be involved in the maintenance of health behaviors. Other research supports this finding; for example, a study involving 18,000 participants reported that those with the strongest SOC were 36 % less likely to be physically inactive than participants with the weakest SOC (Wainwright et al. 2007). Indeed SOC has also been implicated in the uptake of cardiac rehabilitation (Breuer and Etienne 2001). Particularly in CVD patients, a strong SOC may facilitate secondary prevention efforts, such as engaging in exercise, as part of adaptive coping. The understanding that behavior can change prognosis can give patients back control following a seemingly uncontrollable illness. Therefore patients who perceive their condition as manageable, comprehensible, and meaningful, according to the salutogenic model, are more likely to make use of available resources to overcome the challenges they face. Recovery after MI requires adopting and maintaining

lifestyle changes – individuals with low SOC may perceive their condition as overwhelming and beyond their capability to overcome, heeding implementation of preventive behaviors such as exercise.

An individual's SOC is based on the presence or absence of generalized resistance resources (Antonovsky 1979). In the case of physical activity, these may include material and financial resources necessary to engage in sports such as gym membership or equipment; social support, for example, encouragement from a partner; flexibility; knowledge; and physical health status.

SOC, a summary measure of personal, social, psychological, and economic resources, may be used to facilitate identification of high-risk MI survivors. It is easy to determine with a simple questionnaire and can help to identify patients who are less likely to incorporate physical activity in their daily life, who may require additional support in implementing preventive health behaviors, which can dramatically improve post-MI prognosis.

Anxiety

Anxiety is another factor which may affect uptake of exercise in CHD patients and is fairly prevalent following acute coronary events, particularly in younger patients (Lavie et al. 2009). In a group of MI patients assessed for anxiety during hospitalization and 4 months later, anxiety was associated with poorer adherence to exercise, in addition to lower likelihood of smoking cessation (Kuhl et al. 2009). On the other hand, participation in cardiac rehabilitation has the potential to reduce anxiety, as reported by a cardiac rehabilitation nursing team which assessed patients with the hospital anxiety and depression scale. Patients waiting the longest to start rehab had the highest anxiety scores (Harrison 2005). Another study of patients with coronary artery disease also demonstrated significant reductions in anxiety following participation in exercise training and rehabilitation (Lavie et al. 2009).

While rehab may help to reduce anxiety, some patients remain anxious during or after completion of rehab, necessitating psychological intervention. Cognitive behavior therapy has been demonstrated as useful in alleviating both anxiety and depression post-MI (Hambridge et al. 2009).

Social Support

Social support impacts on many areas of life including health outcomes. Social support comprises several elements, including functional/instrumental, emotional, and perceived support as well as size of network. In the context of recovery from MI, the ENRICHD trial followed MI patients with either depression or low social support (Lett et al. 2007) and found that higher levels of perceived social support were associated with improved outcome for nondepressed patients but not for patients with high levels of depression. Quality of relationships is often more important than their mere existence, with marital quality additionally found to be

associated with survival in heart failure patients, independent of baseline disease severity (Rohrbaugh et al. 2006). While not much research has investigated the effect of social support on exercise in CHD patients, in the general population, social support has demonstrated an association with exercise; for example, a study investigating primary cardiovascular risk reported that higher emotional and instrumental social support were associated with more frequent physical activity (Fischer Aggarwal et al. 2008). Furthermore, in a sample of 500 cardiac patients undergoing an intervention to promote physical activity, higher social support also predicted increased activity at 1 year (Aggarwal et al. 2010). It stands to reason that having a supportive partner or social network who encourage exercise, are physically active themselves, or better still, engage in exercise with the patient may increase motivation to get active.

Risks of Exercise in Cardiovascular Patients

Having sung the praises of exercise in recovery from cardiovascular disease, it should be mentioned that some risk does exist among cardiovascular patients, with acute exercise occasionally associated with cardiovascular events, which may sometimes be fatal. Additionally some congenital heart disorders, such as hypertrophic cardiomyopathy, have been associated with exercise intolerance and may even lead to sudden cardiac death during intense physical activity. For this reason, it is important that exercise programs be tailored to the individual patient according to diagnosis, disease severity, and comorbid conditions. However these occurrences are rare; for example, almost 5,000 Norwegian CHD patients were followed as they engaged in both moderate- and high-intensity exercise training rehabilitation, with an average of 37 sessions per person, among which one fatal cardiac arrest and two nonfatal cardiac arrests were reported (Rognmo et al. 2012). Consistent evidence indicates that clinically stable individuals with CVD can safely engage in physical activity with little risk of adverse events (Thomas et al. 2011). High-risk individuals should follow clinicians' recommendations for appropriate activity.

Methodological Considerations

Some recurrent aspects in this field of research should be considered. Activity levels are often self-reported, incurring the inherent problems of inaccurate recall and social desirability bias. Self-report does not usually record intensity of activity, recorded in METS during exercise, rather providing a more crude classification of physical activity. More recent studies have used pedometers for a more accurate and objective measure of activity (Kotseva et al. 2009). Indeed beyond purely providing an objective assessment, it has been reported, albeit in a small study of patients following acute coronary syndrome, that providing pedometers may increase activity levels by raising patients' awareness (Houle et al. 2011). Psychological constructs including depression and SOC are also usually assessed via self-

report questionnaire, although some studies stipulate the use of the Beck Depression Inventory or clinical interview for diagnosis of clinical depression.

Most studies of physical activity in heart patients are observational and thus preclude drawing of causational conclusions. While consistent evidence supports the association between exercise and survival, it is possible that selection bias is involved, with fitter, healthier patients being more active than their more poorly contemporaries.

Conclusion

Physical activity confers a survival advantage on post-MI patients, yet the majority of patients are not regularly active. Regular physical activity has been shown to halve the risk of dying compared with inactive patients, irrespective of pre-MI habits. The advantages of physical activity clearly outweigh the risks in this population, and it is up to healthcare professionals to advise their patients on the importance of exercise and to encourage participation.

Several factors predict uptake of activity post-MI. Patients living in disadvantaged neighborhoods have far greater odds of inactivity, regardless of their own SES. A strong sense of coherence is associated with greater levels of activity after MI, suggesting that SOC may be involved in the maintenance of health behaviors. Depressed patients are less likely to be active. Depressed heart patients not only experience reduced quality of life but indeed have higher mortality risk and are at risk of reinfarction. Anxiety and depressive symptoms should be identified during hospitalization and taken into account in this population and efforts made to enroll patients in exercise-based cardiac rehabilitation.

The low engagement in LTPA in MI patients attests to the difficulties involved in maintenance of an active lifestyle, particularly in deprived neighborhoods. All MI patients should be offered exercise-based rehabilitation, and practitioners should follow up after the official rehabilitation period is over. Beyond rehabilitation, it is clear that encouraging exercise is not sufficient and that appropriate infrastructure must be available to put this into practice, providing free or non-expensive facilities for sports, as well as infrastructure for active commuting. During initial hospitalization for MI, patients can be assessed via simple psychological measures to determine which are less likely to get active and therefore need added support. Research demonstrates that for heart patients, it is never too late to get active.

References

AAFP. (2009). AAFP (American Academy of Family Physicians) guideline for the detection and management of post-myocardial infarction depression. *Annals of Family Medicine, 7*(1), 71–79.

Aggarwal, B., Liao, M., et al. (2010). Predictors of physical activity at 1 year in a randomized controlled trial of family members of patients with cardiovascular disease. *Journal of Cardiovascular Nursing, 25*(6), 444–449.

Al-Khalili, F., Janszky, I., et al. (2007). Physical activity and exercise performance predict long-term prognosis in middle-aged women surviving acute coronary syndrome. *Journal of Internal Medicine, 261*(2), 178–187.

Allan, J. L., Johnston, D. W., et al. (2007). Depression and perceived behavioral control are independent predictors of future activity and fitness after coronary syndrome events. *Journal of Psychosomatic Research, 63*(5), 501–508.

Antonovsky, A. (1979). *Health, stress and coping*. San Francisco: Jossey-Bass.

Antonovsky, A. (1987). *Unravelling the mystery of health: How people manage stress and stay well*. San Francisco: Jossey-Bass.

Antonovsky, A. (1993). The structure and properties of the sense of coherence scale. *Social Science and Medicine, 36*(6), 725–733.

Apullan, F. J., Bourassa, M. G., et al. (2008). Usefulness of self-reported leisure-time physical activity to predict long-term survival in patients with coronary heart disease. *American Journal of Cardiology, 102*(4), 375–379.

Barth, J., Schumacher, M., et al. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine, 66*(6), 802–813.

Bjarnason-Wehrens, B., McGee, H., et al. (2010). Cardiac rehabilitation in Europe: Results from the European Cardiac Rehabilitation Inventory Survey. *European Journal of Cardiovascular Prevention & Rehabilitation, 17*(4), 410–418.

Blumenthal, J. A., Babyak, M. A., et al. (2004). Exercise, depression, and mortality after myocardial infarction in the ENRICHD trial. *Medicine and Science in Sports and Exercise, 36*(5), 746–755.

Booth, J. N., 3rd, Levitan, E. B., et al. (2014). Effect of sustaining lifestyle modifications (nonsmoking, weight reduction, physical activity, and Mediterranean diet) after healing of myocardial infarction, percutaneous intervention, or coronary bypass (from the reasons for geographic and racial differences in stroke study). *American Journal of Cardiology, 113*(12), 1933–1940.

Breuer, B., & Etienne, A. M. (2001). Sense of coherence and commitment to a cardiac rehabilitation program after a myocardial infarction: Preliminary results (French). *Revue Médicale de Liège, 56*(10), 703–708.

Coll-Fernandez, R., Coll, R., et al. (2014). Cardiac rehabilitation and outcome in stable outpatients with recent myocardial infarction. *Archives of Physical Medicine and Rehabilitation, 95*(2), 322–329.

Fischer Aggarwal, B. A., Liao, M., et al. (2008). Physical activity as a potential mechanism through which social support may reduce cardiovascular disease risk. *Journal of Cardiovascular Nursing, 23*(2), 90–96.

Frasure-Smith, N., Lesperance, F., et al. (1995). Depression and 18-month prognosis after myocardial infarction. *Circulation, 91*(4), 999–1005.

Frasure-Smith, N., Lesperance, F., et al. (1999). Gender, depression, and one-year prognosis after myocardial infarction. *Psychosomatic Medicine, 61*(1), 26–37.

Gerber, Y., Myers, V., et al. (2011). Neighborhood socioeconomic status and leisure-time physical activity after myocardial infarction: A longitudinal study. *American Journal of Preventive Medicine, 41*(3), 266–273.

Goldman, L., Hashimoto, B., et al. (1981). Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. *Circulation, 64*(6), 1227–1234.

Gonzalez, P., Cuccurullo, S., et al. (2004). *Cardiac rehabilitation. Physical medicine and rehabilitation board review. S. Cuccurullo*. New York: Demos Medical Publishing.

Hambridge, J. A., Turner, A., et al. (2009). BraveHeart begins: Pilot results of group cognitive behaviour therapy for depression and anxiety in cardiac patients. *The Australian and New Zealand Journal of Psychiatry, 43*(12), 1171–1177.

Harrison, R. (2005). Psychological assessment during cardiac rehabilitation. *Nursing Standard, 19*(27), 33–36.

Heran, B. S., Chen, J. M., et al. (2011). Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database of Systematic Reviews, 7*, CD001800.

Houle, J., Doyon, O., et al. (2011). Innovative program to increase physical activity following an acute coronary syndrome: Randomized controlled trial. *Patient Education and Counseling, 85*(3), e237–e244.

Jaffe, A. S., Krumholz, H. M., et al. (2006). Prediction of medical morbidity and mortality after acute myocardial infarction in patients at increased psychosocial risk in the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) study. *American Heart Journal, 152*(1), 126–135.

Kotseva, K., Wood, D., et al. (2009). EUROASPIRE III: A survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *European Journal of Cardiovascular Prevention & Rehabilitation, 16*(2), 121–137.

Kuhl, E. A., Fauerbach, J. A., et al. (2009). Relation of anxiety and adherence to risk-reducing recommendations following myocardial infarction. *American Journal of Cardiology, 103*(12), 1629–1634.

Lane, D., Carroll, D., et al. (2002a). The prevalence and persistence of depression and anxiety following myocardial infarction. *British Journal of Health Psychology, 7*(Pt 1), 11–21.

Lane, D., Carroll, D., et al. (2002b). In-hospital symptoms of depression do not predict mortality 3 years after myocardial infarction. *International Journal of Epidemiology, 31*(6), 1179–1182.

Lauzon, C., Beck, C. A., et al. (2003). Depression and prognosis following hospital admission because of acute myocardial infarction. *CMAJ, 168*(5), 547–552.

Lavie, C. J., Thomas, R. J., et al. (2009). Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. *Mayo Clinic Proceedings, 84*(4), 373–383.

Lawler, P. R., Filion, K. B., et al. (2011). Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. *American Heart Journal, 162*(4), 571–584.

Lesperance, F., Frasure-Smith, N., et al. (2002). Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation, 105*(9), 1049–1053.

Lett, H. S., Blumenthal, J. A., et al. (2007). Social support and prognosis in patients at increased psychosocial risk recovering from myocardial infarction. *Health Psychology, 26*(4), 418–427.

Leung, Y. W., Ceccato, N., et al. (2007). A prospective examination of patterns and correlates of exercise maintenance in coronary artery disease patients. *Journal of Behavioral Medicine, 30*(5), 411–421.

Lichtman, J. H., Bigger, J. T., Jr., et al. (2008). Depression and coronary heart disease: Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. *Circulation, 118*(17), 1768–1775.

Moholdt, T., Wisloff, U., et al. (2008). Physical activity and mortality in men and women with coronary heart disease: A prospective population-based cohort study in Norway (the HUNT study). *Europe Journal Cardiovascular Prevention and Rehabilitation, 15*(6), 639–645.

Myers, V., Gerber, Y., et al. (2011a). Post-MI depression: Increased hospital admissions and reduced adoption of secondary prevention measures – A longitudinal study. *Journal of Psychosomatic Research, 72*(1), 5–10.

Myers, V. J., Drory, Y., et al. (2011b). Sense of coherence predicts post-myocardial infarction trajectory of leisure time physical activity: A prospective cohort study. *BMC Public Health, 11*, 708.

NACR. (2013). The National Audit of Cardiac Rehabilitation: Annual statistical report 2013. British Heart Foundation http://www.cardiacrehabilitation.org.uk/nacr/docs/2013.pdf

Nielsen, T. J., & Vestergaard, M., et al. (2013). Mental health status and risk of new cardiovascular events or death in patients with myocardial infarction: A population-based cohort study. *BMJ Open, 3*(8).

Oldridge, N. (2012). Exercise-based cardiac rehabilitation in patients with coronary heart disease: Meta-analysis outcomes revisited. *Future Cardiology, 8*(5), 729–751.

Pate, R. R., Pratt, M., et al. (1995). Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA, 273*(5), 402–407.

Petter, M., Blanchard, C., et al. (2009). Correlates of exercise among coronary heart disease patients: Review, implications and future directions. *European Journal of Cardiovascular Prevention & Rehabilitation, 16*(5), 515–526.

Rieckmann, N., Gerin, W., et al. (2006). Course of depressive symptoms and medication adherence after acute coronary syndromes: An electronic medication monitoring study. *Journal of the American College of Cardiology, 48*(11), 2218–2222.

Rognmo, O., Moholdt, T., et al. (2012). Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. *Circulation, 126*(12), 1436–1440.

Rohrbaugh, M. J., Shoham, V., et al. (2006). Effect of marital quality on eight-year survival of patients with heart failure. *American Journal of Cardiology, 98*(8), 1069–1072.

Schleifer, S. J., Macari-Hinson, M. M., et al. (1989). The nature and course of depression following myocardial infarction. *Archives of Internal Medicine, 149*(8), 1785–1789.

Sofi, F., Capalbo, A., et al. (2008). Physical activity during leisure time and primary prevention of coronary heart disease: An updated meta-analysis of cohort studies. *Europe Journal Cardiovascular Prevention and Rehabilitation, 15*(3), 247–257.

Stewart, R., Held, C., et al. (2013). Physical activity in patients with stable coronary heart disease: An international perspective. *European Heart Journal, 34*(42), 3286–3293.

Strik, J. J., Lousberg, R., et al. (2004). One year cumulative incidence of depression following myocardial infarction and impact on cardiac outcome. *Journal of Psychosomatic Research, 56* (1), 59–66.

Thomas, S. G., Goodman, J. M., et al. (2011). Evidence-based risk assessment and recommendations for physical activity clearance: Established cardiovascular disease. *Applied Physiology, Nutrition, and Metabolism, 36*(Suppl 1), S190–S213.

Thombs, B. D., Bass, E. B., et al. (2006). Prevalence of depression in survivors of acute myocardial infarction. *Journal of General Internal Medicine, 21*(1), 30–38.

van Melle, J. P., de Jonge, P., et al. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosomatic Medicine, 66*(6), 814–822.

Wainwright, N. W., Surtees, P. G., et al. (2007). Healthy lifestyle choices: Could sense of coherence aid health promotion? *Journal of Epidemiology and Community Health, 61*(10), 871–876.

Welin, C., Lappas, G., et al. (2000). Independent importance of psychosocial factors for prognosis after myocardial infarction. *Journal of Internal Medicine, 247*(6), 629–639.

West, R., & Jones, D. (2013). Cardiac rehabilitation and mortality reduction after myocardial infarction: The emperor's new clothes? Evidence against cardiac rehabilitation. *Heart, 99*(13), 911–913.

WHO. (2009). *The European Health Report: Health and health systems*. Copenhagen: World Health Organization.

Yen, I. H., & Kaplan, G. A. (1998). Poverty area residence and changes in physical activity level: Evidence from the Alameda County Study. *American Journal of Public Health, 88*, 1709–1712.

Ziegelstein, R. C., Fauerbach, J. A., et al. (2000). Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Archives of Internal Medicine, 160*(12), 1818–1823.

Obesity: Its Relationship with Cardiovascular Disease and Management

Elizabeth Rieger

Contents

Abstract

The serious worldwide challenge posed by the prevalent, and increasing, problem of obesity is well known. Obesity places a substantial health burden on affected individuals, including cardiovascular disease, although the complex biopsychosocial pathways linking obesity with cardiovascular disease have yet to be fully explicated. Three primary approaches have been investigated as treatments for obesity, namely, behavioral (lifestyle) weight-loss programs, pharmacotherapy, and bariatric surgery. Behavioral weight-loss programs (and pharmacotherapy) have been found to result in modest weight losses and reductions in cardiovascular risk factors (e.g., a significantly reduced rate of type 2 diabetes). However, the impact of these programs on cardiovascular morbidity and mortality has been inadequately investigated, with the few studies conducted yielding inconsistent results. Any capacity of behavioral weight-loss programs to reduce cardiovascular disease end points is likely to be limited by the transient nature of treatment-induced weight losses, with weight regain the normative response to these programs. Bariatric surgery has been found to yield large and

E. Rieger (✉)
Research School of Psychology, ANU College of Medicine, Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia
e-mail: Elizabeth.Rieger@anu.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_56

sustained weight losses and, importantly, improved cardiovascular outcomes and yet is limited by its expense and the fact that it is associated with a risk of surgical complications (including the need for operative re-intervention in a sizable number of patients). While the obesity treatment outcome research has elicited pessimistic responses from some researchers and obese patients alike, innovative approaches (e.g., maximizing the support available to obese individuals for sustained weight loss) and integrative responses (that entail shared responsibility for promoting healthy dietary behaviors and physical activity at the individual, interpersonal, and societal levels) are likely needed to meet the obesity challenge.

Keywords

Obesity • Body mass index • Waist circumference • Behavioral weight-loss program • Lifestyle intervention • Weight loss • Weight-loss maintenance

Introduction

It is well known that obesity is a problem of epidemic proportions that carries a profound health, psychosocial, and economic burden for affected individuals and the broader community (Wang et al. 2011). In 2008, 35 % of adults worldwide were either overweight or obese, which comprised a doubling of obesity rates since 1980 (World Health Organization [WHO] 2011). Although prevalence rates of overweight and obesity were highest in the WHO Region of the Americas (where 62 % of adults were overweight or obese) and lowest in the WHO Region for Southeast Asia (where 14 % of adults were overweight or obese) (WHO 2011), the term "globesity" captures the fact that obesity is a major problem in many developed countries and is an emerging problem in other developed and developing countries (where obesity coexists with undernutrition) (WHO 2000). This is of significant concern given the evidence that obesity increases the risk of developing a wide range of diseases, with an estimated 3.4 million deaths in 2010 a result of high body weight (Lim et al. 2012). Indeed, in terms of their impact on the global burden of disease (including cardiovascular disease), high body weight was ranked sixth among 67 risk factors (an increase from tenth position in 1990) and first (e.g., Australasia) or second (e.g., high-income North America) in many regions (Lim et al. 2012). Thus, obesity poses one of the most concerning public health problems facing the world today.

Cardiovascular disease is among the serious conditions associated with obesity. This chapter will begin with a brief overview of the evidence linking overweight and obesity to cardiovascular disease, and the proposed biopsychosocial mechanisms underlying this association. The chapter will then focus on providing a description and evaluation of the main treatment modalities for obesity, with an emphasis on behavioral approaches but also including pharmacological and surgical interventions. These approaches will be evaluated not only in terms of their effects on body weight but also on cardiovascular outcomes.

The Relationship Between Obesity and Cardiovascular Disease

Obesity is defined by the World Health Organization (2000) as abnormal or excessive fat accumulation that presents a risk to health. Body mass index (BMI = weight [kg]/height $[m]^2$) provides a simple index (although an imperfect one given that weight measurements do not distinguish between fat and muscle mass) to classify obesity status, with overweight defined as a BMI $\geq$ 25 and obesity defined as a BMI $\geq$ 30 (which is further categorized as obese class I [30–34.9], obese class II [35–39.9], and obese class III [$\geq$40]) (WHO 2000). In addition to the amount of body fat, the pattern of distribution of fat has important health implications. For individuals with a given BMI (even those in the normal BMI range of 18.5–24.9), the risk of developing certain diseases (including cardiovascular disease such as coronary artery disease and stroke) is increased if fat is stored abdominally (referred to as abdominal, central, or visceral obesity) as measured, for example, by waist circumference (Kuk et al. 2006; Rexrode et al. 1998; Snijder et al. 2006). Health risk is increased at a waist circumference >94 cm in men and >80 cm in women and substantially increased at a waist circumference >102 cm in men and >88 cm in women. Ethnic variations exist in the cutoffs for both BMI and waist circumference (WHO 2008).

In terms of the relationship between overweight/obesity and cardiovascular disease, a meta-analysis found that overweight and obesity (as indexed via BMI and waist circumference) were both associated with an increased incidence of cardiovascular diseases (including stroke, coronary artery disease, and, for obesity alone, congestive heart failure), in addition to an increased incidence of type 2 diabetes (itself a major cause of coronary heart disease and stroke), most cancers, asthma, gallbladder disease, osteoarthritis, and chronic back pain (Guh et al. 2009). Another meta-analysis found a strong relationship between overweight and obesity and cardiovascular disease mortality (Prospective Studies Collaboration 2009). This study found that median overall survival was reduced by 2–4 years for those with a BMI between 30 and 35, and by 8–10 years for those with a BMI between 40 and 45 (akin to the effects of smoking), with the excess mortality largely due to vascular mortality.

There has been some debate regarding the relative contributions of obesity and physical activity in the prediction of cardiovascular disease, although there is evidence that both are strong and independent predictors. For instance, in a 20-year follow-up of middle-aged women enrolled in the Nurses' Health Study, overweight and obesity were associated with an increased incidence of major coronary heart disease events after controlling for other risk factors (Li et al. 2006). Compared with women who had a healthy BMI and were physically active, the relative risks of major coronary heart disease events were 3.44 for women who were obese and sedentary, 2.48 for women who were obese but physically active, and 1.48 for women who had a healthy weight but were sedentary. Based on the body of research linking overweight/obesity and cardiovascular disease, waist circumference and BMI are listed among the modifiable risk factors (along with smoking status, blood pressure, serum lipids, nutrition, physical

activity, and alcohol intake) for the assessment of absolute cardiovascular disease risk (National Vascular Disease Prevention Alliance 2012).

While the preceding research relates to adults, childhood overweight/obesity is also a predictor of increased mortality, primarily as a result of its association with increased cardiovascular risk. For instance, Franks et al. (2010) found that the mortality rate from endogenous causes over a 24-year period for children in the highest BMI quartile was more than twice that of children in the lowest BMI quartile. Another study reported that, compared to their lean counterparts, male adolescents who were classified as overweight experienced a relative risk of 2.3 for mortality from coronary heart disease in the 55-year follow-up period (Must et al. 1992). Highlighting the importance of interventions for childhood obesity, the incidence of cardiovascular risk factors in obese children who become nonobese by adulthood may be comparable to that of individuals who were never obese (Juonala et al. 2011).

There are multiple and complex pathways through which excess body fat is thought to influence cardiovascular health (for an overview see, e.g., Eckel et al. 2005; Gustafson 2010; Lau et al. 2005; Van Gaal et al. 2006). Research suggests that obesity contributes to elevated cardiovascular disease risk both independently and through the development of other cardiovascular disease risk factors (Caterson et al. 2004). Regarding the latter, overweight and obesity result in adverse metabolic effects leading to hypertension, dyslipidemia (i.e., increased levels of triglycerides, small low-density lipoprotein [LDL] particles, and very low-density lipoprotein [VLDL] cholesterol, as well as reduced levels of high-density lipoprotein [HDL] cholesterol), and insulin resistance, all of which are risk factors for coronary heart disease and stroke (WHO 2011). While adipose tissue was traditionally conceptualized as a passive depository for triglycerides and a store for excess free fatty acids to be released as needed, it is now known to be an active endocrine organ (Lau et al. 2005). The increased adipose tissue mass of obesity (especially abdominal obesity) secretes elevated levels of numerous bioactive molecules (e.g., interleukin-6 [IL-6] and tumor necrosis factor-α [TNF-α]) and can impede the secretion of others (e.g., adiponectin), thereby having a negative impact on cardiovascular health through altered lipid levels, insulin resistance, vascular tone, coagulation, fibrinolysis, inflammation, and atherosclerosis (Van Gaal et al. 2006). Much research continues to be undertaken in order to clarify the complex biological pathways through which overweight and obesity contribute to cardiovascular disease.

Relative to the abundant research on the biological mechanisms underpinning the obesity-cardiovascular disease link, investigating potential psychosocial mechanisms mediating this relationship has been neglected. However, it has been proposed that the stigmatization experienced by obese individuals comprises a chronic stressor that may lead to adverse cardiovascular health outcomes (Gearhardt et al. 2012; Puhl and Latner 2007). Certainly, the widespread experience of stigmatization of obesity has been extensively documented in overweight and obese children, adolescents, and adults, occurring in the media and interpersonal, educational, employment, and healthcare settings. While studies have highlighted

the negative consequences of obesity stigma in terms of body dissatisfaction, low self-esteem, depression, and suicidal ideation and behaviors, preliminary research suggests that the effects of weight-based stigmatization might extend to poorer health outcomes. For instance, one study found that adolescents who reported unfair treatment primarily related to their body weight or physical appearance experienced elevated ambulatory blood pressure, even after controlling for potential confounding variables (e.g., BMI and resting blood pressure levels), than those adolescents who did not endorse body weight or physical appearance as the main reason for their mistreatment (Matthews et al. 2005). Indeed, no other basis for mistreatment (e.g., ethnicity or gender) demonstrated a significant link with blood pressure. Given preliminary findings of this kind, further investigation regarding the mediating role of weight-based stigmatization in the relationship between obesity and cardiovascular health is clearly warranted.

The Management of Overweight and Obesity: Behavioral Interventions

Weight loss in overweight and obese individuals is recommended in national guidelines for the management of cardiovascular disease risk, either through lifestyle interventions alone (for those with a low cardiovascular disease risk) or in combination with blood pressure and lipid-lowering pharmacotherapy (for those with a moderate or high cardiovascular disease risk) (National Vascular Disease Prevention Alliance 2012). It has been claimed that, "achieving a healthy body weight through lifestyle interventions is universally endorsed as the first step in improving cardiovascular health" (Lau et al. 2005, p. H2031). This section will critically evaluate the veracity of this recommendation both in terms of the effectiveness of behavioral weight management programs in achieving (1) weight reduction and (2) improved cardiovascular outcomes for overweight and obese individuals.

The effectiveness of behavioral programs in terms of weight reduction. Behavioral (or lifestyle) interventions are those aimed at assisting overweight or obese individuals to modify their weight control behaviors (i.e., dietary behaviors and physical activity), with the most effective programs entailing a combination of education (e.g., recommended caloric intake, nutritional content, and level of physical activity) and instruction in cognitive and behavioral strategies for changing dietary behaviors and physical activity (Greaves et al. 2011; Kirk et al. 2012; Shaw et al. 2005). These cognitive-behavioral skills include self-monitoring, meal planning, strategies for managing cravings (e.g., stimulus control, "urge surfing," and distraction), strategies for managing social situations that trigger overeating (e.g., assertiveness training), strategies for managing emotional triggers of overeating (e.g., pleasant activity scheduling, relaxation training, and cognitive restructuring), strategies for enhancing motivation for weight control, problem-solving skills, identifying and challenging dysfunctional thoughts that trigger overeating, graded physical activity, and skills specific to weight-loss maintenance

(e.g., identifying a maintenance weight range; engaging in weekly, structured self-review sessions for weight tracking and identifying strategies to assist with reaching one's weight goals; and developing a detailed weight maintenance plan).

There is considerable variability in the content, duration, intensity, type of health professional, and format (individual versus group) of behavioral weight-loss programs, making overall statements regarding their effectiveness difficult. For instance, in the studies on dietary/physical activity education combined with behavior therapy reviewed by Shaw et al. (2005), programs ranged from 1 to 26 weeks, with sessions lasting from 40 to 180 min and conducted every second day to monthly. Focusing on behavioral programs entailing 4–6 months of treatment, Fabricatore and Wadden (2006) reported weight losses of 7–10 % of initial body weight at posttreatment. Beyond producing weight loss, behavioral weight-loss programs have also been found to be effective in the treatment of obese individuals with binge eating disorder, resulting in comparable binge eating remission rates to the best established treatment for this disorder (Grilo et al. 2011).

Unfortunately, the success of behavioral programs in yielding weight losses in overweight and obese adults has not extended to the maintenance of these weight losses over time. In general, individuals regain approximately 30–50 % of their lost weight in the year following a lifestyle intervention, and many will regain all of their lost weight over the subsequent 5 years (Fabricatore and Wadden 2006). Thus, weight-loss maintenance is a critical challenge of lifestyle treatments for overweight and obese adults.

There have been numerous responses to this challenge, entailing various modifications to standard behavioral programs in an attempt to enhance weight-loss maintenance. These have included, for instance, relapse prevention training (Perri et al. 1984), increasing social support for weight control by forming self-help groups with peers managing their weight (Perri et al. 1987), providing financial incentives or prepackaged meals (Jeffery and Wing 1995), and emphasizing physical activity (Wing 1999). Yet the long-term outcome data (from the few studies assessing weight-loss maintenance at least 12 months after treatment contact has ceased) are disappointing, with treatment cessation followed by inevitable weight regain. For example, at 12- to 18-month follow-up assessments, relapse prevention training was found to result in 65 % of lost weight being regained (Perri et al. 1984), the use of peer self-help groups for social support resulted in 50 % of lost weight being regained (Perri et al. 1987), prepackaged meals resulted in 62 % of lost weight being regained (Jeffery and Wing 1995), the use of financial incentives resulted in 71 % of lost weight being regained (Jeffery and Wing 1995), and only a minority of interventions that addressed physical activity as well as diet resulted in significant improvements in weight-loss maintenance relative to interventions focused on diet alone (Wing 1999).

In one of the few weight-loss maintenance interventions to be based on a theoretical understanding of the mechanisms underpinning weight regain, Cooper et al. (2010) theorized that growing disappointment regarding the outcomes of engaging in arduous weight control behaviors (e.g., failing to achieve a marked change in appearance) eventually results in abandoning these behaviors and hence

weight regain. Based on this conceptualization, their CBT weight-loss program included a component in which patients were assisted to value more modest weight losses and to use cognitive-behavioral techniques to achieve desired outcomes (e.g., improved body image) irrespective of weight changes. Treatment entailed 24 sessions over a 44-week period. While treatment resulted in a significant mean weight loss of 9 % of initial weight, this was followed by weight regain over the follow-up period. Specifically, by the 12-month follow-up, patients had regained 59 % of their lost weight and by the 36-month follow-up had regained 94 % of their lost weight, with no difference in weight-loss maintenance between the novel treatment and a standard behavioral program.

Thus a substantial body of research attests to the poor maintenance of weight loss in obese adults following treatment by behavioral weight-loss programs. Brownell (2010) summarizes this field of research as follows:

> Obesity has humbled one research group after another. Some of the field's brightest scientists have attempted to subdue obesity by treating it, but now, after decades of work, treatment gains remain small, maintenance is poor, and the field produces effects far below what patients want or expect. (p. 717)

How best to proceed based on this summation of the field has generated some controversy, with four (not necessarily mutually exclusive) discernable views. The first has been to view obesity as a chronic condition, requiring long-term, even lifelong, treatment (Latner et al. 2000; Mauro et al. 2008). There is certainly evidence to support the maintenance of weight losses in obese adults who have participated in extended behavioral programs. Unfortunately, extending treatment beyond the usual 6–12 months of intervention usually only serves to delay (until after treatment ends) rather than prevent weight regain (Perri and Corsica 2002) and can suffer from the limitation of being associated with declining patient attendance (e.g., one study reported an average attendance of 72 % of sessions during the first 6 months of weight-loss treatment but only 49 % over the subsequent 12 months of maintenance treatment) (West et al. 2011). There is some evidence that highly intensive and extended interventions are capable of yielding maintenance of lost weight. In this regard, a unique study found that a six-week day patient program followed by 4 years of weekly sessions (and readmission to the day patient program as needed, with 63 % of patients being readmitted at least once) resulted in weight losses being maintained over the subsequent 10–12-year period (Björvell and Rössner 1985, 1992). However, extended, intensive interventions are limited by the substantial demands (and, indeed, unrealistic demands given the prevalence of obesity) placed on healthcare services.

A second viewpoint is to conclude that behavioral approaches are ineffective for the treatment of obesity and to recommend that this line of psychological research be abandoned to instead focus on prevention (Cooper et al. 2010). Preventative efforts highlight the environmental factors (i.e., the high availability and accessibility of energy-dense foods combined with conditions that encourage sedentary behavior) underpinning the obesity epidemic and, hence, suggest strategies such as

targeting food and physical activity policies in schools and food marketing to prevent weight gain (Brownell 2010; Gearhardt et al. 2012). Yet given the high prevalence of overweight/obesity, and the fact that medical interventions have limitations in the treatment of obesity and also require behavior change, there is still a strong need for developing effective behavioral interventions alongside prevention-oriented research.

Hence, the third view is to encourage innovative approaches in order to develop behavioral weight-loss programs that support long-term weight control while still being realistic and cost-effective solutions translatable to existing healthcare systems. As advocates of this perspective, Jeffery and Levy (2010) state that, "behavioral research specifically on the issue of weight loss maintenance is young, and in our view has barely scratched the surface of possible research questions" (p. 715). Among just some of the innovative lines of research being pursued with the aim of yielding improved weight-loss maintenance in a cost-effective manner are training individuals from the obese person's social network to provide effective weight management support so that continued support is available to the obese person after treatment cessation (Rieger et al. 2014), the use of technological approaches (e.g., text messaging, Internet-based treatment programs, e-mail contact, and prerecorded webinars) that can increase the intensity and duration of interventions without the need for intensive involvement by health professionals (Neve et al. 2010; Svetkey et al. 2008), and, given the finding that intrinsic motivation for weight control predicts weight-loss maintenance (Williams et al. 1996), the use of motivational interviewing (Hardcastle et al. 2013).

The fourth and final response to the data on weight regain following the cessation of behavioral programs is to propose that these outcomes nevertheless have some merit. Specifically, individuals who eventually return to their baseline weight after participating in a behavioral weight-loss program may still weigh less than they would have without treatment given that many adults are prone to weight gain over time. For instance, one study found that Australian adults gained a mean 1.4 kg during a 5-year period, with participants in the 25–34-year age group gaining a mean 3.5 kg over this time (Barr et al. 2006). As Jeffery and Levy (2010) maintain, "we find the idea appealing that in a society where weight gains of half a kilogram per year are normative in adults through much of their life span, stabilization of weight for several years is a good clinical result" (p. 715). It should be noted, however, that it remains to be determined if weight cycling (i.e., weight loss followed by weight regain) itself poses a risk to health, although one study found no increase in the risk of developing hypertension among women who had experienced severe weight cycling in the context of intentional weight loss (Field et al. 1999).

In contrast to the data on obese adults, there is stronger evidence for the effectiveness of behavioral interventions in producing long-term weight-loss maintenance in obese children. Specifically, family-based behavioral programs – in which the eating and physical activity patterns of both the child and parent are targeted, and parents are taught techniques to support behavior change in their children – have been consistently found to be efficacious in the long term

(Epstein et al. 2007). A recent study also reported promising findings for the maintenance of weight loss 2 years after a 16-week cognitive-behavioral program among obese adolescents (Lloyd-Richardson et al. 2012). The greater success of behavioral programs in obese children is likely contributed to by the fact that it is easier to mobilize family support for children, unhealthy eating and physical activity patterns are less entrenched in children, youth are generally more physically active than adults, and weight stabilization (rather than weight loss) may be a sufficient treatment goal given increases in height throughout childhood (Katzmarzyk et al. 2014).

The effectiveness of behavioral programs in terms of improved cardiovascular outcomes. While dissatisfaction with the weight outcomes attained through behavioral programs has been expressed by obese individuals and researchers alike, there is evidence to suggest that such programs can yield noteworthy improvements in medical indices, including cardiovascular disease risk factors (Douketis et al. 2005; Galani and Schneider 2007; Shaw et al. 2005). For instance, the Diabetes Prevention Program demonstrated significant reductions in the incidence of type 2 diabetes in high-risk individuals after they participated in a behavioral weight-loss intervention, namely, the prevention of 58 % of new cases after 4 years (Diabetes Prevention Program Research Group 2002) and 34 % of new cases after 10 years (Diabetes Prevention Program Research Group 2009) relative to the control group. Significant reductions after 10 years were also evident in systolic and diastolic blood pressure, LDL cholesterol, and triglycerides, along with a significant increase in HDL cholesterol; these positive changes in cardiovascular disease risk factors were comparable in the behavioral, medication, and control groups despite the fact that those in the behavioral intervention used significantly less blood pressure and lipid-lowering medication (Diabetes Prevention Program Outcomes Study Research Group 2013). The beneficial effect of a behavioral weight-loss program on weight and cardiovascular disease risk factors has also been found in overweight and obese patients with established type 2 diabetes, both immediately after the 1-year intervention and 4 years later (Look AHEAD Research Group 2007, 2010).

However, these significant reductions in risk factors for the behavioral intervention did not translate to decreased cardiovascular morbidity and mortality compared to the control group after a median follow-up of 10 years (Look AHEAD Research Group 2013). One possible explanation for this unexpected finding is that there was insufficient difference in weight loss between the behavioral and control interventions at the 10-year follow-up (mean weight loss of 6 % of initial body weight versus 3.5 %, respectively) to yield differential rates in cardiovascular events. In addition, the significantly higher use of statins in the control group and medical management during the period following the intervention may have diminished differences in cardiovascular disease end points between the behavioral and control groups.

There has been some research suggesting that behavioral weight-loss programs result in reduced rates of morbidity and mortality. For instance, in a study on older overweight and obese older adults, participation in an 18-month weight-loss

program was associated with a reduced risk of overall mortality (Shea et al. 2010), suggesting that the increased mortality rate associated with weight loss found in some studies on older adults may be due to unintentional (e.g., illness-induced) weight loss (Stevens et al. 2015). In addition, a review reported significantly fewer fatal and nonfatal cardiovascular events for individuals with type 2 diabetes or hypertension following a lifestyle intervention (Ebrahim et al. 2011). Yet, since the reviewed studies included interventions targeting multiple risk factors (i.e., weight loss, diet, physical activity, smoking, alcohol use, stress management, and/or medication compliance), the precise role of weight loss in achieving these reductions in cardiovascular morbidity and mortality remains unknown. Clearly, research is needed to determine whether behavioral weight-loss programs in obese individuals are effective in reducing cardiovascular disease beyond their effects on weight and cardiovascular disease risk factors.

The Management of Overweight and Obesity: Pharmacological and Surgical Interventions

For those obese individuals (or overweight individuals with a BMI $>$ 27 and medical comorbidities) for whom behavioral weight-loss programs alone are ineffective, the addition of weight-loss medications and/or bariatric surgery may be considered (National Health and Medical Research Council [NHMRC] 2013).

Pharmacological interventions. The mechanism of action of obesity medications entails either appetite suppression (e.g., phentermine) or reduced absorption of ingested fat (e.g., orlistat). In their systematic review, Yanovski and Yanovski (2013) reported that, in combination with lifestyle interventions, medications induced additional weight losses relative to placebo of 3–9 % of initial body weight after 1 year. At this time, an estimated 35–70 % of patients treated with medication experienced a clinically meaningful weight loss (i.e., at least 5 % of initial body weight), together with greater reductions in cardiovascular risk factors compared to patients receiving placebo. In adolescents, a meta-analysis found that medication compared to placebo yielded an additional 2–13 % loss of initial body weight after at least 6 months (Czernichow et al. 2010).

However, to date, no weight-loss medication has been shown to significantly reduce cardiovascular morbidity and mortality (Yanovski and Yanovski 2013). Furthermore, the adverse side effects of medications, combined with their modest effects on weight loss, may result in their discontinued use. For example, while orlistat is one of the few obesity medications approved for long-term use (Anthes 2014; NHMRC 2013), few patients continue its use over time. Specifically, less than 10 % of patients prescribed orlistat have been found to take it for at least 1 year, with this medication potentially producing considerable gastrointestinal side effects (Yanovski and Yanovski 2013).

Surgical interventions. Bariatric (weight loss) surgery for obesity is considered when all other measures have emphatically failed (NHMRC 2013). Various surgical procedures entailing modification of the gastrointestinal system have been

utilized, which aim to reduce weight and maintain these weight losses through restriction of food intake (e.g., adjustable gastric banding entails placing a constricting ring around the upper part of the stomach) possibly in combination with malabsorption of food (e.g., along with restricted food intake, gastric bypass results in the lower stomach, duodenum, and first portion of the jejunum being bypassed). Each procedure necessitates postsurgical changes to eating behavior, although these changes are greater for purely restrictive procedures compared to those with a malabsorption component. Hence, behavioral techniques for assisting obese patients to alter their eating behavior are also essential in the surgical context. This assistance is particularly important for patients who engage in binge eating and other forms of disordered eating, with postsurgical disordered eating a robust predictor of significantly lower weight losses (Colles et al. 2008; Niego et al. 2007).

Bariatric surgery has been consistently found to result in greater weight-loss than nonsurgical interventions (Colquitt et al. 2009) and to produce substantial weight loss in obese adults. One study reported the loss of 20–32 % of initial body weight (depending on the type of procedure) 1–2 years after surgery and, importantly, given the challenges of weight-loss maintenance, losses of 14–25 % of baseline weight over a 10-year period (Sjöström et al. 2007).

In addition to the large and sustained weight losses that can be attained by obese adults following bariatric surgery, there are also improvements in cardiovascular disease risk factors, including significant reductions in hypertension and improvements in lipid profiles, some of which remain unchanged after 10 years (Sjöström et al. 2007). As is the case with research on behavioral weight-loss programs and pharmacotherapy for obesity, studies evaluating the effects of surgery on cardiovascular events are lacking but the preliminary findings are promising (for a systematic review and meta-analysis, see Kwok et al. 2014). For example, one study found that, after a median follow-up of 15 years, there was more than a 50 % reduction in cardiovascular deaths in surgical compared to nonsurgical obese patients (Sjöström et al. 2012). There were also significantly fewer first time cardiovascular events (myocardial infarction or stroke) in the surgical patients.

Yet despite the sustained weight loss and subsequent improvements in cardiovascular disease risk factors, morbidity, and mortality evident in surgical patients, bariatric surgery also has several noteworthy limitations. Bariatric surgery is a major surgical intervention that carries a risk of early and late morbidity (which may necessitate a revision or reversal of the procedure) and perioperative mortality. In one study, perioperative complications (such as bleeding, thromboembolism, and abdominal infection) were experienced by 13 % of patients, with 2.2 % of patients requiring reoperation (Sjöström et al. 2007). There were also five deaths (0.25 %) in the 90 days following surgery. Over the subsequent 10-year period, 17–31 % of patients (depending on the type of surgical procedure) required reoperations or reversals. Moreover, the rate of adverse events reported from surgical centers of excellence may be an underestimate of those occurring in the general medical community (NHMRC 2013). There is also the suggestion in the literature that bariatric surgery is associated with an elevated rate of completed suicide

(Peterhänsel et al. 2013). Finally, the expense of surgery is prohibitive in terms of offering a large-scale response to the obesity epidemic.

Conclusion

Despite a substantial research effort, obesity remains a considerable challenge. For the majority of obese individuals, behavioral weight-loss programs and pharmacotherapy result in short-term, modest weight loss, with some evidence of improved cardiovascular disease risk factors but very minimal evidence thus far of reduced cardiovascular morbidity and mortality. Sustained weight loss and improved cardiovascular outcomes have been more solidly documented for obese patients who have undergone bariatric surgery, although this modality is expensive and associated with some risk. The scope and intractable nature of the obesity problem argue for the importance of innovative and integrated efforts aimed at preventing and treating obesity, with shared responsibility for promoting healthy dietary behaviors and physical activity among individuals, interpersonal networks, government agencies, industry, the media, and health, educational, and occupational settings (WHO 2000).

References

Anthes, E. (2014). Treatment: Marginal gains. *Nature, 508*, S54–S56. doi:10.1038/508S54a.

Barr, E., Magliano, D., Zimmet, P., Polkinghorne, K., Atkins, R., Dunstan, D., … & Shaw, J. (2006). *AusDiab 2005: The Australian diabetes, obesity and lifestyle study*. Melbourne: The International Diabetes Institute.

Björvell, H., & Rössner, S. (1985). Long term treatment of severe obesity: Four year follow up of results of combined behavioural modification programme. *British Medical Journal, 291*(6492), 379–382.

Björvell, H., & Rössner, S. (1992). A ten-year follow-up of weight change in severely obese subjects treated in a combined behavioural modification programme. *International Journal of Obesity, 16*(Suppl 2), 623–625.

Brownell, K. D. (2010). The humbling experience of treating obesity: Should we persist or desist? *Behaviour Research and Therapy, 48*, 717–719. doi:10.1016/j.brat.2010.05.018.

Caterson, I. D., Hubbard, V., Bray, G. A., Grunstein, R., Hansen, B. C., Hong, Y., … & Smith, S. C. (2004). Obesity, a worldwide epidemic related to heart disease and stroke. *Circulation, 110,* e476–e483. doi:10.1161/01.CIR.0000140114.83145.59.

Colles, S. L., Dixon, J. B., & O'Brien, P. E. (2008). Grazing and loss of control related to eating: Two high-risk factors following bariatric surgery. *Obesity (Silver Spring), 16*, 615–622. doi:10.1038/oby.2007.101.

Colquitt, J. L., Picot, J., Loveman, E., & Clegg, A. J. (2009). Surgery for obesity. *Cochrane Database of Systematic Reviews,* (2). doi:10.1002/14651858.CD003641.pub3.

Cooper, Z., Doll, H. A., Kawker, D. M., Byrne, S., Bonner, G., Eeley, E., O'Connor, M. E., & Fairburn, C. G. (2010). Testing a new cognitive behavioural treatment for obesity: A randomized controlled trial with three-year follow-up. *Behaviour Research and Therapy, 48*, 706–713. doi:10.1016/j.brat.2010.03.008.

Czernichow, S., Lee, C. M. Y., Barzi, F., Greenfield, J. R., Baur, L. A., Chalmers, J., . . . & Huxley, R. R. (2010). Efficacy of weight loss drugs on obesity and cardiovascular risk factors in obese adolescents: A meta-analysis of randomized controlled trials. *Obesity Reviews, 11,* 150–158. doi:10.1111/j.1467-789X.2009.00620.x.

Diabetes Prevention Program Outcomes Study Research Group. (2013). Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: A report from the DPP Outcomes Study. *Diabetic Medicine, 30*, 46–55. doi:10.1111/j.1464-5491.2012.03750.x.

Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine, 346*(6), 393–403.

Diabetes Prevention Program Research Group. (2009). 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet, 374*, 1677–1686. doi:10.1016/S0140-6736(09)61457-4.

Douketis, J. D., Macie, C., Thabane, L., & Williamson, D. F. (2005). Systematic review of long-term weight loss studies in obese adults: Clinical significance and applicability to clinical practice. *International Journal of Obesity, 29*, 1153–1167. doi:10.1038/sj.ijo.0802982.

Ebrahim, S., Taylor, F., Ward, K., Beswick, A., Burke, M., & Davey Smith, G. (2011). Multiple risk factor interventions for primary prevention of coronary heart disease. *Cochrane Database of Systematic Reviews,* (1). doi:10.1002/14651858.CD001561.pub3.

Eckel, R. H., Grundy, S. M., & Zimmet, P. Z. (2005). The metabolic syndrome. *Lancet, 365*(9468), 1415–1428.

Epstein, L. H., Paluch, R. A., Roemmich, J. N., & Beecher, M. (2007). Family-based treatment, then and now: Twenty-five years of pediatric obesity treatment. *Health Psychology, 26*(4), 381–391.

Fabricatore, A. N., & Wadden, T. A. (2006). Obesity. *Annual Review of Clinical Psychology, 2*, 357–377. doi:10.1146/annurev.clinpsy.2.022305.095249.

Field, A. E., Byers, T., Hunter, D. J., Laird, N. M., Manson, J. E., Williamson, D. F., . . . & Colditz, G. A. (1999). Weight cycling, weight gain, and risk of hypertension in women. *American Journal of Epidemiology, 150*(6), 573–579.

Franks, P. W., Hanson, R. L., Knowler, W. C., Sievers, M. L., Bennett, P. H., & Looker, H. C. (2010). Childhood obesity, other cardiovascular risk factors, and premature death. *New England Journal of Medicine, 362*, 485–493. doi:10.1056/NEHMoa0904130.

Galani, C., & Schneider, H. (2007). Prevention and treatment of obesity with lifestyle interventions: Review and meta-analysis. *International Journal of Public Health, 52*, 348–359. doi:10.1007/s00038-007-7015-8.

Gearhardt, A. N., Bragg, M. A., Pearl, R. L., Schvey, N. A., Roberto, C. A., & Brownell, K. D. (2012). Obesity and public policy. *Annual Review of Clinical Psychology, 8*, 405–430. doi:10.1146/annurev-clinpsy-032511-143129.

Greaves, C. J., Sheppard, K. E., Abraham, C., Hardeman, W., Roden, M., Evans, P. H., . . . & The IMAGE Study Group. (2011). Systematic review of reviews of intervention components associated with increased effectiveness in dietary and physical activity interventions. *BMC Public Health, 11*. Retrieved from http://www.biomedcentral.com/1471-2458/11/119

Grilo, C. M., Masheb, R. M., Wilson, G. T., Gueorguieva, R., & White, M. A. (2011). Cognitive-behavioral therapy, behavioral weight loss, and sequential treatment for obese patients with binge-eating disorder: A randomized controlled trial. *Journal of Consulting and Clinical Psychology, 79*, 675–685. doi:10.1037/a0025049.

Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C. L., & Anis, A. H. (2009). The incidence of co-morbidities related to obesity and overweight: A systematic review and meat-analysis. *BMC Public Health, 9*, 88. doi:10.1186/1471-2458-9-88.

Gustafson, B. (2010). Adipose tissue, inflammation and atherosclerosis. *Journal of Atherosclerosis and Thrombosis, 17*(4), 332–341.

Hardcastle, S. J., Taylor, A. H., Bailey, M. P., Harley, R. A., & Hagger, M. S. (2013). Effectiveness of a motivational interviewing intervention on weight loss, physical activity and cardiovascular disease risk factors: A randomized controlled trial with a 12-month post-intervention

follow-up. *International Journal of Behavioral Nutrition and Physical Activity, 10*. Retrieved from http://www.ijbnpa.org/content/10/1/40

Jeffery, R. W., & Levy, R. L. (2010). Overgeneralization from limited data: A commentary on Cooper et al., 2010. *Behaviour Research and Therapy, 48*, 714–716. doi:10.1016/j.brat.2010.05.016.

Jeffery, R. W., & Wing, R. R. (1995). Long-term effects of interventions for weight loss using food provision and monetary incentives. *Journal of Consulting and Clinical Psychology, 63*(5), 793–796.

Juonala, M., Magnussen, C. G., Berenson, G. S., Venn, A., Burns, T. L., Sabin, M. A., … & Raitakari, O. T. (2011). Childhood adiposity, adult adiposity, and cardiovascular risk factors. *New England Journal of Medicine, 365,* 1876–1885. doi:10.1056/NEJMoa1010112.

Katzmarzyk, P. T., Barlow, S., Bouchard, C., Catalano, P. M., Hsia, D. S., Inge, T. H., … & Yanovski, J. A. (2014). An evolving scientific basis for the prevention and treatment of pediatric obesity. *International Journal of Obesity, 38*, 887–905. doi:10.1038/ijo.2014.49.

Kirk, S. F. L., Penney, T. L., McHugh, T. L. F., & Sharma, A. M. (2012). Effective weight management practice: A review of the lifestyle intervention evidence. *International Journal of Obesity, 36*, 178–185. doi:10.1038/ijo.2011.80.

Kuk, J. L., Katzmarzyk, P. T., Nichaman, M. Z., Church, T. S., Blair, S. N., & Ross, R. (2006). Visceral fat is an independent predictor of all-cause mortality in men. *Obesity (Silver Spring), 14*(2), 336–341.

Kwok, C. S., Pradhan, A., Khan, M. A., Anderson, S. G., Keavney, B. D., Myint, P. K., . . . & Loke, Y. K. (2014). Bariatric surgery and its impact on cardiovascular disease and mortality: A systematic review and meta-analysis. *International Journal of Cardiology, 173*, 20–28. doi:10.1016/j.ijcard.2014.02.026.

Latner, J., Stunkard, A. J., Wilson, G. T., Jackson, M. L., Zelitch, D. S., & Labouvie, E. (2000). Effective long-term treatment of obesity: A continuing care model. *International Journal of Obesity, 24*(7), 893–898.

Lau, D. C. W., Dhillon, B., Yan, H., Szmitko, P. E., & Verma, S. (2005). Adipokines: Molecular links between obesity and atherosclerosis. *American Journal of Physiology - Heart and Circulatory Physiology, 288*, H2031–H2041. doi:10.1152/ajpheart.01058.2004.

Li, T. Y., Rana, J. S, Manson, J. E., Willett, W. C., Stamfer, M. J., Graham, A., … & Hu, F. B. (2006). Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation, 113,* 499–506. doi:10.1161/CIRCULATIONAHA.105.574087.

Lim, S. S., Vos, T., Flaxman, A. D., Danei, G., Shibuya, K., Adair-Rohani, H., … & Ezzati, M. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380,* 2224–2260. doi:10.1016/50140-6736(12)61766-8.

Lloyd-Richardson, E. E., Jelalian, E., Sato, A. F., Hart, C. N., Mehlenbeck, R., & Wing, R. R. (2012). Two-year follow-up of an adolescent behavioral weight control intervention. *Pediatrics, 130*, 281–288. doi:10.1542/peds.2011-3283.

Look AHEAD Research Group. (2007). Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes. *Diabetes Care, 30*, 1374–1383. doi:10.2337/dc07-0048.

Look AHEAD Research Group. (2010). Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: Four-year results of the Look AHEAD trial. *Archives of Internal Medicine, 170*(17), 1566–1575.

Look AHEAD Research Group. (2013). Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *New England Journal of Medicine, 369*, 145–154. doi:10.1056/NEJMoa1212914.

Matthews, K. A., Salomon, K., Kenyon, K., & Zhou, F. (2005). Unfair treatment, discrimination, and ambulatory blood pressure in black and white adolescents. *Health Psychology, 24*, 258–265. doi:10.1037/0278-6133.24.3.258.

Mauro, M., Taylor, V., Wharton, S., & Sharma, A. M. (2008). Barriers to obesity treatment. *European Journal of Internal Medicine, 19*, 173–180. doi:10.1016/j.ejim.2007.09.011.

Must, A., Jacques, P. F., Dallal, G. E., Bajema, C. J., & Dietz, W. H. (1992). Long-term morbidity and mortality of overweight adolescents: A follow-up of the Harvard Growth Study of 1922 to 1935. *New England Journal of Medicine, 327*(19), 1350–1355.

National Health and Medical Research Council. (2013). *Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia*. Melbourne: Author.

National Vascular Disease Prevention Alliance. (2012). *Guidelines for the management of absolute cardiovascular disease risk*. Retrieved from https://strokefoundation.com.au/health-professionals/clinical-guidelines/guidelines-for-the-assessment-and-management-of-absolute-cvd-risk/

Neve, M., Morgan, P. J., Jones, P. R., & Collins, C. E. (2010). Effectiveness of web-based interventions in achieving weight loss and weight loss maintenance in overweight and obese adults: A systematic review and meat-analysis. *Obesity Reviews, 11*, 306–321. doi:10.1111/j.1467-789X.2009.00646.x.

Niego, S. H., Kofman, M. D., Weiss, J. J., & Geliebter, A. (2007). Binge eating in the bariatric surgery population: A review of the literature. *International Journal of Eating Disorders, 40* (4), 349–359.

Perri, M. G., & Corsica, J. A. (2002). Improving the maintenance of weight loss in behavioral treatment of obesity. In T. A. Wadden & A. J. Stunkard (Eds.), *Handbook of obesity treatment* (3rd ed., pp. 357–379). New York: Guilford.

Perri, M. G., Shapiro, R. M., Ludwig, W. W., Twentyman, C. T., & McAdoo, W. G. (1984). Maintenance strategies for the treatment of obesity: An evaluation of relapse prevention training and posttreatment contact by mail and telephone. *Journal of Consulting and Clinical Psychology, 52*(3), 404–413.

Perri, M. G., McAdoo, W. G., McAllister, D. A., Lauer, J. B., Jordan, R. C., Yancey, D. Z., & Nezu, A. M. (1987). Effects of peer support and therapist contact on long-term weight loss. *Journal of Consulting and Clinical Psychology, 55*(4), 615–617.

Peterhänsel, C., Petroff, D., Klinitzke, G., Kersting, A., & Wagner, B. (2013). Risk of completed suicide after bariatric surgery: A systematic review. *Obesity Reviews, 14*, 369–382. doi:10.1111/obr.12014.

Prospective Studies Collaboration. (2009). Body-mass index and cause-specific mortality in 900 000 adults: Collaborative analyses of 57 prospective studies. *Lancet, 373*, 1083–1096. doi:10.1016/SO140-6736(09)60318-4.

Puhl, R. M., & Latner, J. D. (2007). Stigma, obesity, and the health of the nation's children. *Psychological Bulletin, 133*, 557–580. doi:10.1037/0033-2909.133.4.557.

Rexrode, K. M., Carey, V. J., Hennekens, C. H., Walters, E. E., Colditz, G. A., Stampfer, M. J., . . . & Manson, J. E. (1998). Abdominal adiposity and coronary heart disease in women. *Journal of the American Medical Association, 280*(21), 1843–1848.

Rieger, E., Treasure, J., Swinbourne, J., Adam, B., Manns, C., & Caterson, I. (2014). The effectiveness of including support people in a cognitive-behavioural weight loss maintenance program for obese adults: Study rationale and design. *Clinical Obesity, 4*, 77–90. doi:10.1111/cob.12042.

Shaw, K., O'Rourke, P., Del Mar, C., & Kenardy, J. (2005). Psychological interventions for overweight and obesity. *Cochrane Database of Systematic Reviews,* (2). doi:10.1002/14651858.CD003818.pub2.

Shea, M. K., Houston, D. K., Nicklas, B. J., Messier, S. P., Davis, C. C., Miller, M. E., . . .& Kritchevsky, S. B. (2010). The effect of randomization to weight loss on total mortality in older overweight and obese adults: The APAPT study. *Journals of Gerontology Series A: Biological Sciences and medical Sciences, 65,* 519–525. doi:10.1093/Gerona/glp217.

Sjöström, L., Narbro, K., Sjöström, C. D., Karason, K., Larsson, B., Wedel, H., . . . & Carlsson, L. M. (2007). Effects of bariatric surgery on mortality in Swedish obese subjects. *New England Journal of Medicine, 357*(8), 741–752.

Sjöström, L., Peltonen, M., Jacobson, P., Sjöström, C. D., Karason, K., Wedel, H., . . . & Carlsson, L. M. (2012). Bariatric surgery and long-term cardiovascular events. *Journal of the American Medical Association, 307,* 56–65. doi:10.1001/jama.2011.1914.

Snijder, M. B., van Dam, R. M., Visser, M., & Seidell, J. C. (2006). What aspects of body fat are particularly hazardous and how do we measure them? *International Journal of Epidemiology, 35*, 83–92. doi:10.1093/ije/dyi253.

Stevens, J., Bradshaw, P. T., Truesdale, K. P., & Jensen, M. D. (2015). Obesity paradox should not interfere with public health efforts. *International Journal of Obesity, 39,* 80–81. doi:10.1038/ijo.2014.60.

Svetkey, L. P., Stevens, V. J., Brantley, P. J., Appel, L. J., Hollis, J. F., Loria, C. M., . . . & Aicher, K. (2008). Comparison of strategies for sustaining weight loss: The weight loss maintenance randomized controlled trial. *Journal of the American Medical Association, 299,* 1139–1148. doi:10.1001/jama.299.10.1139.

Van Gaal, L. F., Mertens, I. L., & De Block, C. E. (2006). Mechanisms linking obesity with cardiovascular disease. *Nature, 44*, 875–880. doi:10.1038/nature5487.

Wang, Y. C., McPherson, K., Marsh, T., Gortmaker, S. L., & Brown, M. (2011). Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet, 378*, 815–825. doi:10.1016/S0140-6736(11)60814-3.

West, D. S., Gorin, A. A., Subak, L. L., Foster, G., Bragg, C., Hecht, C., . . . & Wing, R. R. (2011). A motivation-focused weight loss maintenance program is an effective alternative to a skills-based approach. *International Journal of Obesity, 35,* 259–269. doi:10.1038/ijo.2010.138.

Williams, G. C., Grow, V. M., Freedman, Z. R., Ryan, R. M., & Deci, E. L. (1996). Motivational predictors of weight loss and weight-loss maintenance. *Journal of Personality and Social Psychology, 70*(1), 115–126.

Wing, R. R. (1999). Physical activity in the treatment of adulthood overweight and obesity: Current evidence and research issues. *Medicine and Science in Sports and Exercise, 31* (11, Suppl 1), S547–S552.

World Health Organization. (2000). *Obesity: Preventing and managing the global epidemic* (WHO Technical Report Series 894). Geneva: Author.

World Health Organization. (2008). *Waist circumference and waist-hip ratio: Report of a WHO expert consultation*. Geneva: Author.

World Health Organization. (2011). *Global status report on noncommunicable diseases 2010*. Retrieved from http://www.who.int/chp/ncd_global_status_report/en/

Yanovski, S. Z., & Yanovski, J. A. (2013). Long-term drug treatment for obesity: A systematic and clinical review. *Journal of the American Medical Association, 311*, 74–86. doi:10.1001/jama.2013.281361.

Part VII

The Summing Up: From Evidence to Practice

Psychocardiology Now and Where the Evidence Promises to Take Us in the Future: A Summing Up

Marlies E. Alvarenga and Don Byrne

Contents

Keywords
Cardiovascular disease (CVD) • Psychocardiology • Cardiac Psychology • Stress, Psychopathology and Cardiovascular Disease • Anxiety • Personality • Psychobiological mechanisms • Psychological management of, patients • Life style of, cardiac patients • Depression

The Evidence Now: Presentations in the *Handbook of Psychocardiology*

The link between heart and mind is now so well established that it can no longer be considered a farfetched speculation; rather there is now a robust body of respectable empirical and clinical evidence which strongly asserts the nature of this relationship

M.E. Alvarenga (✉)
MonashHEART, Monash Cardiovascular Research Centre, Monash Health and Department of Medicine (SCS at Monash), Monash University, Melbourne, VIC, Australia
e-mail: marlies.alvarenga@monash.edu

D. Byrne
ANU Medical School, College of Medicine Biology and Environment, Australian National University, Acton, Canberra, ACT, Australia

ANU Medical School, Research School of Psychology, Australian National University, Acton, Canberra, ACT, Australia
e-mail: Don.Byrne@anu.edu.au

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7_60

as both congruous and complimentary. It is now clear that strong emotional distress, whether in the context of acute or chronic stress or from mental illness, is commonly reciprocated by elevated risk factors for cardiovascular disease (CVD) and increased cardiac morbidity and even cardiac mortality. The *Handbook of Psychocardiology* is the first fully comprehensive volume examining this now accepted heart/mind nexus. The book showcases a unique collaboration between research scientists and clinicians across the fields of behavioral medicine and psychology, neuroscience, cardiology, and psychiatry. It was by bringing together such a seemingly diverse and eclectic mix of scientists and practitioners that we have been able to fully highlight the commonalities and complimentary aspects of this relationship.

In examining the contents of this volume, readers will note that we have categorized the book into six sections. The first section looks at *The Foundations of Cardiac Psychology*. Here the needs and motivations for the *Handbook* are eloquently outlined in chapters "▶ Psychogenesis and Heart Disease Now: The Thinking Heart in Action" and "▶ Cardiac Psychology: Ancient and Modern History", moving from the poetic observations of yesteryear to Esler and Schwarz's journey to the modern day picture of cardiac psychology. This is indeed a journey which takes us from the anecdotal to empirical research and to the origins of behavioral medicine in CVD research. The *Handbook* then moves to provide us with an overview of the principal organ at the center of our exploration, namely, the heart, by giving a detailed outline of its anatomy and mechanics and providing us with an intricate yet gentle introduction to cardiology for the non-cardiologist, which comprehensively covers current trends in cardiology as well as a clinically relevant discussion of cardiovascular disorders.

The seminal work of the Framingham studies, which led to the identification of risk factors, both behavioral (such as a sedentary lifestyle and smoking) and biological (such as hypercholesterolemia, hypertension, and diabetes), has given way to an increased awareness of ways to lower the risk factors responsible for the development of heart disease. The worldwide framework for tobacco control and other public health measures such as collaboration with the food industry are proposed solutions (Reid, chapter "▶ Epidemiology of Cardiovascular Disease") as are such individual approaches as reducing "sitting time" and "screen time" during our day (Vaddadi, chapter "▶ Cardiovascular Risk Factors: Role of Lifestyle"). Evidence suggests that over 80 % of cardiovascular risk factors have a behavioral component (Oldenburg et al., chapter "▶ Changing Lifestyle Behaviors to Improve the Prevention and Management of Cardiovascular Disease"). Close examination of the motivations for taking up and maintaining chronic tobacco consumption is therefore undertaken by looking at the origins of smoking in adolescence (chapters "▶ Cardiovascular Risk Factors: Role of Lifestyle," "▶ Smoking and Cardiovascular Risk: Role of Stress in the Genesis of Smoking Behavior" and "▶ Smoking and Cardiovascular Risk: Role of Personality in Adolescent Smoking"). There is a plethora of work which highlights late adolescence and early adulthood as the most pivotal period in life to develop mental illnesses (AIHW 2003; Rotter and Smith 1995), and it could very well be that it is here that the onset of other behaviors which place the individual at an increased risk of heart

disease is developed also. Interventions to reduce cardiovascular disease risk, such as smoking cessation exercise and dietary change are valuable in lowering CVD risk at any age; however, as Reid (chapter "▶ Epidemiology of Cardiovascular Disease") points out, instituting the "right" lifestyle choices from childhood – or even from conception is likely to have the greatest impact on reducing the long-term burden of this disease. Another well-known problem which begins in youth relates to the use and abuse of alcohol. Lubman and colleagues (chapter "▶ Alcohol and Cardiovascular Risk") highlight the commonly held belief that alcohol can have cardioprotective qualities, yet their research points out that such beliefs are currently inconclusive while the use of even low levels of alcohol might pose a cardiac risk in older adults. The use and abuse of tobacco and alcohol appear to be tied up to heightened levels of stress. In this way, we introduce the second section of the book examining *Stress*, *Psychopathology*, *and Cardiovascular Disease*.

Moksnes and Espnes (chapter "▶ Stress: Concepts, Models, and Measures") give a detailed overview of the concept of "stress" and explanatory models of stress, where stress is seen as the mediating factor in the link between mental processes and the development of atherosclerotic cardiovascular disease, particularly coronary heart disease (CHD). Indeed, the concept of stress is one which is revisited by many authors throughout the *Handbook*. Stress is seen as a trigger, a mediating factor, and as both a precursor and an aftermath of both mental illness and CVD. The stress-health relationship is one of the most active areas in psychosomatic research and has been strongly centered on investigating cardiovascular reactivity in response to mental stress, where exaggerated cardiac reactivity has been associated with the development of hypertension, atherosclerosis, and CVD while blunted or low reactivity has been related to depression and obesity. Phillips (chapter "▶ Stress and Cardiovascular Reactivity") gives evidence of this dynamic by highlighting cutting-edge research which identifies the impact of stress reactivity on pathways leading to the development of heart disease.

The *Handbook* then proceeds to focus on psychopathology by examining the most well-researched mental illness associated with heart disease, namely, clinical depression. It is estimated that by 2020, depression will follow CVD as the leading cause of morbidity and disability worldwide (Murray and Lopez 1996). Major depression is common in those suffering cardiovascular disease, and likewise cardiovascular disease is common in those suffering major depression (Lichtman et al. 2008), and thus understanding the association between these two high prevalence disorders is imperative in ensuring ways of minimizing their potential impact on health worldwide.

Dhar et al. (chapter "▶ Depression and Cardiovascular Disease: Psychobiological Mechanisms") provide an assertive chapter which eloquently defends the role of depression as an independent risk factor for heart disease. Of note here is the epidemiological evidence linking depression to increased mortality in individuals with CHD. These authors then proceed to delineate various explanatory models of this relationship, including behavioral and lifestyle factors, the sympathetic nervous system, platelet function, and the autoimmune and inflammatory systems. Byrne et al. (chapter "▶ Stress, Depression, and Cardiovascular Risk in Children") trace the origins of the stress-depression-CVD relationship to childhood. The LOOK

(Lifestyle of Our Kids) study makes a predictive estimate of risk factors associated with the development of CVD in later life by tracing insulin resistance and fitness deficits to early distress and depression in young children. Olive et al. (chapter "▶ Childhood Stress, Emotional Distress, and Cardiovascular Function in Adolescents") shift the focus from childhood to adolescence by examining the effect of psychosocial stress and depression on endothelial function and the measure of arterial stiffness, both predictive markers of future heart disease. These two chapters highlight the need for primary prevention health strategies at the level of childhood and adolescence, with the message essentially being that looking after the mental well-being of children and adolescents today translates to ensuring future adults are at lower risk of CVD.

At the other end of the lifespan, stress associated with the sense of loss also significantly affects cardiac health. As the proportion of older persons increases, examining the effect of bereavement and its impact on their heart becomes more significant. Bartrop et al. (chapter "▶ Bereavement and the Risk of Cardiovascular Disease") highlight the effect that the loss of a loved one has on the surviving spouse, giving yet again an appreciation of the neurobiological processes and mechanisms associated with one of life's greatest stressors, normally experienced at the later stages of life. This very pertinent chapter highlights the importance of identifying even culturally expected, indeed universal, psychological distress in cardiac practice.

Chapter "▶ Anxiety and Cardiovascular Disease: Epidemiology and Proposed Mechanisms" examines the other main psychiatric disorder associated with cardiac morbidity and mortality, namely, anxiety. Patients with CVD tend to manifest intense anxiety, particularly after recovering from acute cardiac events. Yet the role of anxiety in heart disease has not received as much attention in the literature as has depression. Epidemiological studies indicate that there is an increased risk of sudden death and myocardial infarction in patients experiencing panic anxiety and the pathophysiologic correlates of anxiety appear to contribute logically and casually to an increase in cardiac risk, leading to the appreciation that anxiety disorders might in fact constitute a risk to life. Explanatory mechanisms of cardiac risk once again point to the established link between anxiety and heart disease being mediated by stress and giving way to increased cardiac sensitivity and reactivity. Vaccarino and Bremmer (chapter "▶ Posttraumatic Stress Disorder and Risk of Cardiovascular Disease") elaborate on the anxiety-heart disease relationship by drawing special attention to the role of posttraumatic stress disorder as both a cause and consequence of acute, life-threatening cardiovascular events. They highlight the evidence that individuals with trauma tend to engage in adverse lifestyle behaviors, such as smoking, which can worsen existing heart disease or predispose individuals to the development of cardiac disorders. The pathophysiology of the anxiety/heart disease relationship elaborates on and follows from the proposed explanatory models outlined in chapter "▶ Anxiety and Cardiovascular Disease: Epidemiology and Proposed Mechanisms" earlier. An understanding of the psychobiological mechanisms involved in the development of CVD provides a platform for appreciating the phenomena of sudden cardiac death as seen during and right after experiencing natural disasters of one kind or another. Mulder and Zarifeh

(chapter "▶ Natural Disasters and the Risk of Cardiovascular Disease") discuss acute mental stress in response to the experience of a natural disaster, in the context of it being a trigger for increased sympathetic output and the creation of a hypercoagulable state which leaves coronary artery plaque vulnerable to rupture, thrombosis, and subsequent myocardial infarction or death.

However, it is not only acute stress that puts individuals at risk of cardiac morbidity and mortality. The overview by Bosanac and Castle (chapter "▶ Psychoses and Cardiovascular Disease: The Heart and Mind of the Matter") covers the overrepresentation of CVD in people suffering from psychotic disorders, such as schizophrenia, which are marked by chronic stress sensitivity. As in depression and anxiety disorders, adverse lifestyle behaviors are pronounced in this patient group, highlighting the stress/heart disease relationship once again. For psychotic patients, however, there is also the increased risk to cardiac health from the psychotropic medications given to treat and manage their condition, which can (inter alia) significantly affect their weight. Other risk factors seen in depression, anxiety, and psychosis are disorders of sleep (Noughton, chapter "▶ Disorders of Sleep and Cardiovascular Disease"), their associated effect on the respiratory system, and impact on the heart. By recognizing and addressing sleep problems in stressed patients, we can expect improved clinical outcomes in both mental and cardiac health.

A significant source of stress comes from our workplaces. In industrialized countries the role of work has become increasingly more significant in people's lives over the past century. The workplace has become the environment to which the concept of life's success has shifted. Men and women train most of their childhood, adolescence, and early adulthood to achieve a job with some emphasis on prestige and material reward. Once there, many face competition, bullying, and discrimination as well as the pressure to achieve even further success in their chosen field. Unsurprisingly, there is now emerging research pointing to occupational stress as a significant source of CVD (chapter "▶ Occupational Stress and Cardiovascular Disease").

The demands of work are most notably exemplified in the manifestation of high blood pressure. Esler (Chapter "▶ Psychogenic Hypertension"), quoting Geisbock (1905), writes: *one finds an unusual frequency of* [*hypertension*] *in those who as directors of big enterprises have a great deal of responsibility and demanding jobs, and who, after a long period of mental overwork, became nervous* (Esler, p. 2, chapter "▶ Psychogenic Hypertension"). However, although epidemiological and clinical studies provide increasingly strong support for the notion that behavioral and psychological factors are of importance in the pathogenesis of human hypertension, current standard medical practice still fails to see hypertension as a psychosomatic disorder. Wittstein (chapter "▶ Stress Cardiomyopathy") links the effects of acute psychological stress on cardiac contractile function by providing an overview of stress cardiomyopathy (SCM). Just as in hypertension, SCM appears to be mediated by an excessive stimulation at the level of the sympathetic nervous system. Such stimulation is linked with both depression and anxiety.

But it is not just that mental illness impacts onto the development of CVD. In conditions such as congenital heart disease (CHD), the need for psychological input

post diagnosis is now seen as necessary. Chessa et al. (chapter "▶ Congenital Heart Diseases") and Callus and Quadri (chapter "▶ Psychosocial Aspects of Adults with Congenital Heart Disease") explain that this condition manifests behavioral and psychiatric abnormalities in sufferers, leading these authors to suggest that psychological interventions should be commenced early and ideally, from childhood (chapter "▶ Congenital Heart Diseases"), and should be continued throughout life (chapter "▶ Psychosocial Aspects of Adults with Congenital Heart Disease") to ensure patients feel psychologically well adjusted to their condition. In valvular heart disease (Gooley et al., chapter "▶ The Interaction Between Psychological Health and Valvular Heart Disease: Pathogenesis, Clinical Course, and Treatment"), where the patient is usually older as well as physically and emotionally frail, psychological support and psychotherapeutic interventions, if appropriately applied, can ensure a better quality of care for this cohort. Again, these suggestions are important for improving current clinical practice in cardiac care.

Another condition receiving much attention is that of psychogenic syncope. Vaddadi and Alvarenga (chapter "▶ The Psychosocial Impact of Syncope") review the psychosocial impact of this condition and point that cardiologists need to be mindful of mental status in these patients as a key component in their management. Indeed, the ability to bounce back (resilience) after having experienced an adverse cardiac event is crucially important. Turner and O'Neil (chapter "▶ Psychological Responses to Acute Coronary Syndrome") examine the aftermath of surviving an acute coronary syndrome and outline the role of attitudinal responses as clear indicators of recovery or clinical deterioration. Murphy et al. (chapter "▶ Anxiety, Depression, and Psychological Adjustment After an Acute Cardiac Event") go on to outline important considerations in the screening of depression and anxiety in cardiac patients. Here we appreciate the importance of psychological input in cardiac clinical practice, where elucidating patient's beliefs and understanding around illness assists in modifying any maladaptive beliefs which can act as a barrier to treatment. Of course, being aware of psychological aspects is not merely a matter of achieving clinical end points but it also assists in ensuring a higher quality of life, both general and health related, in cardiac patients. Lazarewicz et al. (chapter "▶ Quality of Life in Survivors of Myocardial Infarction") propose this and highlight the evidence that psychosocial characteristics (such as self-esteem, self-efficacy, dispositional optimism, sense of coherence, and social support) can reliably predict improvements in survivors of myocardial infarction. The importance of quality of life issues in cardiac patients has also been highlighted in patients with implantable cardioverter defibrillators (Sears et al., chapter "▶ Psychological Consultation for Patients with Implantable Cardioverter Defibrillator: Confounding Challenges of Cardiac Disease, Technology, and the Patient Experience") and after cardiac surgery and cardiac transplantation (Ackerman and Shapiro, chapter "▶ Psychological Effects of Invasive Cardiac Surgery and Cardiac Transplantation"). Indeed, it is crucial to ensure that patients who undergo these quite intrusive and invasive procedures feel psychologically adapted on board with their treatment and better focused on their recovery, particularly as postsurgical psychopathology is both conspicuously associated with impaired cognition (Bruce

et al., chapter "▶ Cognitive Impairment After Cardiac Surgery: Confounding Factors and Recommendations for Improved Practice") and also confers significant post-interventional morbidity and mortality.

Our third section *Personality, The Social Environment, and Cardiovascular Disease* begins with Bishop's (chapter "▶ Personality and Cardiovascular Disease: Overview") overview of one of the most contentious issues in the mind/heart link, the issue of the role of personality in the development and progression of CVD. Since Friedman and Rosenman's pioneering proposal of the type A behavior pattern (TABP), as a coronary risk, a causal relationship between an individual's attitude to life and resulting CVD has been better understood. Espnes and Byrne (chapter "▶ Type A Behavior and Cardiovascular Disease") provide a timely review of TABP noting that this construct is still as valid today as it was when first proposed over five decades ago. The concept of anger and hostility is also reviewed (Fernandez and Smith, chapter "▶ Anger, Hostility, and Cardiovascular Disease in the Context of Interpersonal Relationships"), and new therapeutic formulations are proposed to best deal with these emotions which traditionally have been strongly linked to the development of CVD.

Espnes et al. (chapter "▶ Gender Differences in Psychological Risk Factors for Development of Heart Disease") highlight an area which has not received as much attention as it deserves until very recently, and that is the impact of gender on heart disease. This is indeed an issue of women's health that has been neglected by both clinical and investigative medicine. Most women still believe that they are more likely to die from cancer than from heart disease (Tibblin and Orth-Gomer 1998) despite the clear evidence that heart disease is the number one cause of death both in Australian women (NHF 2015) and worldwide (WHO 2013). In a remarkable contribution which examines psychobiological pathogenic pathways to CVD, Orth-Gomer (chapter "▶ Stress and Social Support in Cardiovascular Disease") further highlights the role of gender and the impact of social isolation in the development of CVD. Aside from depression, social isolation is arguably the other universally recognized psychological risk factor for the development of CVD.

Feeling socially isolated, indeed marginalized and disconnected from society, is unfortunately a common experience of refugees. Minas (chapter "▶ Mental Health and Cardiovascular Disease Risk in Refugees") provides a timely and contemporary review of the adverse effects on cardiac health experienced by people who have been forcibly displaced as a result of persecution, conflict, generalized violence, or human rights violations. While a high prevalence of mental disorders is expected in this group, there is also a greater presence of poorer physical health, higher all-cause mortality, and higher cardiovascular mortality than one might find in non-displaced persons matched for cultural background. Once again, stress seems to constitute a central element of this relationship. This chapter highlights the need for health professionals and health agencies as well as governments to appreciate the health issues of refugees and of the socially disadvantaged in our society more generally (Krokstad et al., chapter "▶ Social Disadvantage and Cardiovascular Disease Risk") not only from a humanitarian stance but also from a public health perspective.

In light of the evidence presented in the first three sections of the handbook, the case for a clear psychogenic component to CVD is indeed strong. The fourth section of this book, *Psychology and Cardiovascular Biology – the Linking Mechanisms*, then offers a series of chapters which now go to specific explanatory psychobiological mechanisms for the heart/mind relationship.

There is no doubt whatsoever that the cardiovascular system is under the direct influence of the autonomic nervous system. At times of stress, such as during the fight/flight response, there is acute activation of the sympathetic nervous system (SNS) which normally returns to homeostasis once external stressors have passed. However, chronic SNS activation is associated with initiation of disease processes such as hypertension, atherosclerosis, insulin resistance, and cardiac dysfunction, as may be seen, for example, in left ventricular hypertrophy and diastolic dysfunction. Lambert and Esler (chapter "▶ Role of the Sympathetic Nervous System in Cardiovascular Disease") present evidence for the pivotal role of the SNS in generating cardio-metabolic illness. Examining how hypothalamic and amygdaloid projections induce sympathetic nervous activation, it becomes clear that sustained SNS influences hypothalamic signaling which not only increases glucose production but also insulin resistance, leading to an increase in fat mass and lipolysis (chapter "▶ Role of the Sympathetic Nervous System in Cardiovascular Disease"), which in turn increase the risk of fatal and nonfatal CVD (Levitan et al. 2004).

Keegan and Naumovski (chapter "▶ Insulin Resistance, Glucose Regulation, Obesity, and Mood") further examine this relationship while drawing parallels with the effect depression and its influence on the SNS have on the development of Type II diabetes, itself a powerful risk marker for CVD. Adriaanse and Pouwer (chapter "▶ Diabetes, Depression, and Cardiovascular Risk") also highlight the evidence that depression can lead to cardiovascular complications in people with diabetes, both through behavioral pathways and, again, through biological mechanisms which implicate the role of the SNS. These chapters concur in that where obesity is present, insulin resistance appears to be heightened, in turn influencing hypothalamic signaling, such as can be seen in acute stress, leading to insulin resistance, hyperglycemia, and eventually CVD. Clearly then, psychosocial stress and its immediate psychobiological sequelae appear to be a fundamental aspect mediating the heart/mind link. However, more work needs to be done in expanding our current knowledge of the link between emotion, the development of Type II diabetes, and eventual CVD.

Lambert and Esler (chapter "▶ Role of the Sympathetic Nervous System in Cardiovascular Disease") and Sverrisdottir (chapter "▶ Sympathetic Nerve Activity, Stress, and Cardiovascular Risk") focus on the role of SNS overactivity and its impact on the development of cardiac pathologies, particularly cardiomyopathy. Immune dysregulation, and in particular, inflammation, is another area of focus which can explain the effect that mental illnesses may have on cardiovascular pathology (chapter "▶ Immunology, Inflammation, Mental Disorders, and Cardiovascular Risk"). Baune (chapter "▶ Immunology, Inflammation, Mental Disorders, and Cardiovascular Risk") examines immune dysregulation in clinical depression,

as depression has been strongly associated with raised inflammatory markers, which themselves have been linked to cardiac risk. Inflammation has also been linked to obesity and cardiac pathologies, such as atherosclerosis and thrombus formation. It seems clear then that in the presence of sustained stress, the role of the SNS in inflammatory processes and immune dysregulation are also key players in mechanisms delineating the relationship between brain mechanisms and CVD and open the possibility for anti-inflammatory treatment interventions as remedies for both mental illnesses and CVD.

Of course, undertaking research on the psychobiological mechanisms mediating the heart/mind nexus in humans is challenging since there are limitations with regard to the difficulty of controlling and standardizing people's unique experiences and different backgrounds in strictly experimental paradigms. Animal studies, which control the social environment, allow for partially overcoming these limitations. Nalivaiko et al. (chapter "► Animal Models of Psychogenic Cardiovascular Disorders") examines experimental evidence on the link between psychosocial factors and cardiovascular dysfunction in rodents, focusing on studies which model stress-induced sudden cardiac death, cardiac arrhythmias, stress cardiomyopathy, and psychogenic hypertension. Animal models allow for the investigation of both acute and chronic stress and the different impacts these parameters have on the heart. Their review suggests that acute stress shows neurally mediated increases in SNS activity leading to malignant ventricular arrhythmias, a finding which is clearly in accord with human data (chapters "► Role of the Sympathetic Nervous System in Cardiovascular Disease," "► Sympathetic Nerve Activity, Stress, and Cardiovascular Risk" and "► Immunology, Inflammation, Mental Disorders, and Cardiovascular Risk"). Dealing with an organ as complex as the heart, however, might mean that results of cardiac research need to take into account irregular variations in output parameters of pulse and pressure. Gregson (chapter "► Nonlinear Analyses of Data in Cardiovascular Physiology and Epidemiology") inventively puts forth the case for better understanding the complex dynamics of the heart/mind link by expanding the scope of statistical analyses of cardiac data using the mathematical framework of nonlinear dynamic examinations of cardiac action in response to environmental stress.

Some of the most novel research into the stress-CVD link has focused on examining the association between cardiac sympathetic nerve biology and brain monoamine turnover in panic disorder (PD). This is because PD has been identified as an ideal clinical model to examine this relationship (Esler et al. 2004). In untreated patients with PD, there is evidence that the neuronal reuptake of norepinephrine is impaired, as shown by the overall clearance and transcardiac extraction of norepinephrine and epinephrine from plasma being lower than normal in people with PD, thus indicating a dysfunction at the level of the cardiac norepinephrine transporter (NET; Esler et al. 2004; Marlies E. Alvarenga et al. 2006). Several regulatory determinants coordinate the actions of norepinephrine transporter gene expression, with recent epigenetic evidence suggesting that chromatin-modifying enzymes which regulate NET expression might be implicated in neurocardiology (Bayles and El-Osta, chapter "► Genetics and Epigenetics in Cardiac Psychology").

Cohen-Woods and Harkess (chapter "▶ Gene-Environment Interactions, Stress, and Depression") expand on what might make up the determinants of disease generally, and CVD in particular, by highlighting the role of environmental factors, such as toxic stress, impacting on gene function in those with mental disorders like depression. Thus, when researching cardiac mechanisms which can predispose to the development of heart disease, taking into account environmental factors likely to impact onto gene expression at both the levels of the brain and the heart ensures a more comprehensive understanding of the brain/heart relationship and assists in the development of novel treatment approaches to both mental illnesses and CVD.

Section 5 of the *Handbook* focuses on *The Psychological Management of Patients with Cardiovascular Disease*. In this section the chapters pay attention to both the management of the emotional experience of having CVD, in particular the management of anxiety and depression, issues of adaptation, and the impact of treatment on cardiovascular disease progression and recovery. Jackson et al. (chapter "▶ Psychosocial Interventions for Patients After a Cardiac Event") begin this section by giving an overview which highlights the importance of psychosocial interventions after cardiac events. While anxiety and depression would be considered to be highly prevalent after surviving a cardiac event, these authors argue that neglecting to address depressed mood and social isolation in cardiac rehabilitation has the potential to compromise any gains made in cardiac rehabilitation.

Cardiac rehabilitation programs in Australia last between 6 and 10 weeks, however, the National Heart Foundation of Australia estimates that participation rates are as low as 10–30 % (NHF 2014). This is an alarming figure when we take into account that a third of heart attacks are repeat events, costing the national economy an estimated $8 billion (Deloitte 2011). When considering that undertaking cardiac rehabilitation decreases the likelihood of repeat cardiac events (NHSI 2013), it seems that both patients and health-care providers need to be better informed about the importance of taking part in cardiac rehabilitation programs. A further criticism in Australia is that cardiac programs have only a small "counseling" component to them, which might not be sufficient to address the emergence of significant psychopathology such as major depression or posttraumatic stress disorder. Clarke et al. (chapter "▶ Psychological and Behavioral Contributions to Rehabilitation and Recovery in Heart Disease") highlight these issues and propose a "*wholistic* approach to cardiac rehabilitation" – one that takes into account the thoughts, feelings, and behaviors of the patients to enhance motivation and commitment by learning to adapt to their cardiac event and adopt lifelong changes to enhance the quality of their lives and their overall mental and cardiac health. This "whole person model" integrates the principles of cognitive behavior therapy into a framework of chronic disease management. Worcester (chapter "▶ In-Hospital Management of Psychological Responses to Acute Cardiac Events") also reviews the role of psychology and psychiatry for patients in hospital following acute cardiac events. She points out that anxiety and depression are high prevalence disorders in cardiac wards, both as a consequence of cardiac interventions and also as pre-existing conditions. The role of early detection of depression is highlighted as essential. Again, there is recognition that health professionals need to be aware of

the detrimental effects of significant depression and anxiety on a patient's recovery and that patients are encouraged to attend cardiac rehabilitation programs.

Sood et al. (chapter "▶ Treatment of Anxiety Within the Practice of Cardiology") outline the different psychosocial treatment interventions that can be utilized with anxious cardiac patients. These interventions are also discussed in patients with implantable cardioverter defibrillators (ICDs) in Rosman et al. (chapter "▶ Adding Psychological Intervention to High-Tech Care for Patients with Implantable Cardioverter Defibrillators"). Indeed, anxiety secondary to disease management and fear of ICD shock are among the most common concerns that lead to development and maintenance of psychological distress in these cardiac patients and their families. A list of resources for ICD patients and mental health professionals is also provided at the end of the chapter. Among the most successful psycho-behavioral interventions with cardiac patients with anxiety and depression is the use of mindfulness. Meadows (chapter "▶ Mindfulness- and Meditation-Based Healthcare Approach Implications for Prevention, Detection, and Treatment in Cardiology") has given a captivating account into the intricacies of this intervention in cardiac patients. Indeed readers might find themselves transfixed by the examples of applying mindfulness and meditation approaches in the clinical management of cardiac patients. These psychosocial strategies all aim to assist the cardiac patients to consistently and continuously lower their heightened fight/flight responses through cognitive and behavioral means.

However, psychotropic medication is also often used for this purpose. Beach et al. (chapter "▶ Psychopharmacology in the Treatment of Patients with Cardiovascular Disease") outline the role of psychopharmacology in CVD, both to treat reactive mental illness due to CVD and as a pre-existing aspect in many cardiac patients suffering from mental illness. The chapter provides a detailed account of the impact psychotropic medications have on cardiac processes, and recommendations are given in regard to psychotropic medications used and their safety in cardiac patients. However, just as psychotropic medications can impact cardiac functioning, cardiac medications have also been shown to affect mood. Chapter ▶ Impact of Cardiac Medications on Mood" discusses the effect of β-blockers, cardiac glycosides, and antiarrythmics on the central nervous system and mood expression. Head (chapter "▶ Impact of Cardiac Medications on Mood") tackles this much needed topic in the literature by reviewing the evidence and outlining possible mechanisms of action of cardiac medications, which lead to the development of depression in cardiac patients. He also discusses the role that cardiac medications can play on improving fear states, such as anxiety, aggression, and posttraumatic stress disorder. This lateral way of thinking provides an exciting potential for novel treatment methodologies for mental disorders in people at risk of CVD. The need for further work in this area is therefore apparent and imperative.

The *Handbook*'s final section focuses on *Lifestyle Management in Cardiovascular Disease*, with a focus on prevention and secondary interventions. A key objective of incorporating psychosocial strategies in CVD is to both enhance the quality of life of cardiac patients and prevent the future reoccurrence of cardiac disease and events. Oldenburg et al. (chapter "▶ Changing Lifestyle Behaviors to

Improve the Prevention and Management of Cardiovascular Disease") highlight that up to 80 % of cardiovascular risk factors in the general population are attributable to lifestyle factors. Therefore, it makes logical sense that primary (preventing CVD from occurring) and secondary (reducing the impact of existing CVD and improving its management) prevention interventions would be the most effective way to tackle the challenge of CVD in our communities. However, initiating and sustaining new lifestyle changes is challenging. These authors identify the most significant changes that can impact the course and severity of CVD as nutrition and unhealthy dietary behaviors, physical inactivity, and smoking. A lack of physical activity is one of the most serious behaviors which contributes to the development of CVD, worsens the prognosis of existing CVD, and inhibits successful recovery following a cardiac event. Myers and Gerber (chapter "► Physical Activity and Recovery from Cardiovascular Disease: A Psychological Perspective") outline the challenge of inactivity on the recovery from CVD and point out that this is indeed what makes CVD a disease of the modern world. Malnutrition (involving undernutrition, poor nutrition, being overweight, and obesity) is another major challenge which all of humanity has to work on addressing due to its impact on health and quality of life. While the world has focused on eliminating hunger in the still one fifth of the population, constituting mainly developing countries, wealthier nations are also having to improve nutrition to address a polar burden of poor nutrition which leads to being overweight and obesity. In affluent countries obesity has achieved epidemic proportions. The prevalence of obesity and being overweight has increased steadily and rapidly worldwide, particularly over the last 30 years. In Australia around 63 % of the adult population and 25 % of children are classified as overweight or obese (AIHW 2015). In 2015, 10 % of adults are more obese than a decade ago (ABS 2013). In 2003, overweight and obesity accounted for 7.5 % of the burden of disease in Australia (just 0.3 % less than tobacco), 55 % of diabetes and associated burden, and 20 % of cardiovascular disease (Beggs et al. 2007). Rieger (chapter "► Obesity: Its Relationship with Cardiovascular Disease and Management") examines the relationship of obesity to CVD by focusing on three primary approaches as treatments for obesity, namely, behavioral (lifestyle) weight loss programs, pharmacotherapy, and bariatric surgery. The chapter outlines that the obesity treatment outcome research has thus far elicited pessimistic responses from those looking for a definitive solution to CVD and other diseases where excessive body weight is a risk factor; however, there is optimism in the knowledge that innovative approaches to weight management continue to be developed, and increased multidisciplinary approaches appear to be the best way forward in tackling this issue.

Signposts for Future Research and Practice

The phrase which comes immediately to our minds in summing up the *Handbook of Psychocardiology* then is "Unity in Diversity." It is perhaps a hackneyed phrase, but it is one we think is particularly apt – the confluence of widely diverse

disciplines and research methodologies focused on the unitary goal of explaining and treating (or preventing) CVD. There is no doubt whatsoever – and this is confirmed in many chapters throughout the *Handbook* – that the goal is an important one. The burden of CVD seen worldwide is truly significant, not just as reflected in raw data on morbidity and mortality but also in the experience of personal suffering, long-term disability, the impact which serious illness in individuals has on their families, personal economic hardship and reductions in population productivity, and of course demands on national health service budgets. And so a concerted focus on the emerging linkages between the heart and the mind – a new and evolving approach to the long-existing problem of CVD – presents exciting potentials for growth both in cardiology and in the two sibling disciplines of psychology and psychiatry.

The *Handbook* uncovers a rich mine both of cutting-edge evidence, much of it still new in the journals, and innovative approaches to clinical practice and patient management. But as individual chapters revealed to us their unique compartments of knowledge, recurrent themes emerged which indicated overlapping domains of evidence, findings so consistent with one another that they gave luminous signposts to future research and practice, and so obvious a porosity of disciplinary borders as to fully underscore the essential unity of psychocardiology. And so in no particular order of importance, but in an order more reflecting the organization of the *Handbook*, here briefly is what we have distilled from the scholarly contributions our authors have given to the work.

The epidemiological evidence – and there is now rather a large amount of it – is clear in several respects. The illness burden of CVD worldwide remains alarmingly high, and its demographic representation is broad and pervasive. The role of the historically important risk factors remains undiminished, but a closer examination of the nature of those risk factors suggests that they are often as much to do with how people behave as they are of what is happening at a strictly biological level. Obesity, for example, long known to reflect CVD risk, is as much a function of the behavioral patterns of diet as it is of the functions of the digestive processes and the liver in dealing biologically with what is in the diet. The abuse of tobacco and alcohol, other well-established risk factors for CVD, are purely and simply discretionary human behaviors, albeit with some rather toxic biological consequences. And so it is not surprising that the term *health risk behaviors* is gaining new recognition in the epidemiological quest to further explain rates of CVD in a wide variety of populations. A concerted and continuing research effort not simply on health risk behaviors and their influence on CVD but also very importantly on the role that modification of these behaviors plays in the prevention of CVD would therefore seem to be a self-evident priority.

Mental illness, burden enough on its own, now constitutes an established and indeed a clear, significant, and widely accepted risk factor for CVD. The evidence is unequivocal for some clinical manifestations of anxiety, and particularly for posttraumatic stress disorder, that clinically significant anxiety elevated risk of CVD. The evidence is possibly even more pronounced for clinical depression, where this form of mental illness is now widely accepted as a CVD risk factor of

a similar magnitude to, say, cigarette smoking. And there is emerging evidence, though perhaps somewhat more complex in its nature, that psychosis also constitutes a CVD risk factor. Clearly, the field of mental illness and CVD risk is a field ripe for further investigations of an intensive kind. But there is another issue here. It now challenges clinical psychologists and psychiatrists, traditionally the front line for the diagnosis and treatment of mental illness, to be well aware that their patients may also be at risk of CVD – and to consider referral to cardiologists if there is any indication that this may be the case.

The role of the psychosocial environment – commonly operationalized as stress – in elevating CVD risk has always been just a little controversial, not so much because the case in evidence does not exist for the link but because of the difficulties in measuring stress and its psychosocial antecedents. Some of this controversy has now been resolved with the development of more finely tuned psychometric instruments and in the use of more novel technologies such as stress interview techniques. There is also increasing evidence from technically sophisticated studies both in the field and in the laboratory that stress defined in various ways (exposure to social stressors, difficult cognitive challenges, and the like) can result in significant changes to cardiovascular activity which may be prodromal to cardiac dysfunction. We will note a little further on that the psychobiological links between the mind and heart are now being extensively investigated in more and more sophisticated ways – but this is part and parcel of what now seems very clear, that a continuing investigation into the role of the psychosocial environment in clarifying links between the mind and heart is now very definitely justified.

And on the matter of the psychosocial environment, there is increasing evidence that particular domains of psychosocial stressors constitute particular risks for CVD. One obvious example here is that of the unique stressors inherent in the occupational environment; another confronts the neglected role of gender in determining the varying nature and impact of psychosocial stressors more broadly. It is therefore concerning to us, as we evaluate the evidence here, that the definitive prospective epidemiological study of psychosocial stress and CVD (in any of its clinical manifestations) – a study with a sample size sufficient to endow strong statistical power, using state-of-the-art-measures on all levels, and a long enough follow-up period to allow the emergence of clear outcome variance – has yet to be done. It would be a mammoth undertaking, expensive and time consuming, but it would resolve – one way or another – one of the most longstanding controversies in psychocardiology.

But no association between the mind and the heart, however statistically compelling, can be sustained in the absence of clear, replicable, and ideally causal evidence establishing the psychobiological mechanisms leading from one to the other. The evidence presented in the *Handbook* has indicated not just one but three very plausible and scientifically cogent pathways through which, with the benefit of further accumulating research, this link may be confidently confirmed. The central role of the autonomic nervous system when faced with both acute and chronic stress, or in the presence of psychopathology, is perhaps first and foremost among these. Another is the role of immunology and inflammation, again following the

experience of psychosocial stress or the presence of a mental illness, in laying down the pathophysiological foundations of future clinical CVD. And the third, possibly a little more in its infancy but rapidly developing, addresses the interaction between the psychological context broadly viewed and an individual's genetic makeup, in elevating risk of CVD. The demonstration of causal mechanisms is justifiably seen by many in the area as the linchpin of contemporary research in psychocardiology. Without this, associations between psychological circumstances and clinical events, however tempting at a statistical level, cannot be taken to the higher plane of causal hypotheses. We agree and see much of the future of psychocardiology to rest on continuing research to elucidate and confirm hypothesized causal mechanisms linking the mind with the heart.

Of course, the real value of most areas of medical or psychological science lies with the capacity to take good evidence derived from scrupulously conducted research and direct it to applications which will ultimately benefit person-kind. The rich and diverse substance of psychocardiology lends itself particularly well to this enterprise. With that end point in mind, we enter the realms of what is now called *Translational Medicine*. And so it is fitting that we conclude this chapter with a brief overview of those avenues of translation which are recommended by the evidence that the *Handbook* has reviewed – and we say "brief" advisedly since a good deal of the translational research remains to be done.

In quite recent times, the field of cardiovascular disease generally has seen a recognition not just of the value but of the necessity of translating evidence into best-practice interventions. In a comprehensive account of needs and opportunities facing translational research in CVD, Sipido et al. (2009) suggested the fundamental research strategy as a recursive one, commencing with clinical observation, leading to basic research, from which follows proof of concept, feeding then back again into clinical application and further observation. Lauer and Skarlatos (2010) subtitled a scholarly review of the field of translational research into CVD as ... *moving from bench to bedside and from bedside to community* (p. 929). This latter point – bedside to community – is one we believe to be worth highlighting since the evidence of psychocardiology can clearly inform not only the better management of those with diagnosed CVD or identified risk of CVD in vulnerable populations but also prevention of future CVD among those not yet afflicted with identifiable pathology.

Looking back on the *Handbook*'s presentations, a number of issues stand out for us as worthy of serious attention. First, the origins of CVD – though not necessarily the existence of measurable cardiovascular pathology itself – are to be found as early as in childhood and adolescence. This being so, the foundation for prevention should be focused on these age groups and applied in both the school environment and in the community. The domains of obesity and poor diet, alcohol and tobacco use, and an inadequate pattern of physical exercise (well-recognized health risk behaviors) stand out for attention – and these are so often supported and funded in little more than a perfunctory manner. And even where that focus may be neglected, the evidence clearly points to the efficacy of addressing health risk behaviors among young adults. The default justification for not doing this is

so often that young people do not see the salience of modifying CVD risk at an early age where even early signs of CVD are not present – but the evidence from social psychology tells us quite clearly that these barriers can be overcome if only we were to intelligently apply that evidence. The field of health risk behavior modification and its potential for CVD prevention are just too compelling to be left to drift along.

And then, there is the now incontrovertible evidence linking mental illness – and particularly depression – with elevated risk for CVD. That evidence applies not only to the initial clinical episode of CVD (typically but not always a myocardial infarction) but also to the clinical course of the condition once the acute episode has occurred and passed. Yet we are, as clinicians, not giving sufficient emphasis, we believe, to researching the management of mental illness in the context either of elevated CVD risk or of those patients having already experienced a clinical event of CVD. And this is an area of research which so self-evidently requires more – and better funded – research attention.

Finally, and as we have identified a little earlier, the issue of the psychobiological mechanisms linking the mind with the heart is absolutely central to intervention and patient management. A clearer specification of those mechanisms – and this is well within what we could expect in the very near future, given appropriate attention by high level research of an ongoing kind – has the inescapable potential to provide direct and targeted guidelines for the management of those both with elevated CVD risk and with already manifest clinical CVD. Systematic clinical trials based on evidence coming from research into the psychobiological mechanisms linking the mind and heart do not seem to us to be very far into the future – or at least they should not be.

These are, of course, not the only domains of potential translation into practice which we can see as emerging from the contributions offered in the *Handbook of Psychocardiology*. Our readers will no doubt see more – we have simply identified some meta-themes and we hope that you, the readers of this book, will draw your own links between research and practice. It is our fervent wish, however, that we have at least been able to provide you with the organizational framework, the source material, the wealth of evidence, and so importantly the critical and scholarly accounts which the contributors of individual chapters have offered up, to allow you then to draw your own conclusions and to take those conclusions – if it is appropriate to do so – into your own work as scientists and clinicians.

References

ABS. (2013). Obesity and overweight. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4338.0~2011-13~Main%20Features~Overweight%20and%20obesity~10007. Accessed 7 Aug 2015.

AIHW. (2015). Overweight and obesity. http://www.aihw.gov.au/overweight-and-obesity/. Accessed 3 Aug 2015.

Alvarenga, M. E., Richards, J. C., Lambert, G., & Esler, M. (2006). Psychophysiological mechanisms in panic disorder: A correlative analysis of noradrenaline spillover, neuronal

noradrenaline reuptake, power spectral analysis of heart rate variability and psychological variables. *Psychosomatic Medicine, 68*, 8–16.

Australian Institute of Health and Welfare (AIHW). (2003). *Australia's young people: Their health and wellbeing*. Canberra: AIHW.

Begg, S., Vos, T., Barker, B., Stevenson, C., Stanley, L., & Lopez, A. (2007). *The burden of disease and injury in Australia 2003*. Canberra: Australian Institute of Health and Welfare. PHE 82.

Deloitte Access Economics. (2011). *ACS in perspective: The importance of secondary prevention*. Canberra: Deloitte Access Economics Pty Ltd.

Esler, M., Alvarenga, M., Lambert, G., Kaye, D., Hastings, J., Jennings, G., Morris, M., Schwartz, R., & Richards, J. (2004). Cardiac sympathetic nerve biology and brain monoamine turnover in panic disorder. *Annals of the New York Academy of Sciences, 1018*, 505–514.

Geisbock, F. Cited in Julius, S., & Esler, M., (Eds.). (1905). *The nervous system in arterial hypertension* (p. xii). Springfield: Charles C Thomas.

Lauer, M. S., & Skarlatos, S. (2010). Translational research for cardiovascular diseases at the National Heart, Lung and Blood Institute: Moving from bench to bedside and from bedside to community. *Circulation, 121*, 929–933.

Levitan, E. B., Song, Y., Ford, E. S., & Liu, S. (2004). Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. *Archives of Internal Medicine, 164*, 2147–2215.

Lichtman, J. H., Bigger, J. T., Blumenthal, J. A., Frasure Smith, N., Kauffman, P. G., Lesperance, F., Mark, D. B., Sheps, D. S., Barr Taylor, C., & Froelicher, E. S. (2008). Depression and coronary heart disease: Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation, 118*, 1768–1775.

Murray, C. J. L., & Lopez, A. D. (1996). *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Geneva: WHO.

NHF (2014). Improving the delivery of cardiac rehabilitation in Australia: The Heart Foundation's Cardiac Rehabilitation Advocacy Strategy. Melbourne: National Heart Foundation of Australia.

NHF. (2015). Women and heart disease. http://www.heartfoundation.org.au/your-heart/women-heart-disease/Pages/default.aspx. Accessed July 2015.

NHSI. (2013). *Making the case for cardiac rehabilitation: Modelling the potential impact on readmissions*. Leicester: National Health Service Improvement – Heart.

Rutter, M., & Smith, D. J. (1995). *Psychosocial disorders in young people, time trends and their causes*. Chichester: Wiley.

Sipido, K. R., Tedgui, A., Kristensen, S. D., Pasterkamp, G., Schunkert, H., Wehling, M., Steg, P. G., Eisert, W., et al. (2009). Identifying needs and opportunities for advancing translational research in cardiovascular disease. *Cardiovascular Research, 83*, 425–435.

Tibblin, G., & Orth-Gomer, K. (1998). Women, stress and heart disease: Concluding remarks, Chapter 16. In K. Orth-Gomer, M. A. Chesney, & N. K. Wenger (Eds.), *Women, stress and heart disease*. Mahwah: Lawrence Erlbaum.

WHO. (2013). Women's health: Fact sheet no. 334. http://www.who.int/mediacentre/factsheets/fs334/en/. Accessed Aug 2015.

Index

M.E. Alvarenga, D. Byrne (eds.), *Handbook of Psychocardiology*,
DOI 10.1007/978-981-287-206-7