Ihor Gussak · Charles Antzelevitch *Editors*
Arthur A.M. Wilde · Brian D. Powell · Michael J. Ackerman
Win-Kuang Shen *Co-Editors*

Electrical Diseases of the Heart

Volume 2: Diagnosis and Treatment

Second Edition

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Ihor Gussak and Charles Antzelevitch (Eds.)

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Editors
Ihor Gussak, MD, PhD, FACC
Ono Pharmaceutical USA
Lawrenceville
NJ, USA

Department of Internal Medicine
University of Medicine and Dentistry
of New Jersey
Robert Wood Johnson Medical School
New Brunswick, NJ
USA

Charles Antzelevitch, PhD, FACC, FAHA, FHRS
Gordon K. Moe Scholar
Masonic Medical Research Laboratory
Utica, NY
USA

Co-Editors
Arthur A.M. Wilde, MD, PhD, FESC, FAHA
Department of Cardiology, Heart Center
Academic Medical Center
University of Amsterdam
Amsterdam, The Netherlands

Michael J. Ackerman, MD, PhD, FACC
Department of Medicine
Division of Cardiovascular Diseases
Department of Pediatric and Adolescent
Medicine
Division of Pediatric Cardiology
Department of Molecular Pharmacology
and Experimental Therapeutics
Mayo Clinic
Rochester, MN, USA

Brian D. Powell, MD
Division of Cardiovascular Diseases
Sanger Heart & Vascular Institute
Charlotte, NC
USA

Win-Kuang Shen, MD
Division of Cardiovascular Diseases
Department of Medicine
Mayo Clinic College of Medicine
Mayo Clinic Arizona
Phoenix, AZ
USA

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We dedicate this book to the thousands of investigators whose collective works have brought us to this exciting juncture in the history of science and medicine and on whose shoulders we stand. We are proud to dedicate this compendium to these pioneers of cardiac electrophysiology as well as to our mentors, collaborators and fellows who have assisted us in advancing the field and last but certainly not least to our families, whose understanding and support permitted us to dedicate the time and effort needed to formulate this text.

Ihor Gussak
Charles Antzelevitch

Foreword

I presented the following "case report" in the preface of the first edition of this book to illustrate the progress in cardiac electrophysiology over a period of 20-odd years. The evolution is still relevant:

She was about 35 years old when she first became my patient in 1975. She had suffered from bouts of a supraventricular tachycardia (SVT) as far back as she could remember. "In the early days," she recalled, "when I was a kid, they would give me something in the emergency room that elevated my blood pressure and damn near tore my head off. What a headache I would get! But a lot of times it didn't work. Then they stuck my head in a bucket of cold water and told me to 'bear down.' Finally, they would give me more digitalis in my vein until I started vomiting. That usually stopped the SVT."

But nothing seemed to prevent recurrences. She was on a full dose of digitoxin and was one of the first to try a β(beta) blocker (propranolol) in the late 1960s. Her episodes were fast, around 220/min, and frightened her terribly, so much so that she would ride the tractor alongside her farmer-husband all day long just to be near him in case she had a recurrence.

Then came one of the first breakthroughs. Gordon Moe had published a "case report" of a dog with probable atrioventricular node reentry (AVNRT), showing that such a tachycardia could be started and stopped by external stimuli. Clinical studies followed (though somewhat belatedly) and replicated such responses in humans. Medtronic developed an implantable pacemaker (5998 RF unit) that was triggered by an external battery-driven stimulator held over the passive receiver to deliver a burst of rapid stimuli to the epicardial electrodes implanted on her right atrium. Magic! She terminated her own SVT with unerring reliability and never precipitated atrial fibrillation. Now a free woman, she no longer needed tractor rides. But she never left her house without the RF generator and always carried a spare battery in her pocket.

Over time she discontinued her medications and gradually stopped coming for return visits because she had complete control of her SVT. About 15 years later she showed up unannounced after one of the wires in her hand held unit fractured and she no longer could stop the SVT. "Could I get her a replacement or send the broken unit for repairs?" she asked. The next day she was in the EP laboratory, had a slow pathway ablation, cure of the AVNRT, and eventual removal of the implanted unit.

This patient benefited from knowledge derived from animal and clinical research, as well as technological discoveries, over a period of some 15–20 years. And hundreds of thousands of patients like her have similarly profited from such advances. The work of basic and clinical scientists continues to uncover complex mechanisms and anatomic sites responsible for these and other arrhythmias, providing understanding ranging from molecular to clinical. Such advances, along with new mapping, imaging and recording modalities, and catheter and ablation innovations, help us toward our goal of translating science into improved patient care. We are also beginning to understand the pervasive role of genetics, not just for the classic inherited syndromes, but also for polygenic diseases such as sudden death in coronary disease and heart failure, and to manipulate genes for therapy.

Once again this book captures this new information, with sections on basic electrophysiology and heritable channelopathies, primary and secondary electrical diseases and sudden cardiac death, diagnostic methods and tools, risk stratification, and treatment. It is a tour de force, and one that is certain to fulfill the reading tastes and intellectual demands of both researchers and clinicians.

Congratulations to the editors and authors for creating the second edition of this popular work.

Indianapolis, IN *Douglas P. Zipes, MD*

Preface

In this second edition of *Electrical Disease of the Heart*, our goal was to embrace and highlight the explosion of knowledge that our field has witnessed since the publication of the first edition of this book. Building on the success of our first edition, our approach continues to be one of bridging basic and clinical science in an attempt to meaningfully advance our understanding of heart diseases and identify the knowledge gaps that exist.

Each chapter includes up-to-date results of studies aimed at providing an understanding of the electrical function of the heart in health and disease, established and evidence-based knowledge of clinical outcomes, areas of controversy, and future trends. Our goal is to provide a contemporary and succinct distillation of the state of the art. Although many of the chapters are highly sub-specialized, this book is designed for a broad audience, ranging from medical and graduate students to clinicians and scientists.

The book is the result of a collaboration that has brought together the skills and perspectives of researchers, scientists, and clinicians. We are deeply indebted to our associate editors and to all of the authors for their valuable contributions.

Ihor Gussak
Charles Antzelevitch

Contents

†Deceased.

Contributors

Michael J. Ackerman MD, PhD, FACC
Department of Medicine,
Division of Cardiovascular Diseases,
Department of Pediatric and Adolescent Medicine,
Division of Pediatric Cardiology,
Department of Molecular Pharmacology and Experimental Therapeutics,
Mayo Clinic,
Rochester, MN, USA

Anna Baritussio, MD
Division of Cardiology, Department of Cardiac, Thoracic and Vascular Sciences,
Padua Medical School,
Padua, Italy

Cristina Basso, MD, PhD
Cardiovascular Pathology,
Department of Cardiac, Thoracic and Vascular Sciences,
University of Padua Medical School,
Padova, Italy

David M. Benson, MD
Division of Cardiology,
Department of Medicine,
New York Methodist Hospital,
Brooklyn, NY, USA

David H. Birnie, MD
Division of Cardiology,
Department of Medicine,
University of Ottawa Heart Institute,
Ottawa, ON, Canada

Preben Bjerregaard, MD, DMSc
Division of Cardiology, VA Medical Center,
Washington University in St. Louis,
St. Louis, MO, USA

J. Martijn Bos, MD, PhD
Department of Molecular Pharmacology and Experimental Therapeutics,
Mayo Clinic, Rochester, MN, USA

Alfred E. Buxton, MD
Clinical Electrophysiology Laboratory,
Cardiovascular Division,
Department of Medicine,
Beth Israel Deaconess Medical Center,
Harvard Medical School,
Boston, MA, USA

Hugh Calkins, MD
Department of Cardiology, School of Medicine,
Johns Hopkins University School of Medicine,
Baltimore, MD, USA

Department of Cardiology,
The Johns Hopkins Hospital,
Baltimore, MD, USA

Yong-Mei Cha, MD
Cardiovascular Diseases and Internal Medicine,
Mayo Clinic, Rochester, MN, USA

Pow-Li Chia, MBBS, M Med
Department of Cardiology,
St. Vincent's Hospital,
Sydney, NSW, Australia

Sumeet S. Chugh, MD
The Heart Institute,
Cedars-Sinai Medical Center,
Los Angeles, CA, USA

Domenico Corrado, MD, PhD
Division of Cardiology,
Department of Cardiac,
Thoracic and Vascular Sciences,
University of Padua,
Padova, Italy

Ottorino Costantini, MD
The Heart and Vascular
Center Case Western Reserve
University/ MetroHealth Campus,
Cleveland, OH, USA

Lia Crotti, MD, PhD
Department of Molecular Medicine,
University of Pavia and Fondazione IRCCS
Policlinico S. Matteo,
Pavia, Italy
Department of Cardiology,
University of Pavia and Fondazione IRCCS
Policlinico S. Matteo,
Pavia, Italy

Nicolas Derval, MD
Department of Electrophysiology,
CHU de Bordeaux, Hopital Cardiologique
du Haut Leveque,
Pessac CEDEX, France
IHU LIRYC, INSERM, Bordeaux University,
Bordeaux, France

Nynke van Dijk, MD, PhD
Department of General Practice,
Family Medicine, Academic Medical Center,
University of Amsterdam,
Amsterdam, The Netherlands

Benjamin C. Eloff, PhD
Division of Epidemiology,
Office of Surveillance and Biometrics,
Center for Devices and Radiological Health,
United States Food and
Drug Administration,
Silver Spring, MD, USA

Nabil El-Sherif, MD
Division of Cardiology, Department of Medicine,
New York Harbor Veterans Administration
Healthcare System,
Brooklyn, NY, USA

N.A. Mark Estes III, MD
Department of Medicine,
Tufts University School
of Medicine,
Boston, MA, USA
Tufts Cardiac Arrhythmia Center,
Boston, MA, USA

David M. Ficker, MD, FAAN
Department of Neurology,
College of Medicine,
University of Cincinnati Academic
Health Center,
Cincinnati, OH, USA

Vincent M. Figueredo, MD
Cardiovascular Medicine Department,
Institute for Heart and
Vascular Health,
Einstein Medical Center,
Philadelphia, PA, USA

Paul A. Friedman, MD
Division of Cardiovascular
Medicine,
Mayo Clinic, Rochester,
MN, USA

Apoor S. Gami, MD, MSc
Section of Electrophysiology,
Midwest Heart Specialists,
Elmhurst, IL, USA

Yi Gang, MD, PhD
Division of Clinical Sciences,
Cardiovascular Sciences Research centre,
St. George's, University of London,
London, UK

Joseph Gard, MD
Division of Cardiovascular
Diseases,
Mayo Clinic, Rochester, MN, USA

Robin Germany, MD
Cardiovascular Division,
Department of Medicine,
University of Oklahoma,
Oklahoma City, OK, USA

John R. Giudicessi, BA
Divisions of Cardiovascular Diseases
and Pediatric Cardiology,
Departments of Medicine,
Pediatrics, and Molecular Pharmacology &
Experimental Therapeutics,
Windland Smith Rice Sudden Death Genomics
Laboratory, Mayo Clinic,
Rochester, MN, USA

Michael Glikson, MD
Davidai Arrhythmia Center,
Leviev Heart Center,
Sheba Medical Center
and Tel Aviv University,
Tel Hashomer, Israel

Michael H. Gollob, MD
Arrhythmia Research Laboratory,
Division of Cardiology,
Department of Medicine,
University of Ottawa Heart Institute,
Ottawa, ON, Canada

Robert M. Gow, MD
Division of Cardiology,
Department of Medicine,
Children's Hospital of Eastern Ontario,
University of Ottawa,
Ottawa, ON, Canada

Martin S. Green, MD
Division of Cardiology,
Department of Medicine,
University of Ottawa Heart Institute,
Ottawa, ON, Canada

Lorne J. Gula, MD
Division of Cardiology,
University of Western Ontario,
London, ON, Canada

Hiie M. Gussak, MD
Medicine Department,
UMDNJ, Newark, NJ, USA
New Jersey Medical School,
Hackensack University Medical Center,
Hackensack, NJ, USA

Ihor Gussak, MD, PhD, FACC
Ono Pharmaceutical USA,
Lawrenceville, NJ, USA
Department of Internal Medicine
University of Medicine and Dentistry
of New Jersey,
Robert Wood Johnson Medical School,
New Brunswick, NJ, USA

Michel Haïssaguerre, MD
Department of Electrophysiology,
CHU de Bordeaux, Hopital Cardiologique
du Haut Leveque,
Pessac CEDEX, France
IHU LIRYC, INSERM,
Bordeaux University,
Bordeaux, France

Rasmus Havmöller, MD, PhD
Cedars-Sinai Heart Institute,
Los Angeles, CA, USA
Department of Cardiology,
Karolinska University Hospital,
Stockholm, Sweden

Mélèze Hocini, MD
Department of Electrophysiology,
CHU de Bordeaux, Hopital Cardiologique
du Haut Leveque,
Pessac CEDEX, France
IHU LIRYC, Bordeaux University,
Bordeaux, France

Kristin T.L. Huang, MD
Department of Medicine,
Brigham and Women's Hospital,
Boston, MA, USA

Adriana Huertas-Vazquez, PhD
Cedars-Sinai Heart Institute,
Los Angeles, CA, USA

Leonard Ilkhanoff, MD, MS
Division of Cardiology,
Electrophysiology Section,
Department of Medicine,
Northwestern Memorial Hospital,
Northwestern University,
Chicago, IL, USA

Jason T. Jacobson, MD
Division of Cardiology, Columbia University,
Mount Sinai Medical Center,
Miami Beach, FL, USA

Pierre Jaïs, MD
Department of Electrophysiology,
CHU de Bordeaux, Hopital Cardiologique
du Haut Leveque,
Pessac CEDEX, France
IHU LIRYC, INSERM, Bordeaux University,
Bordeaux, France

Roy M. John, MBBS, PhD
Division of Cardiology,
Department of Medicine,
Brigham and Women's Hospital,
Harvard Medical School,
Boston, MA, USA
Medicine Department, Harvard University,
Boston, MA, USA
Cardiac Arrhythmia Service, SH5,
Brigham and Women's Hospital,
Boston, MA, USA

Mark E. Josephson, MD
Cardiovascular Medicine Division,
Harvard Medical School,
Harvard-Thorndike Electrophysiology Institute
and Arrhythmia Service,
Beth Israel Deaconess Medical Center,
Boston, MA, USA

Lilian P. Joventino, MD
Department of Cardiology,
Wentworth-Douglass Hospital,
Dover, NH, USA

Alan H. Kadish, MD
Office of the President,
New York Medical College,
Valhalla, NY, USA

Akihiko Kandori, PhD(Eng), PhD(Med)
Central Research Laboratory,
Life Science Research Center,
Hitachi Ltd., Tokyo, Japan

George J. Klein, MD
Division of Cardiology,
University of Western Ontario,
London, ON, Canada

Sébastien Knecht, MD
Department of Electrophysiology,
CHU de Bordeaux, Hopital Cardiologique
du Haut Leveque,
Pessac CEDEX, France
IHU LIRYC, INSERM, Bordeaux University,
Bordeaux, France

Anneke J. van der Kooi, MD, PhD
Department of Neurology,
Academic Medical Centre,
Amsterdam, The Netherlands

Andrzej S. Kosinski, PhD
Department of Biostatistics and Bioinformatics,
Duke University School of Medicine,
Duke Clinical Research Institute,
Durham, NC, USA

John B. Kostis, MD
UMDNJ-Robert Wood Johnson Medical School,
Cardiovascular Institute,
New Brunswick, NJ, USA

Andrew D. Krahn, MD
Division of Cardiology, Gordon and Leslie Diamond
Health Care Centre,
University of British Columbia,
Vancouver, BC, Canada

Hon-Chi Lee, MD, PhD
Division of Cardiovascular Diseases,
Department of Internal Medicine,
Mayo Medical School,
Mayo Clinic, Rochester, MN, USA

Peter Leong-Sit, MD
Division of Cardiology,
University of Western Ontario,
London, ON, Canada

Emerson H. Liu, MD
Cardiovascular Division, Medicine Department,
Beth Israel Deaconess Medical Center,
Harvard Medical School, Boston, MA, USA

David Luria, MD
Davidai Arrhythmia Center,
Leviev Heart Center,
Sheba Medical Center and Tel Aviv University,
Tel Hashomer, Israel

Frank Marcus, MD
Division of Cardiology,
The University of Arizona,
Sarver Heart Center,
Tucson, AZ, USA

Barry J. Maron, MD
Hypertrophic Cardiomyopathy Center,
Minneapolis Heart Institute Foundation,
Minneapolis, MN, USA

Christina M. Murray, MD
Medicine Department,
Cardiovascular Section,
University of Oklahoma Health Sciences
Center and OU Medical Center,
Oklahoma City, OK, USA

Jan Němec, MD, FACC
Department of Medicine and Clinical Cardiac
Electrophysiology,
Cardiovascular Institute,
University of Pittsburgh,
Pittsburgh, PA, USA

Eyal Nof, MD
Davidai Arrhythmia Center,
Leviev Heart Center,
Sheba Medical Center and Tel Aviv University,
Tel Hashomer, Israel

Louise R.A. Olde Nordkamp, MD
Department of Cardiology,
Heart Failure Research Center,
Academic Medical Center,
University of Amsterdam,
Amsterdam, The Netherlands

Steve R. Ommen, MD
Department of Molecular Pharmacology
and Experimental Therapeutics,
Mayo Clinic, Rochester,
MN, USA

Mai Ots-Rosenberg, MD, PhD
Nephrology Division,
Internal Department,
Tartu University,
Tartu, Estonia

Rod Passman, MD, MSCE
Medicine Department,
Cardiology, Electrophysiology Section,
Northwestern University Feinberg
School of Medicine,
Chicago, IL, USA

Antonio Pelliccia, MD
Department of Medicine,
Institute of Sport Medicine and Science,
Rome, Italy

Yigal M. Pinto, MD, PhD
Heart Failure Research Center,
Heart Center, Academic Medical Center,
Amsterdam, The Netherlands

Bhaskar Purushottam, MD
Cardiovascular Medicine Department,
Institute for Heart and Vascular Health,
Einstein Medical Center,
Philadelphia, PA, USA

Florian Rader, MD, MSc
Cedar Sinai Medical Center,
LA, USA

Robert F. Rea, MD
Internal Medicine,
Cardiovascular Diseases,
Mayo Clinic, Rochester, MN, USA

Kyndaron Reinier, PhD, MPH
Cedars-Sinai Heart Institute,
Los Angeles, CA, USA

Dwight W. Reynolds, MD
Medicine Department,
Cardiovascular Section,
University of Oklahoma Health Sciences Center and OU Medical Center,
Oklahoma City, OK, USA

Ingrid A.W. van Rijsingen, MD
Heart Failure Research Center, Heart Center,
Academic Medical Center,
Amsterdam, The Netherlands

David S. Rosenbaum†, MD
The Heart and Vascular Center Case Western Reserve University/ MetroHealth Campus,
Cleveland, OH, USA

Frédéric Sacher, MD
Department of Electrophysiology,
CHU de Bordeaux, Hopital Cardiologique du Haut Leveque,
Pessac CEDEX, France
IHU LIRYC, INSERM, Bordeaux University,
Bordeaux, France

Rafeeq Samie, MD
Division of Cardiology,
Department of Medicine,
University of Ottawa Heart Institute,
Ottawa, ON, Canada

Hartzell V. Schaff, MD
Cardiovascular Surgery Division,
Surgery Department, Mayo Clinic,
Rochester, MN, USA

Maurizio Schiavon, MD
Department of Social Health,
Center for Sports Medicine and Physical Activity,
Padua, Italy

Peter J. Schwartz, MD
Department of Molecular Medicine,
University of Pavia and Fondazione IRCCS Policlinico S. Matteo,
Pavia, Italy

Department of Cardiology,
Fondazione IRCCS Policlinico S. Matteo,
Pavia, Italy

Rashmi R. Shah, BSc, MBBS, MD, FRCP, FFPM
Rashmi Shah Consultancy Ltd.,
Gerrards Cross,
London, UK

Win-Kuang Shen, MD
Division of Cardiovascular Diseases,
Department of Medicine,
Mayo Clinic College of Medicine,
Mayo Clinic Arizona,
Phoenix, AZ, USA

Wataru Shimizu, MD, PhD
Division of Arrhythmia and Electrophysiology,
Department of Cardiovascular Medicine,
National Cerebral and Cardiovascular Center,
Suita, Osaka, Japan

Division of Cardiology,
Department of Internal Medicine,
Nippon Medical School,
Bunkyo-ku, Tokyo, Japan

Mariachiara Siciliano, MD
Division of Cardiology, Department of Cardiac, Thoracic and Vascular Sciences,
Padua Medical School,
Padua, Italy

Allan C. Skanes, MD
Division of Cardiology,
University of Western Ontario,
London, ON, Canada

Elson L. So, MD
Department of Neurology, Mayo Clinic,
Rochester, MN, USA

Virend K. Somers, MD, PhD
Division of Cardiovascular Diseases and Internal Medicine,
Mayo Clinic College of Medicine,
Rochester, MN, USA

William G. Stevenson, MD
Division of Cardiology,
Department of Medicine,
Brigham and Women's Hospital,
Harvard Medical School,
Boston, MA, USA
Medicine Department,
Harvard University,
Boston, MA, USA

Marco Stramba-Badiale, MD, PhD
Pediatric Arrhythmias Center,
IRCCS Istituto Auxologico Italiano,
Milan, Italy

John M. Stulak, MD
Cardiovascular Surgery Division,
Surgery Department,
Mayo Clinic, Rochester, MN, USA

Rajesh N. Subbiah, MBBS, PhD
Department of Cardiology,
St. Vincent's Hospital,
University of New South Wales,
Darlinghurst, Sydney,
NSW, Australia

Carmen Teodorescu, MD, PhD
Cedars-Sinai Heart Institute,
Los Angeles, CA, USA

David J. Tester, BS
Cardiovascular Diseases Division,
Department of Medicine, Mayo Clinic,
Rochester, MN, USA

Sergio G. Thal, MD
Cardiology Department,
Cardiac Electrophysiology,
Southern Arizona VA Health Care Center,
Tucson, AZ, USA
Medicine Department,
University of Arizona,
Tucson, AZ, USA

Gaetano Thiene, MD, FRCP
Cardiovascular Pathology, Department of
Cardiac, Thoracic and Vascular Sciences,
University of Padua Medical School,
Padova, Italy

Patricia Tung, MD
Cardiology Division, Medicine Department,
Beth Israel Deaconess Medical Center,
Boston, MA, USA

Gioia Turitto, MD
Division of Cardiology,
Department of Medicine,
New York Methodist Hospital,
Brooklyn, NY, USA

Audrey Uy-Evanado, MD
Cedars-Sinai Heart Institute,
Los Angeles, CA, USA

Wouter Wieling, MD, PhD
Department of Internal Medicine,
Academic Medical Center,
University of Amsterdam,
Amsterdam, The Netherlands

Bruce L. Wilkoff, MD
Department of Cardiovascular Medicine,
Heart and Vascular Institute,
Cleveland Clinic,
Cleveland, OH, USA
Medicine Department,
Cleveland Clinic Lerner College
of Medicine, Case Western
Reserve University,
Cleveland, OH, USA

Lance D. Wilson, MD
The Heart and Vascular
Center Case Western Reserve
University/MetroHealth Campus,
Cleveland, OH, USA

Brian C. Wong, MD
Division of Cardiology,
Department of Medicine,
New York Methodist Hospital,
Brooklyn, NY, USA

Satsuki Yamada, MD, PhD
Division of Cardiovascular Diseases,
Department of Medicine,
Molecular Pharmacology and
Experimental Therapeutics,
and Medical Genetics,
Mayo Clinic, Rochester, MN, USA

Raymond Yee, MD
Division of Cardiology,
University of Western Ontario,
London, ON, Canada

Peter J. Zimetbaum, MD
Cardiology Division,
Medicine Department,
Beth Israel Deaconess Medical Center,
Boston, MA, USA

Douglas P. Zipes, MD
Indiana University School of Medicine,
Krannert Institute of Cardiology;
HeartRhythm,
Indianapolis, IN, USA

Part I
Secondary Hereditary and Acquired Cardiac Channelopathies and Sudden Cardiac Death

Arthur A.M. Wilde, Michael J. Ackerman, Charles Antzelevitch, and Ihor Gussak

A.A.M. Wilde, MD, PhD, FESC, FAHA
Department of Cardiology, Heart Center,
Academic Medical Center, University of Amsterdam,
Meibergdreef 9, 1105 AZ,
Amsterdam, The Netherlands

M.J. Ackerman, MD, PhD, FACC
Department of Medicine,
Division of Cardiovascular Diseases,
Department of Pediatric and Adolescent Medicine,
Division of Pediatric Cardiology,
Department of Molecular Pharmacology and
Experimental Therapeutics,
Mayo Clinic, Rochester, MN, USA
e-mail: ackerman.michael@mayo.edu,
haglund.carla@mayo.edu

C. Antzelevitch, PhD, FACC, FAHA, FHRS
Gordon K. Moe Scholar,
Masonic Medical Research Laboratory,
Utica, NY, USA

I. Gussak, MD, PhD, FACC
Ono Pharmaceutical USA,
Lawrenceville, NJ, USA

Department of Internal Medicine,
University of Medicine and Dentistry of New Jersey,
Robert Wood Johnson Medical School,
New Brunswick, NJ, USA
e-mail: igussak@hotmail.com

1
Introduction to Part Three: Cardiac Remodeling

N.A. Mark Estes III

The concept of remodeling of the heart has evolved to include a broad spectrum of inherited or acquired electrical and structural myocardial alterations that are important in the pathogenesis of multiple cardiac arrhythmias [1–3]. The rhythm abnormalities associated with myocardial diseases discussed in this section include those encountered with hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular dysplasia (ARVD), dilated cardiomyopathies (DCM), and skeletal myopathies. Functional electrophysiologic abnormalities frequently develop in association with structural and electrical remodeling with these myocardial diseases [1–3]. Also discussed in this section are functional cardiac alterations that can be inherited as channelopathies, such as the long QT syndromes (LQTS), catecholaminergic polymorphic ventricular tachycardia, Brugada Syndrome, and the early repolarization syndromes. These functional abnormalities of ion channels also can be acquired, as occurs with drug induced QT prolongation and resultant Torsades de Pointes. Brugada type pattern on the electrocardiogram represents another example of an acquired condition induced by pharmacologic agents. These and other abnormalities of electrical activation are considered as forms of electrical remodeling, typically but not always, without significant structural remodeling. Thus when considered from the perspective of cardiac remodeling, the chapters in the section have a common thematic basis. These alterations of electrical depolarization, repolarization and myocardial structure assume clinical significance as they are mechanistically linked to a spectrum of cardiac arrhythmias [1–3]. Understanding the fundamental cellular and molecular mechanisms of remodeling is a requisite to identify novel therapeutic targets for the prevention or treatment of cardiac arrhythmias with the cardiac conditions discussed in this section [1–3].

The remodeling processes associated with HCM, ARVD, dilated cardiomyopathies and cardiac dysfunction associated with skeletal myopathies, as noted in the subsequent chapters are complex and only partially understood [1–4]. Mechanism based prevention and therapy for these conditions, as well as the channelopathies discussed in the ensuing chapters, are not possible with current knowledge [1–4]. Nevertheless, the application of current techniques of cellular and molecular biology has improved the understanding of the multiple factors causing anatomic and functional remodeling [1–4]. It also has resulted in insights into the complex interaction of underlying anatomic or functional substrate abnormalities with triggering mechanisms that determine whether arrhythmias will arise in association with these clinical conditions [1–4].

N.A.M. Estes III, MD
Department of Medicine,
Tufts University School of Medicine,
Boston, MA, USA

Tufts Cardiac Arrhythmia Center, Boston, MA, USA
e-mail: nestes@tuftsmedicalcenter.org

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The mechanistic complexity of cardiac arrhythmia associated structural abnormalities of the myocardium becomes evident in considering our knowledge about abnormal rhythms in HCM [5]. Multiple mechanisms and arrhythmias have been elucidated with this condition [5]. These include reentrant tachycardias and focal automaticity arising from the atria and ventricles in addition to bradyarrhythmias [5]. The fundamental structural abnormalities in HCM are pathologically characterized by myocardium consisting of areas of fibrosis, disruption of cellular architecture, and hypertrophied/dysplastic myocytes, creating an inhomogeneous and unstable, arrhythmogenic electrical milieu [5]. Commonly the condition progresses with ventricular remodeling with dilatation [5]. These conditions are associated with regional inhomogeneity in action potential durations (APDs) and enhanced spatial and temporal dispersion of APDs forming the basis for reentry [5]. Alteration in gap junctions, transmural and transseptal dispersion of repolarization, cell-to-cell coupling, and intracellular calcium homeostasis lead to dyshomogeneity of APDs [5]. Defective repolarization predisposes to delayed and early afterdepolarization, a source of extrasystoles [5]. Small afterpotentials with low amplitude and high frequency in the ventricle represent a local abnormality of impulse propagation and can lead to reentrant arrhythmia [5]. Patients with atrial remodeling due to volume overload from mitral regurgitation and abnormal loading conditions are prone to AF and other supraventricular arrhythmias [5]. Conditions such as electrolyte imbalance from diuretic treatment and QT interval prolongation, and proarrhythmic properties of antiarrhythmic drugs may trigger these arrhythmias [5]. The underlying pathophysiological abnormality leading to SCD ranges from supraventricular tachycardia, sinus arrest, ventricular tachycardia, myocardial ischemia, and acute hemodynamic changes caused by physical or emotional stress [5].

Another common clinical form of cardiac remodeling that has relevance in other myopathic conditions includes that seen with structural and functional remodeling commonly occur in response to pathological myocardial stress. These include pressure and volume overload in the myocardial diseases noted in this section as well hypertension, myocardial infarction, valvular heart disease, and other cardiomyopathies [1–3, 6–8]. Pathological stresses can lead to left-ventricular dilatation and/or wall thickening with all of these conditions [1–3, 6–8]. Clinical insights into the molecular and cellular basis of excitability, conduction and electrical remodeling in heart failure have come from investigation of tachycardia induced canine heart failure [1–3,6–8]. The electrophysiologic remodeling of cells and tissues isolated from failing hearts are characterized by prolongation of action potential duration (APD) and conduction slowing [1–3,6–8]. APD prolongation results principally from K^+ current down regulation and typically leads to arrhythmias by inducing afterdepolarizations [1–3, 6–8]. In human studies and animal models of heart failure, functional down regulation of K^+ currents and alterations in depolarizing Na^+ and Ca^{++} currents and transporters are demonstrated [1–3, 6–8]. Heart failure also profoundly dysregulates Ca^{++} handling genes and proteins, increasing Na^+/Ca^{++} exchange, decreasing sarcoplasmic reticulum Ca^{++}-ATPase and impairing Ca^{++}-release channel (RyR2a) function [1–3, 6–8]. Alterations in intercellular ion channels and extracellular matrix contribute to heterogeneity of APD and conduction slowing [1–3, 6–8]. Systolic heart failure is also associated with upregulation of myocardial fetal and stretched-response genes, and numerous targets and regulators controlling hypertrophy, including phosphoinositol-3-kinase (PI3K), calcineurin, microRNAs and gene mutations are recognized [1–3, 6–8]. Alterations in ion channels, connexins and ion transporters lead to arrhythmogenesis [1–3, 6–8]. The changes in cellular and tissue function are regionally heterogeneous, particularly in hypertrophy [1–3, 6–8].

In models of pacing induced dyssynchronous left ventricular contraction dilation, the electrophysiologic and mechanical abnormalities can be returned toward normal by cardiac resynchronization therapy (CRT) [6–8]. The extent to which this dyssynchrony also alters expression and/or function of ion channels and other gene products critical in cardiac electrophysiology is not fully understood [6–8].

However, emerging evidence indicates that such a relationship exists [1–3, 6–8]. CRT partially reverses the down regulation of K^+ current and improves Na^+ channel gating in heart failure. CRT significantly improves Ca^{++} homeostasis and restores blunted beta-adrenergic receptor responsiveness [1–3, 6–8]. CRT abbreviates prolongation of APD, reduces the left ventricular regional gradient of APD and suppresses development of early afterdepolarizations [1–3, 6–8]. CRT partially restores this electrophysiological remodeling, abnormal Ca^{++} homeostasis, blunted beta-adrenergic responsiveness, and regional heterogeneity of APD, and thus may suppress ventricular arrhythmias and contribute to the mortality benefit of CRT as well as improving mechanical performance [1–3, 6–8].

The counterpart to pacing-induced ventricular failure in experimental animals is tachycardia-induced electrical remodeling of the atria [9]. The concept of electrical remodeling originated from the novel observation that prolonged rapid atrial pacing reduces the atrial refractory period and diminishes or reverses the normal rate adaptation of the refractory period [9]. This remodeling is accompanied by reductions in the densities of the L-type voltage-gated Ca^{++} current, the transient outward K^+ current, and the ultrarapid delayed rectifier K^+ current develop in atrial myocytes [9]. These changes, referred to in isolation as electrical remodeling are coupled with contractile derangements likely related to a reduction in the Ca^{++} inward current [1–3, 9]. Notably rapid atrial pacing and persistent atrial fibrillation can also result in changes in the structure of atrial myocytes structurally similar to those seen in hibernating ventricular myocytes [1–3, 9]. These changes include an increase in cell size, perinuclear accumulation of glycogen, and central loss of sarcomeres associated with fragmentation of the sarcoplasmic reticulum [9]. The extent to which these structural alterations further contribute to the ongoing atrial fibrillation is difficult to identify. As noted for ventricular remodeling the changes in the atrium are potentially reversible [1–3, 9]. The time dependence and the cause–effect relationships between electrical remodeling and structural remodeling are complex and not fully elucidated [1–3, 9]. Conceptually the notion that altered structure begets altered function which then begets altered structure observed in pacing induced AF becomes a common theme with respect to cardiac remodeling and the arrhythmias linked it [1–3, 9].

Remodeling of the atria may be due to AF itself in addition to fibrotic changes associated with aging, and progression of underlying heart disease [10]. The concept of primary prevention of AF with interventions targeting the development of substrate and modifying risk factors for AF has emerged as a result of recent experiments that suggested novel targets for mechanism-based therapies for prevention of atrial remodeling [10]. Upstream therapy refers to the use of non-antiarrhythmic drugs that modify the atrial substrate- or target-specific mechanisms of AF to prevent the occurrence or recurrence of the arrhythmia [10]. Such agents include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, n-3 (ω-3) polyunsaturated fatty acids, and possibly corticosteroids [10]. Animal experiments have compellingly demonstrated the protective effect of these agents against electrical and structural atrial remodeling in association with AF [10]. The key targets of upstream therapy are structural changes in the atria, such as fibrosis, hypertrophy, inflammation, and oxidative stress, but direct and indirect effects on atrial ion channels, gap junctions, and calcium handling is also applied [10]. While there have been no formal randomized controlled studies (RCTs) in the primary prevention setting, retrospective analyses and reports from the studies in which AF was a pre-specified secondary endpoint have shown a reduction in new-onset AF with ACEIs and ARBs in patients with underlying heart disease including left ventricular dysfunction and hypertrophy [10]. There is a decreased incidence of AF mediated by inflammation after cardiac surgery in patients treated with statins and colchicines [10].

Comprehension of cellular and molecular mechanisms of functional and structural remodeling, in both the forward and reverse directions, is a requisite to identify novel therapeutic targets for the prevention or treatment of disturbances of the cardiac rhythm [1–3]. In this respect, we are far from the goal of effective mechanism-based

therapy [1–3]. While considerable progress has been made in elucidating the molecular and cellular pathways that are involved in the complex cardiac remodeling processes, it is evident that understanding of fundamental molecular and cellular mechanisms of arrhythmias remains a challenge [1–3].

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2
Arrhythmias and Arrhythmia Management in Hypertrophic Cardiomyopathy

J. Martijn Bos, Steve R. Ommen, and Michael J. Ackerman

Abstract

Cardiomyopathies are diseases of the myocardium associated with cardiac dysfunction. According to the World Health Organization (WHO) classification, cardiomyopathies are classified either as primary or secondary cardiomyopathies. Based on morphological and functional criteria, heritable cardiomyopathies are classified into four primary categories including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy (RCM). More recently, left ventricular non-compaction (LVNC) syndrome has been recognized as a separate cardiomyopathy. Secondary cardiomyopathies include for example ischemic and hypertensive cardiomyopathy. This chapter focuses solely on HCM, the most common heritable cardiovascular disease (estimated prevalence 1:500) and the most common cause of sudden cardiac death (SCD) in young adolescents and athletes. This chapter discusses HCM's clinical and genetic substrate, genetic testing and screening, and has particular focus on its arrhythmogenic features and the role and indication of the implantable cardioverter defibrillator (ICD) and prevention of SCD.

Keywords

Hypertrophic cardiomyopathy • HCM • Genetics • Sudden cardiac death • ICD

Introduction

Cardiomyopathies are diseases of the myocardium associated with cardiac dysfunction. According to the World Health Organization (WHO) classification, cardiomyopathies are classified either as primary or secondary cardiomyopathies. Based on morphological and functional criteria, heritable cardiomyopathies are classified into four primary categories including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy (RCM). More recently, left ventricular non-compaction (LVNC) syndrome has

J.M. Bos, MD, PhD • S.R. Ommen, MD
Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN, USA

M.J. Ackerman, MD, PhD, FACC (✉)
Department of Medicine, Division of Cardiovascular Diseases, Department of Pediatric and Adolescent Medicine, Division of Pediatric Cardiology, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN, USA
e-mail: ackerman.michael@mayo.edu

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been recognized as a separate cardiomyopathy. Secondary cardiomyopathies include for example ischemic and hypertensive cardiomyopathy. This chapter focuses solely on HCM with particular attention to its arrhythmogenic features.

Definition

HCM is a primary myocardial disease associated with increased cardiac mass and typically, asymmetric but diffuse or segmental left (and occasionally right) ventricular hypertrophy [1]. Genetically, HCM is a heterogeneous disease with mutations identified in over 2727 HCM-susceptibility genes, permitting a genomics-based classification of HCM into myofilament/sarcomeric-HCM, Z-disc-HCM, calcium-handling HCM and energetic/storage disease (metabolic)-HCM (Table 2.1).

Nomenclature

HCM is encompassed by a confusing nomenclature that includes numerous alternative disease labels like hypertrophic obstructive cardiomyopathy (HOCM), familial hypertrophic cardiomyopathy (FHC), and idiopathic hypertrophic subaortic stenosis (IHSS). Since left-ventricular outflow tract obstruction (LVOTO) is not a pre-requisite for the disease process, the entity of unexplained cardiac hypertrophy is referred to as hypertrophic cardiomyopathy (HCM) throughout this chapter [2]. Approximately 25–50 % of patients with HCM do not have obstructive disease.

Epidemiology of HCM and Sudden Cardiac Death (SCD)

HCM is one of the most common heritable cardiovascular diseases with a prevalence of 0.2 % (1:500) in the adult general population across multiple ethnicities based on echocardiographic screening [2–4]. Accordingly, an estimated 500,000 people in the United States have HCM. In developed countries, sudden cardiac death (SCD) causes more deaths than any other medical condition. In the United States for example, nearly 1,000 people die suddenly every day and over 300,000 SCDs occur each year with the majority of these deaths stemming from coronary artery disease involving the middle aged or elderly [5]. However, in cases of SCD in the young, heritable cardiomyopathies like HCM and ARVC represent common identifiable causes [5].

In a population based study of sudden death in young individuals from Australia encompassing >90 % of all sudden death, >50 % were of cardiac origin [6]. In the United States, HCM is the most common cause of SCDs occurring on

Table 2–1. Summary of hypertrophic cardiomyopathy (HCM) susceptibility genes

Gene	Locus	Protein	Frequency (%)[a]
Myofilament HCM			
MYH7	14q11.2–q12	β-myosin heavy chain	15–25
MYBPC3	11p11.2	Cardiac myosin-binding protein C	15–25
TNNT2	1q32	Cardiac troponin T	1–5
ACTC	15q14	α -cardiac actin	Rare
MYH6	14q11.2–q12	α-myosin heavy chain	Rare
MYL2	12q23–q24.3	Ventricular regulatory myosin light chain	Rare
MYL3	3p21.2–p21.3	Ventricular essential myosin light chain	Rare
TNNC1	3p21.1	Cardiac troponin C	Rare
TNNI3	19p13.4	Cardiac troponin I	Rare
TPM1	15q22.1	α-tropomyosin	Rare
TTN	2q24.3	Titin	Rare
Z-disc HCM			
ACTN2	1q42–q43	Alpha-actinin 2	Rare
ANKRD1	10q23.33	Ankyrin repeat domain 1	Rare
CSRP3	11p15.1	Muscle LIM protein	Rare
MYOZ1	10q22.1	Myozenin 1	Rare
TCAP	17q12–q21.1	Telethonin	Rare
VCL	10q22.1–q23	Vinculin/metavinculin	Rare
ZASP/LBD3	10q22.2–q23.3	Z-band alternatively spliced PDZ-motif protein/LIM binding domain 3	Rare
Calcium-handling HCM			
JPH2	20q12	Junctophilin-2	Rare
PLN	6q22.1	Phospholamban	Rare
RYR2	1q42.1–q43	Cardiac ryanodine receptor	Rare
Storage disease HCM			
GLA	Xq22	Alpha-galactosidase A	Rare
FRDA	9q13	Frataxin	Rare
LAMP2	Xq24	Lysosome-associated membrane protein 2	Rare
PRKAG2	7q35–q36.36	AMP-activated protein kinase	Rare

[a]Top 3 HCM-associated genes (*MYH7, MYBPC3* and *TNNT2*) are listed first; from there all genes are listed alphabetically. Estimated disease frequency of these "rare" HCM genes is <1 %

the athletic field (36 %) with no previous warning signs in almost 50 % of these patients [5]. The majority of competition-related SCDs involves males and happens during or immediately following exertion (90 %) [5]. In a large analysis of 1,866 sudden athletic deaths, it was found that the majority (56 %) were of cardiovascular origin with 36 % of CV-deaths caused by HCM and 17 % by coronary abnormalities [7]. The major non-cardiovascular causes of sudden death were blunt force trauma and/or commotio cordis (25 %) [7]. Notably, in Italy, the most common cause of youthful SCD is ARVC, followed by HCM, a difference that might be attributed to genetic predisposition for ARVC or possibly due to the increased primary prevention for HCM due to screening efforts in Italy [5, 8]. For HCM, the overall annual incidence of SCD is ~1 %/year. Many individuals with HCM are destined to a lifelong asymptomatic state [1, 9, 10]. In contrast, the highest risk subset of HCM exhibits a 5–10 %/year risk of SCD and here HCM is truly an "arrhythmogenic malignancy" [11].

This chapter focuses on the current understanding of the molecular pathogenic mechanisms and arrhythmias of HCM, SCD risk stratification, clinical management, athletics in HCM, and screening for HCM.

Diagnosis of HCM

HCM is characterized by unexplained and usually asymmetric, diffuse or segmental hypertrophy associated with a non-dilated and hyperdynamic left ventricle (LV) independent of the presence of LVOTO. Conventional two-dimensional echocardiography is the diagnostic modality of choice for the clinical diagnosis of HCM [12]. Cardiac magnetic resonance imaging (CMR) is however being utilized increasingly for the evaluation and diagnosis of HCM. CMR with delayed gadolinium hyper-enhancement may also indicate the degree of intramyocardial fibrosis present [13, 14]. Echocardiography can further provide details of location, degree of hypertrophy, mitral valve and subvalvular apparatus position and function, and assessment of systolic and diastolic cardiac function [1].

HCM can be subdivided into at least four anatomical/morphological variants based on the shape of the septal myocardium: sigmoidal septal contour, reverse septal curvature, neutral septal contour and apical-HCM hypertrophy (Fig. 2.1) [15, 16]. A left ventricular wall thickness (LVWT) ≤12 mm is typically regarded as normal in adults. LVWT measuring 13–15 mm is generally classified as borderline LVH while measurements ≥15 mm is the absolute cut-off generally accepted for the clinical diagnosis of HCM in an adult (in children, 2 or more standard deviations from the mean relative to body surface are; *z*-score of 2 or more) [12]. However, it should be appreciated that cut-off values will result inevitably in misclassifications. For example, patients can have LVWT well in the normal range but have genetically proven HCM (non-penetrance) while athletes without any genetic perturbations may exceed this 15 mm cut-off value nonetheless.

Clinical Presentation of HCM

The clinical presentation of HCM is often underscored by extreme variability, ranging from an asymptomatic course to that of severe heart failure, arrhythmias and premature and/or SCD. The age of presentation varies from infancy to 90 years of age, with the majority of patients presenting during adolescence and young adulthood [2, 3]. Twenty five percent of patients achieve normal life span (75 year or more) [12, 17]. Most patients with HCM are asymptomatic or only mildly symptomatic and the first manifestation may be SCD [2]. HCM occurs equally in men and women, but may be under diagnosed in women, minorities and underprivileged populations [12, 18].

Symptomatic patients may present with exertional dyspnea, chest pain, and syncope/presyncope. Physical findings of a dynamic systolic ejection murmur with characteristic response to bedside maneuvers and bifid pulse are classic signs indicating LVOTO and obstructive HCM. Progression to "end stage" disease with systolic dysfunction and heart failure occurs in approximately 5 % of patients [19, 20]. Other serious life threatening complications such as embolic stroke and arrhythmias can occur as a consequence of HCM [12].

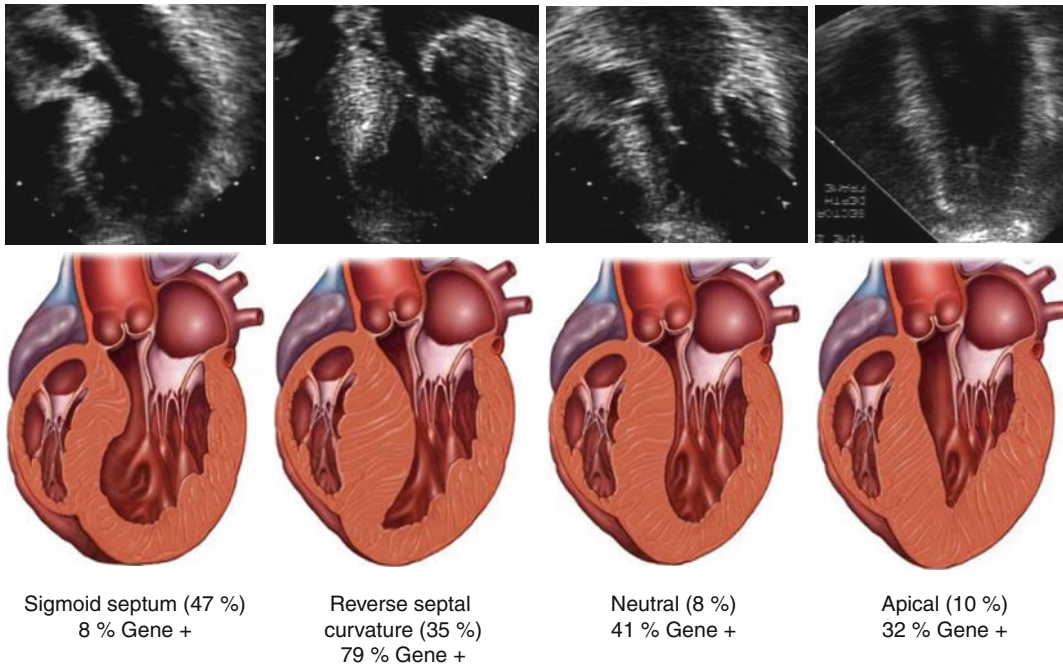

Figure 2–1. Hypertrophic cardiomyopathy septal morphology subtypes and yield of myofilament genetic testing. Starting with the highest yield, the morphologic sub-type classification from left to right sigmoidal contour, reverse curve-, neutral-, and apical-, HCM based on standard echocardiography long-axis views taken at end-diastole. The percentage behind the contour type indicates the relative frequency of that particular morphological subtype seen at Mayo Clinic. The percentage at the *bottom of each panel* indicates the yield of the commercially available genetic test for each particular HCM morphology. Gene+ = presence of myofilament mutation

Arrhythmias and Arrhythmogenic Mechanisms in HCM

The exact mechanism that precipitates SCD in HCM is thus far unclear. HCMs underlying pathophysiological abnormality leading to SCD ranges from supraventricular tachycardia, sinus arrest, ventricular tachycardia, myocardial ischemia, and acute hemodynamic changes caused by physical or emotional stress. The various mechanisms and types of arrhythmias in HCM include ventricular premature beats (VPBs), non-sustained ventricular tachycardia (NSVT) and ventricular tachycardia (VT), ventricular fibrillation (VF) which can lead to SCD. HCM is characterized by a myocardium consisting of areas of fibrosis, disruption of cellular architecture and hypertrophied/dysplastic myocytes, creating an inhomogeneous and unstable, proarrhythmic electrical milieu and possible substrate for SCD [21, 22]. Regional inhomogeneity in action potential duration (APDs) and enhanced spatial and temporal dispersion of APDs form the basis for reentry [23]. Alteration in gap junctions, transmural and transseptal dispersion of repolarization, cell to cell coupling, and intracellular calcium homeostasis leads to inhomogeneity in APDs. Defective repolarization predisposes to delayed and early after depolarization, a source of extrasystole [22, 23].

Patients with atrial enlargement due to valvular pathology or abnormal loading conditions are prone to supraventricular arrhythmias, especially atrial fibrillation (AF). In some patients, supraventricular tachyarrhythmias could trigger ventricular tachyarrhythmias. Associated conditions like electrolyte imbalance secondary to diuretic treatment and QT prolongation, and proarrhythmic properties of antiarrhythmic drugs may precipitate cardiac arrhythmias.

Atrial Fibrillation

AF is the most common arrhythmia observed in HCM [2]. Ultimately, paroxysmal or chronic AF occurs in 20–25 % of patients with HCM, and are

linked with left atrial enlargement and increasing age [2, 24, 25]. Older patients with chronic high LV end diastolic pressures and diastolic dysfunction are prone to chronic sustained AF secondary to dilating left atrium [24]. Young patients with significant outflow tract obstruction and dilated left atrium also have higher propensity to develop paroxysmal AF. AF in HCM is associated with progressive heart failure, stroke and disease progression [24]. Due to the increased risk of systemic thrombo-embolization, the threshold for initiation of anticoagulant therapy (i.e. coumadin) should be low and started after one or two episodes of paroxysmal AF. In some patients, supraventricular tachyarrhythmias could trigger ventricular arrhythmias [26]. However currently, there is insufficient evidence linking AF to SCD in HCM. Nevertheless, AF is associated independently with heart failure-related death and occurrence of fatal and nonfatal stroke. Amiodarone is the drug of choice for prevention of paroxysmal AF, whereas chronic AF can be treated with rate control medications, beta-blockers and verapamil [2]. There is no consensus regarding the various modalities for treatment of AF (i.e. radio-frequency ablation, the surgical MAZE procedure, or implantable atrial defibrillators) [25].

Other SVT

Other arrhythmias include supraventricular tachycardia, AV block and sinus bradycardia. Wolf Parkinson White (WPW) syndrome can also be seen. In fact, the presence of WPW in HCM should prompt the consideration for glycogen storage-HCM mediated by mutations in *PRKAG2* [27].

Ventricular Arrhythmias

Ventricular arrhythmias are an important clinical feature in adults with HCM. In a study of 178 adults with HCM, 90 % had ventricular arrhythmias including premature ventricular contractions (88 %), ventricular couplets (42 %), non-sustained bursts of ventricular tachycardia (NSVT) (31 %) and supraventricular tachycardia (SVT) (37 %) recorded by routine ambulatory (Holter) 24-h ECG monitoring [28].

Bradyarrhythmias

Bradycardia may cause syncope and sudden death, although SCD is less frequently due to bradycardia. Bradycardia was found to be more common in patient with hypertrophy involving the mid-low part of ventricular septum. Some patients with bradyarrhythmias may require back-up pacing. Routine ambulatory monitoring has low positive (9 %) and high negative predictive value (95 %) for SCD [28].

Pathology and Pathogenetics of HCM

By histopathology, HCM is characterized by unexplained, markedly enlarged and bizarre shaped myocytes, myocyte disorientation (myofibrillar disarray) and interstitial fibrosis, likely caused by premature death of hypertrophic muscle cells [2, 4]. The areas of myocyte disarray vary from focal to extensive involvement of myocardium.

Molecular Basis of HCM and Yield of Genetic Testing

HCM is viewed as a "disease of the sarcomere" or more accurately a "disease of the myofilament", with hundreds of mutations identified in the thick, intermediate, and thin cardiac myofilaments that comprise the cardiac sarcomere. However, mutations in proteins of the cardiac Z-disc, proteins involved in calcium handling, and glycogen storage diseases also cause HCM (see Table 2.1). HCM has an autosomal dominant mode of inheritance, although autosomal recessive forms and spontaneous germ-line mutations have also been identified. A familial history of HCM is present in 33–50 % of all index cases [4].

Among various, ethnically diverse cohorts of patients with HCM, *MYH7*, *MYBPC3*, and *TNNT2* are cited as the three most common HCM-associated genes accounting for respectively 15–25, 15–25, and <5 % of all HCM cases (see Table 2.1) [29–32]. Derived from the largest published cohort of unrelated patients with HCM, the Mayo Clinic series reported that nearly 40 % of patients with clinical HCM had an identifiable mutation localizing to one of

eight myofilament-encoding genes that comprise the commercially available HCM genetic test, with the two most common genetic subtypes being MYBPC3- and MYH7-HCM [29–32]. Variable expressivity and age-dependent penetrance has been described in patients with HCM mutations. MYBPC3-HCM, for example, has been associated with delayed onset of hypertrophy [3, 33]. However, in one large series, there was no difference in age at diagnosis between MYBPC3-HCM and MYH7-HCM [29]. Rarely, infants and young children may present with heart failure, and these patients have poor prognosis [3, 34]. SCD can be the tragic sentinel event for HCM in children, adolescents, and young adults. More recently, a large Italian study showed that in long term follow up that patients with an HCM-associated mutation showed an increased risk of combined end-points of cardiovascular death, nonfatal stroke, or progression to heart failure irrespective of genotype involved when compared to those patients with HCM and a negative genetic test [35].

Non-sarcomeric protein missense mutations involving gamma-2-regulatory subunit of AMP-activated protein kinase encoded by *PRKAG2* and lysosome-associated membrane protein 2 encoded by *LAMP2* have been associated with HCM [36]. PRKAG2-HCM is associated with minimal hypertrophy, conduction system defects, glycogen accumulation in myocyte in the absence of characteristic myocyte disarray, ventricular pre-excitation, and progressive conduction disease with heart block [27]. Mutations in *LAMP2* lead to the glycogen storage disease of Danon's syndrome showing HCM with massive hypertrophy and pre-excitation on surface electrocardiogram (ECG) [3, 4]. Besides the aforementioned primary HCM-causing genetic substrates, the variability in expression of these causal genes may be modulated by single nucleotide polymorphisms (SNPs) located in coding or regulatory region of other genes not to mention other acquired factors [23, 37–39].

The yield of genetic testing ranges from about 30–70 % depending on the series of patients with HCM examined. The yield of genetic testing is higher with positive family history, severe hypertrophy, young age at diagnosis, and presence of ICD [31, 32]. Moreover, the yield was most dependent and in multivariate analyses, exclusively dependent upon the manifest septal morphology [15]. For the 8 myofilament-encoding genes that constitute the clinically available HCM genetic test, the yield ranged from <10 % for sigmoidal contour-HCM to nearly 80 % for reverse septal curvature-HCM (see Fig. 2.1) [15]. These two anatomical/morphological subtypes represent the two most common clinical subsets of HCM suggesting a possible role for echo-guided genetic testing.

Although many mutations in genes encoding myofilament, Z-disc or calcium handling proteins have been identified, the exact mechanism by which these cause HCM remains unclear and controversial [40–42]. Initial studies showed that myofilament mutations enhanced sarcomere biophysical properties (hypercontractility), altered cardiac relaxation and calcium signaling and impaired ATP-usage all affecting myocyte contraction and leading to compensatory hypertrophy [43–46]. More recently, with growing knowledge and the identification of mutations in other proteins of the cardiomyocyte, other mechanism have been implicated, such as impaired calcium cycling and sensitivity, increased myocardial fibrosis, disturbed biomechanical stress sensing, and altered energy homeostasis (reviewed in [47]).

SCD Risk Stratification in HCM

HCM accounts for over half of all cases of SCD in young individuals <25 years of age. Overall, the annual mortality is <1 % but reaches 5–10 %/year for the highest risk subset of patients [12]. High risk HCM constitutes a small part of the total HCM population. SCD is more frequent in adolescents and young adults (<35 years old), and could be the first presenting symptom of the disease. No single clinical, morphologic, genetic, or electrophysiological factor has emerged as a single reliable predictor of risk in HCM. However, clinical studies have established five major risk factors for SCD in HCM (Fig. 2.2). Besides these five risk factors, the patients at highest risk of SCD are those that already have experience and survived an out-of-hospital cardiac arrest (OHCA), ventricular fibrillation (VF) and/or sustained VF [9, 10, 12]. From a primary

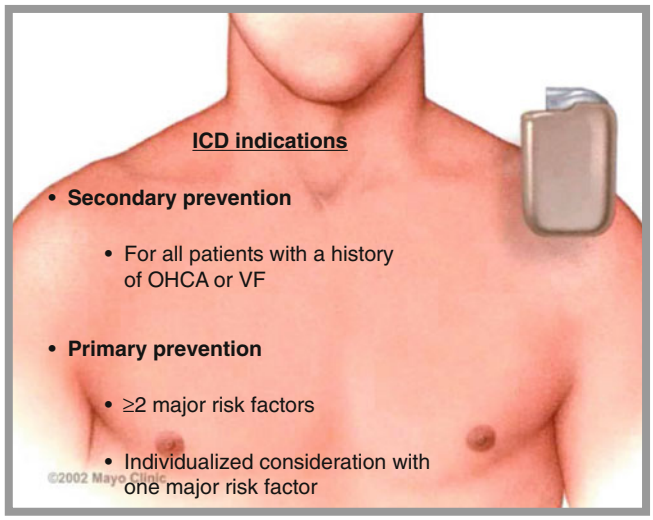

Figure 2–2. Summary of ICD indications and the major risk factors and possible modifying factors in sudden death risk stratification in HCM

prevention perspective, the established major risk factors for SCD (in alphabetic order) are an (1) abnormal blood pressure response during exercise, (2) extreme cardiac hypertrophy, (3) a family history of SCD, (4) non-sustained ventricular tachycardia (NSVT) on 24 h Holter monitoring, and (5) unexplained syncope, especially when occurring during exercise. In addition, gadolinium-derived measurements of fibrosis by CMR, the genetic substrate, and LVOTO may be "disease modifiers" in clinical risk stratification of SCD. SCD risk stratification based solely on the genetic test result should not be performed [48, 49].

Established Major Risk Factors

Abnormal Blood Pressure Response to Exercise

Abnormal blood pressure response to exercise is defined as hypotension or failed blood pressure increase (<20 mmHg) with exercise. A hypotensive blood pressure response during exercise can occurs in over 20 % of a community-based patient cohort with HCM, and is associated with higher incidence of cardiovascular mortality and SCD (odds ratio of 4.5) in patients <50 years old [50].

Extreme Hypertrophy

In one study, the risk of SCD was directly related to septal wall thickness. Hypertrophy of 30 mm or more is associated with a 2 %/year mortality (overall annual mortality for HCM is around 0.5–1 %) in contrast to an extremely low yearly mortality associated with wall thickness <20 mm [51]. There is a direct and continuous relationship between maximal LV thickness and risk of SCD [11, 52]. However, it is possible to have a predisposition for SCD despite minimal hypertrophy [52]. Some investigators have reported massive hypertrophy being a higher risk factor for sudden death in young patients <30 years, but not in middle-aged and older patients [11, 51, 53, 54]. In patients over 60 years old with massive hypertrophy, higher mortality is secondary to heart failure, atrial fibrillation and stroke.

Family History of Sudden Death

A family history of SCD is a major risk factor in risk factor in HCM although it must be recognized that studies have shown extreme variability in the definition of family history of SCD using SCD in a first-degree relative, SCD in ≥2 relatives <40 years, SCD in ≥2 first-degree

relatives <40 years or SCD in ≥1 relative with HCM or SCD in ≥1 close relative without the diagnosis of HCM < HCM [55]. A meta-analysis of family history of SCD showed its hazard ratio to be 1.27 (95 % CI: 1.16–1.38) [55].

Non-sustained Ventricular Tachycardia

Especially in young patients, non-sustained ventricular tachycardia (NSVT) may be a risk factor for SCD [26]. In a study of 531 patients followed for 70 ± 40 months, 20 % of patients showed NSVT. Incidence of NSVT had direct correlation with LV wall thickness and LA diameter. The annual mortality was approximately 4 %/year when NSVT was recorded compared to ~1 % when absent [26]. Although clearly associated with SCD, it must be recognized the definition of NSVT as to number of beats/runs recorded to attribute the risk factor is unclear as the literature uses a wide range of criteria [55].

Unexplained Syncope

Although the exact mechanisms are unclear, syncope in HCM can be caused by neurally mediated responses leading to cardioinhibition and/or vasodepression [20, 56]. In young patients with HCM, syncope with exertion or at rest should be considered a risk factor for sudden death [25, 57].

Other Potential Testing for SCD Risk Stratification

While strongest evidence exists for the major risk factors discussed above, some clinical or genetic risk factors can be included as possible SCD risk modifiers, including delayed enhancement on CMR, genetic substrate or LVOTO. Various other proposed tests for recognition of substrates for SCD, including electrophysiologic study, signal averaged ECG, microvolt T-wave alternans, QT dispersion, ejection fraction, number of ventricular premature beats, heart rate variability, and baroreceptor sensitivity are available, but strong evidence for increased risk of SCD is not available [26]. These tests and clinical history should be repeated periodically to re-stratify the risk as the disease progresses.

Gadolinium Hyper-enhancement by CMR

Gadolinium hyper-enhancement by CMR is a marker of irreversible myocardial injury and fibrosis. Myocardial hyper-enhancement in HCM may indicate areas of replacement fibrosis. In a cohort of 42 patients myocardial hyper-enhancement was found in 79 %. Extent of hyper-enhancement was greater in patients with progressive disease (28.5 % vs. 8.7 %, $p < 0.001$) and in patients with two or more risk factors for SCD (15.7 % vs. 8.6 %, $P = 0.02$) [14]. Over the last few years, multiple studies have now demonstrated a relationship on the presence and/or amount of gadolinium enhancement representing fibrosis and scarring and the risk of SCD or its ICD substrate of appropriate ICD discharges [58–61].

Genetic Testing for SCD Risk

The role of genetic testing in SCD risk stratification for HCM is controversial. One study showed a higher incidence of ECG abnormalities with mutations in Troponin I (99 %), Troponin T (88 %) and Myosin-binding protein C (83 %) as compared to 79 % in other patients [62]. ST-T wave abnormalities were observed more frequently in patients with Troponin T mutation (81 %) compared to 55 and 66 % with Troponin I and Myosin-binding protein C respectively [62]. The ECG might have a significant role in screening of family members of HCM patients, athletes and military recruits [13]. ECG changes may precede phenotypic manifestation on echocardiography especially in young children providing invaluable clinical clue [33, 62–64]. P wave duration (134.5 ms) and P-wave dispersion (>52.5 ms), a marker of intra-atrial and inter-atrial conduction time, has a sensitivity of 90 % + and specificity of 80 % + in predicting AF and LA enlargement [65]. ECG Late potentials have low sensitivity and prevalence in detection of subclinical VT.

Initial genotype-phenotype correlative studies suggested the possibility of specific genotype-phenotype correlations, particularly

specific mutations being associated with a 'malignant' or 'benign' natural history and SCD risk. Some experts consider HCM precipitated by mutations in troponin T and troponin I, tropomyosin, and particular missense mutations (R403Q, R453C, and R719W for example) in the beta-myosin heavy chain as being associated with increased risk of sudden death [66]. However, this association was not seen in other studies and the frequency of specific so-called "malignant mutations" in HCM cohorts is very low (1 %) [49]. Mutations in *TNNT2* seem to be associated with little hypertrophy, consistent with animal models also [67], and high risk of ventricular arrhythmias and SCD [43, 68, 69]. However, these observations were done in highly penetrant large families and have yet to be confirmed. In the current era, the genetic test result should not be used as a principal determinant of SCD risk [32].

Instead, each HCM-associated mutation provides the fundamental pathogenetic substrate but the degree of penetrance and expressivity varies based on gene modifiers, epigenetic factors, and environmental triggers [32]. At present, it is difficult to prognosticate based upon the genetic mutation. A decision to place an internal cardioverter-defibrillator (ICD) should not be based on the patient's HCM-causing mutation [32]. Clinical genetic testing for HCM is currently available through different laboratories and companies. Each company's HCM test includes the most important HCM-susceptibility genes.

Left Ventricular Outflow Tract Obstruction

LVOTO is a predictor of death due to adverse cardiovascular events [8]. The risk of progression to NYHA class III or IV or death specifically from heart failure or stroke was also greater among patients with obstruction [70]. There are some reports of symptomatic patients with severe LVOTO being an independent risk factor for SCD/ICD in HCM (relative risk, 2.0) [55, 70]. A recent study, however, showed with an increasing number of risk factors, there was a significant trend towards increased mortality in patients with or without LVOTO.

ECG Findings in HCM

Traditionally, 12–lead electrocardiography has played a significant role in screening and evaluation of family members and athletes for HCM [71]. The 12-lead ECG is abnormal in 75–95 % of patients who have HCM [2, 52]. However, the ECG in HCM is nonspecific and does not predict clinical status, magnitude of hypertrophy and degree of left ventricular outflow tract (LVOT) obstruction. The ECG may show high voltage, nonspecific ST and T wave changes, abnormal Q waves, left atrial enlargement, diminished R waves in left precordial leads, LVH, and in few patients RVH [62]. QT dispersion and QT interval prolongation may be seen. Longer QRS duration and prolonged QT interval are common findings in HCM.

QT-prolongation is a common feature in HCM and has been reported in several cohorts of patients with HCM [72–75]. A recent large, two-center study showed of over 700 patients with HCM, 13 % of patients had a QTc over 480 ms and 5 % of patients had a QTc over the pro-arrhythmic threshold of 500 ms [75]. QT-prolongation was only weakly correlated with LVWT and LVOTO, and no correlation with SCD in HCM was found [75]. In adults, a weak correlation between ECG voltages and the magnitude of LVH assessed by echocardiography was observed [71].

The various voltage criteria (Romhilt-Ester score, Cornell voltage score, LV strain pattern, sum of R and S waves in 12 leads, and sum of S wave in lead V1 or V2 and R wave in V6 or V5) have weak correlation (correlation coefficients of 0.2–0.3) with LV hypertrophy [71]. In one study, Rohmilt-Ester voltage criteria and 12-lead ECG criteria was found to be 23 % sensitive in diagnosis of pre-hypertrophic carrier state [63]. It seems that inclusion of ST-T wave changes in ECG criteria increases the sensitivity. The relationship of voltage criteria with severity of hypertrophy and SCD risk is not very strong [71, 76]. Less than 50 % of patients with massive hypertrophy have ECG abnormalities [71].

Echocardiography for SCD Risk

Apart from the value of echocardiography in identifying the SCD substrates; degree of

hypertrophy and LVOTO, Doppler myocardial imaging derived intra-left ventricular electromechanical asynchrony and delay has high sensitivity and specificity in identifying patients with HCM and a subset with higher risk of SCD. An intra-ventricular conduction delay >30 ms identify patients with HCM and >45 ms is associated with NSVT on Holter monitoring and higher risk of SCD [77]. Intra-ventricular conduction delay also help to differentiate true HCM and athlete's heart. Maximal left atrial volume is also a sensitive indicator predicting susceptibility for paroxysmal AF.

Clinical Management of HCM

The Impact of Symptomatic Therapies on SCD Risk

The Role of Impact of Pharmacological Therapy

Negative Inotropic Therapy

Beta-Blockers

Beta-blockers due to its negative inotropic effects are the traditional mainstay of HCM therapy. Beta blockers are used in symptomatic patients with or without obstruction to control heart failure and anginal chest pain. The dose response relationship of these medications varies significantly from patient to patient. Commonly used beta blockers include propranolol, atenolol, metoprolol and nadolol [25, 78].

Calcium-Blocker Therapy

The calcium channel antagonist verapamil is another drug used in HCM for its negative inotropic effect. It should be avoided in infants and used with caution in patients with heart failure and/or significant obstruction [12].

Disopyramide

Disopyramide is a negative inotrope and type 1-A antiarrhythmic agent. It may help some patients with obstruction. It decreases cardiac output in nonobstructive HCM and is used primarily in patients not responding to beta blocker and/or calcium channel blocker therapy. There are no data that these medications alter the risk of sudden death [12].

Drugs to be Used with Caution in Obstructive HCM

Angiotensin converting enzymes inhibitors (ACE-inhibitors), angiotensin II blockers, nifedipine and other afterload reducing agents should be used with caution, as afterload reduction may worsen LVOTO [9, 25]. Beta-adrenergic agents like dopamine, dobutamine or epinephrine, agents with increased inotropic activity may worsen LVOTO [12].

Anti-arrhythmic Drug Therapy

Amiodarone

Medical treatment strategies with beta-blocker, quinidine, procainamide and amiodarone have shown variable and conflicting results in reduction in SCD risk [10]. To be sure, the possible protective effect is dwarfed by the safety profile and efficacy of ICD in long-term primary and secondary prevention of SCD [10]. In the current era, medical therapy does not play a principal role in primary or secondary prevention of SCD [4, 79].

The Role and Impact of Non-pharmacological Therapy

Septal Myectomy Surgery

Ventricular septal myectomy remains the gold standard for treating drug refractory obstructive HCM [27, 80, 81]. Surgery is usually indicated in patients with peak instantaneous LVOT Doppler gradient of 50 mmHg or higher under rest or provocation and/or severely symptomatic patients (NYHA class III or IV) whose symptoms are refractory to pharmacotherapy [12, 25, 81]. This profile represents approximately 5 % of patients with HCM [78]. More extensive, extended septal myectomy involving the anterolateral papillary muscle and mitral valvuloplasty may be needed in patients with abnormal papillary muscle apparatus and mitral valve abnormalities [82]. The surgical mortality is <1 % in HCM centers of excellence [2, 81]. Long-term survival after surgical myectomy is equal to that observed in the general population [82]. Surgery

provides long term improvement in LVOT gradient, mitral valve regurgitation and symptomatic improvement [2, 81, 82].

Alcohol Septal Ablation

Alcohol septal ablation technique whereby ethanol (95 % alcohol 1–3 mL) is injected in specific septal branches of the left anterior descending artery producing a controlled septal infarction which often provides dramatic symptomatic improvement in some patients [12, 83]. The criteria for patient selection for alcohol septal ablation are similar to myectomy with the following caveat - the impact of alcohol septal ablation on SCD risk is unknown. Scarring associated with alcohol septal ablation may create a permanent arrhythmogenic substrate [12]. Complications include complete atrioventricular block requiring permanent pacemakers (5–10 % of patients), large myocardial infarction, acute mitral valve regurgitation, ventricular fibrillation and death (2–4 %) [9, 25, 80]. Alcohol septal ablation is not suitable for patients with LVOTO secondary to abnormal mitral valve apparatus and unusual location of hypertrophy away from the area supplied by septal perforator. Given the unknown future risks of alcohol septal ablation, it is not recommended in children or young adults [12].

Dual-Chamber Pacing

There has been a great deal of debate surrounding the use of pacing as a means of relieving ventricular obstruction. Some studies have shown a beneficial effect, while others demonstrated significant placebo effect [12]. The average decrease in LVOTO gradient with pacing ranged from a modest, 25–40 % and varied substantially [12]. There is evidence to suggest that appropriately used dual chamber pacing may decrease LVOT gradient and provide symptomatic relief [84]. Thus, there may be a limited role of dual chamber pacing in a select group of patients, for example patients with advanced age (>65 years), with higher surgical mortality. There is no evidence to suggest any change in SCD risk or disease progression [20].

MAZE-Procedures

Surgical Maze procedure combined with myectomy may be a feasible therapeutic option in HCM with LVOTO and AF. There are small case series reporting low operative mortality and morbidity and a high likelihood of patients remaining in sinus rhythm post procedure [85]. Larger studies with longer follow-up are needed to better define the risks and benefits of surgical MAZE procedure in HCM.

The ICD in HCM

Functions of ICD

The internal cardioverter-defibrillator (ICD) plays an important role in primary and secondary prevention of SCD. In many young patients, the ICD prolongs life substantially and provides the potential for near-normal life expectancy. Risk-stratification and decision to implant an ICD is a complex process that is based on clinical data, evaluation of risk and benefits and an extensive discussion with the patient and family discussing all implications involved. Clinically, the indication to implant an ICD is based on secondary or primary prevention of ICD (see Fig. 2.2). In a multi-center study of ICDs in patients with HCM, the device intervened appropriately, terminating ventricular tachycardia/fibrillation, at a rate of 5 % per year for those patients implanted as primary prevention and 11 % per year for secondary prevention, over an average follow-up of 3 years [4]. A more recent, large multicenter ICD registry study demonstrated that the rate of appropriate ICD discharges was 10.6 % in case of secondary prevention, while for primary prevention, there was no significant difference between patients with either 1 or ≥2 of the established major risk factors (3.83, 2.65, and 4.82 per 100 person-years, respectively; $p = .77$), although not all five risk factors were evaluated systematically in every patient [86].

In a case of secondary prevention, an ICD is therefore absolutely indicated. Based on this data, as primary prevention, an ICD is indicated in the presence of two or more major risk factors or should be considered in the setting of one major risk factor, particularly if that single risk factor is extreme hypertrophy [87]. In the latter case, a decision can be based on presence of additional modifiers, special circumstances and wishes and expectations of the patient and his/her family.

The three main functions of the ICD are detection of arrhythmia; delivery of appropriate electrical therapy; and storage of diagnostic information, including electrocardiograms and details of treated episodes. In addition, ICDs provide antibradycardia pacing. In patients with sinus node dysfunction, supraventricular tachyarrhythmias precipitating VT/VF, paroxysmal or sustained AF, a dual chamber ICD is preferred [20].

Single- or Dual-Chamber System

In general, a single chamber ICD is indicated for primary/secondary prevention of SCD. Dual chamber devices are utilized if pacing is needed/anticipated or if the patient also has paroxysmal AF.

Complication of ICD Use

There are several potential complications of ICD therapy, particularly in young patients with long term ICD use. These risks include: (1) perforation, (2) high pacing thresholds; (3) inadequate sensing or pacing (4) contraindication for magnetic resonance imaging, (5) infection, (6) thrombosis, (7) valvular regurgitation, (8) unwarranted shock therapy/inappropriate discharges, and (9) multiple battery changes [20]. Malfunction of transvenous ICD lead, fracture and erosion can occur at an estimated frequency of 4–7 %/year [20, 88]. This is an important issue to be considered in young patients with HCM as revisions and replacements (and complications of those procedures) might be needed. In a large multicenter study, the rate of inappropriate discharges was 27 % [86]. Given the primary prevention rate of 5 %/year, families/patients must be informed that the patient is as likely to experience a complication from the ICD as he/she will experience a potentially life-saving, VF-terminating therapy when the device is implanted as primary prevention.

Summary of ICD Indications in HCM (Fig. 2.2)

Secondary Prevention (Aborted Cardiac Arrest)

In general, secondary prevention ICD therapy is indicated for all patients with a history of out of hospital cardiac arrest, aborted cardiac arrest, VF, or sustained ventricular tachycardia (Class I) [12, 87, 89].

Primary Prevention

ICD implantation for primary prevention of SCD depends on the presence of established risk factors as discussed before, but also involves a large measure of individual clinical judgment as discussed in the recent ACCF/AHA guidelines [87]. The decision needs to be discussed with the patient, risk and benefits need to be conveyed and should be balanced to patient and their family member's concerns and anxiety, particularly in children and young adults where there will be a long period of ICD follow-up [87].

Low Risk Group

Asymptomatic patients, with hypertrophy less than 20 mm, no family history of sudden death, LVOTO gradient <30 mmHg, normal atrial size, normal blood pressure response to exercise, and absence of NSVT on Holter, have low risk of sudden death and life expectancy similar to general population [12]. There is no evidence that, in such low risk individuals, either standard pharmacological therapy or device therapy may change the course of disease [12, 56, 78].

One Major Risk Factor Group

In contrast to European experts, experts from United States strongly advocate consideration for ICD implantation in the setting of only a single major risk factor [17, 79, 87, 90]. The recent ACCF/AHA guidelines state that it **is reasonable to recommend** ICD when there is a family history of SCD in first degree relative, LVWT ≥ 30 mm, or recent, unexplained syncope (Class IIa) [87]. If only NSVT or abnormal blood pressure response on exercise are present, ICD **can be useful** in presence of risk modifiers (Class IIa) and its use is uncertain in absence of risk modifiers (Class IIb) [87].

Two or More Risk Factors Group

There is essentially global consensus on use of ICD for primary prevention of SCD in patients

with multiple risk factors (two or more major risk factors) [25].

Contradictions for ICD Therapy

1. Wolff-Parkinson-White syndrome presenting with VF secondary to AF should undergo catheter or surgical ablation if their accessory pathways are amenable to such treatment.
2. NYHA Class IV drug-refractory congestive heart failure who are not candidates for cardiac transplantation, or with a life expectancy not exceeding 6 months.
3. Patients with incessant VT or VF not responsive to anti-tachycardia pacing or pharmacological therapy are not suitable candidates for a device.
4. A history of psychiatric disorders, including uncontrolled depression and substance abuse that interfere with the meticulous care and follow-up needed by these patients, is a relative contraindication to device therapy.
5. Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias is not an indication for ICD therapy.
6. Life expectancy <1 year (for other reasons).

Screening in HCM

Non-genetic Screening Recommendations in HCM

Periodically, all patients with HCM should undergo examination with meticulous recording of personal and family history, two-dimensional echocardiography and/or cardiac magnetic resonance (CMR), 12-lead ECG and 24–48 h ambulatory Holter electrocardiogram, and exercise stress testing (for evaluation of exercise tolerance, blood pressure, and ventricular tachyarrhythmias) [12]. All first and second degree relatives of an index case of HCM should be screened by an ECG and echocardiogram. In general, annual screening is recommended for adolescents and young adults (age 12–25 years) and athletes [83]. Before age 12 and after age 25, some periodicity of screening is advised (every 3–5 years) although yearly evaluations is probably most prudent if individual is an athlete, has symptoms, or family history suggests early onset disease.

Role of Genetic Testing and Family Screening and HCM

Commercial genetic testing for HCM is now available and a recent HRS/EHRA Expert Consensus Statement provides detailed information for the physician on the role of genetic testing in HCM [91]. According to the HRS/EHRA guidelines, (1) Comprehensive or targeted (*MYBPC3, MYH7, TNNI3, TNNT2, TPM1*) genetic testing **is recommended** for any patient with a clinical diagnosis of HCM and (2) mutation-specific genetic testing **is recommended** for family members and appropriate relatives of the index case with mutation-positive HCM [91]. The recent 2011 HCM Taskforce states that genetic counseling **is recommended** for all patients whereas genetic testing **is reasonable** (Class 2a) [87].

Genetic testing is not recommended for the diagnosis of HCM in patients with non-diagnostic features outside the setting of expert clinical and detailed family assessment as the absence of an HCM-causing mutation can not rule out familial HCM [91]. If the HCM-causing mutation is known, first degree relatives should have confirmatory genetic testing in addition to the screening ECG and Echo.

Depending on the established familial versus a sporadic pattern, confirmatory genetic testing should proceed in concentric circles of relatedness. For example, if the HCM-associated mutation is established in the patient's father, then the patient's paternal grandparents should be tested, and if necessary, then the paternal aunts and uncles and so forth. Genetic testing will play a key role in screening and identification of at-risk family members, even with preclinical HCM, and guide proper surveillance of those harboring a HCM-predisposing genetic substrate.

The Interaction Between Athletics and HCM

One of the important diagnostic challenges is distinguishing between HCM and the "athlete's heart". Caution should be exercised in diagnosis of "athlete's heart," as even among very elite

competitive athletes, only a small portion will develop LVH. Differentiating features include absence of family history of HCM and genetic mutation, some degree of LV dilation in addition to their hypertrophy, absence of SAM, female gender, normal diastolic filling pattern, lack of left atrial enlargement, absence of abnormal ECG findings, above-normal oxygen consumption, and LV wall thickness rarely exceeding 15 mm [2, 92]. If necessary, a period of deconditioning may help distinguish between the two entities as this will typically produce a regression of hypertrophy in "athlete's heart".

Sports Participation and Screening

Intense physical exertion can potentially trigger SCD in individuals with HCM. According to the 2005 Bethesda Conference #36 recommendations, athletes with HCM should be excluded from participation in contact and most organized competitive sports, with the possible exception of low intensity, class IA, sports (golf, bowling, cricket, billiards, and riflery) [93]. According to these expert-opinion guidelines, the presence of an ICD does not alter these recommendations [93].

Athletes with a Family History of HCM

Athletes with family history of HCM should undergo a detailed cardiac evaluation including ECG, ambulatory (Holter) 24-h ECG monitoring, exercise testing, echocardiogram, and genetic testing for disease screening and risk stratification, before they are cleared for sports.

Athletes with an HCM Mutation (Genotype Positive) but Normal Echocardiogram (Phenotype Negative)

Athletes with HCM mutation and normal echocardiogram, diagnosed by family screening, should undergo comprehensive clinical evaluation similar to patients with known HCM before they are cleared for sports. Currently, there is no data on usefulness of drug therapy in prevention or delaying of symptoms or hypertrophy. Although SCD has been reported among patients with troponin T mutations for example and minimal hypertrophy, overall there is lack of data on SCD risk in asymptomatic patients with a positive genetic test but normal echocardiogram (i.e. Genotype positive/phenotype negative). Although the ESC guidelines advise restricting such a patient from competitive sports, this is not based on extensive data and is viewed by some as too restrictive [12]. In fact, the subsequent North American guidelines (Bethesda 36) supported continuation in sports for genotype positive/phenotype negative athletes citing insufficient evidence to compel a recommendation for disqualification.

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3
Sudden Cardiac Death in Dilated Cardiomyopathy and Skeletal Muscular Dystrophy

Ingrid A.W. van Rijsingen, Anneke J. van der Kooi, and Yigal M. Pinto

Abstract

Skeletal Muscular Dystrophies are a heterogeneous group of neuromuscular disorders, that have a hereditary origin and all cause muscle weakness. Over the past decades, the enigmatic pathogenic origins of most common forms of skeletal muscular dystrophy have been defined. The identification of causative genes made it possible to differentiate between the different forms of muscular dystrophy. Since the identification of the genetic origins of the different muscular dystrophy forms, it has become apparent that a significant overlap exists between muscular dystrophy and cardiac abnormalities, in particular dilated cardiomyopathy. Although neurological and cardiac abnormalities may occur as isolated disorders, cardiac abnormalities often occur in association with skeletal muscular dystrophy, with genetic defects involving the sarcolemma, sarcomere, sarcoplasm and nuclear membrane. The type and extent of cardiac manifestation are specific to the type of skeletal muscular dystrophy, and varies from mild to severe heart failure or sudden cardiac death. Therefore, in most individuals with skeletal muscular dystrophies (early) cardiac evaluation is essential.

Keywords

Skeletal Muscular Dystrophies • Dilated cardiomyopathy • Sudden cardiac death • Heart failure • Dystrophinopathies • Myotonic dystrophy

Introduction

Skeletal Muscular Dystrophies are a heterogeneous group of neuromuscular disorders that have a hereditary origin and cause muscle weakness. Over the past decades, the enigmatic pathogenic origins of most common forms of skeletal muscular dystrophy have been defined [1]. The identification of causative genes made it possible to differentiate between the different forms of muscular dystrophy. Since the identification of the genetic origins of the different muscular dystrophy forms, it has become

I.A.W. van Rijsingen, MD • Y.M. Pinto, MD, PhD (✉)
Heart Failure Research Center, Heart Center,
Academic Medical Center, Meibergdreef 9,
Amsterdam 1105 AZ, The Netherlands
e-mail: i.a.vanrijsingen@amc.uva.nl;
y.pinto@amc.uva.nl

A.J. van der Kooi, MD, PhD
Department of Neurology,
Academic Medical Centre,
Amsterdam, The Netherlands
e-mail: a.j.kooi@amc.uva.nl

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apparent that a significant association exists between muscular dystrophy and cardiac abnormalities, in particular dilated cardiomyopathy. Although neurological and cardiac abnormalities may occur as isolated disorders, cardiac abnormalities often occur in association with skeletal muscular dystrophy, with genetic defects involving the sarcolemma, sarcomere, sarcoplasm and nuclear membrane [2]. The type and extent of cardiac manifestation are specific to the type of skeletal muscular dystrophy, and varies from mild to severe heart failure or sudden cardiac death. Therefore, in most individuals with skeletal muscular dystrophies (early) cardiac evaluation is essential.

The goal of this chapter is not to exhaustively describe dilated cardiomyopathy or the different skeletal muscular dystrophies, but to give an overview of the most frequent cardiac complications of skeletal muscular dystrophies. Furthermore, the risk of sudden cardiac death is discussed for dilated cardiomyopathy and for the most important forms of muscular dystrophy.

Dilated Cardiomyopathy

Dilated cardiomyopathy is a prevalent cardiomyopathy subtype. During the last decades the definition of cardiomyopathies has changed; from the World Health Organization (WHO) definition in 1980 "heart muscle diseases of unknown cause" to the definition of the European Society of Cardiology's working group on myocardial and pericardial disease in 2008 "A myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to explain the observed myocardial abnormality" [3, 4].

Dilated cardiomyopathy is characterized by dilation and systolic dysfunction of the left ventricle with or without right ventricular involvement, in the absence of abnormal loading conditions or coronary artery disease. The differential diagnosis of dilated left ventricular impairment is long and includes ischemic, infectious, toxic and hypertensive heart disease. The exclusion of the different causes of dilated left ventricular impairment is clinically challenging and the underlying aetiology is not always (directly) detectable.

Individuals with dilated cardiomyopathy have an impaired left ventricular function and can, develop severe heart failure. Dilated cardiomyopathy is one of the most common causes of heart failure and the most common reason for cardiac transplantation. Besides heart failure, individuals with dilated cardiomyopathy may develop both atrial and ventricular arrhythmias, and sudden cardiac death can occur at any stage of the disease.

A familial form of dilated cardiomyopathy is found in 20–50 % of individuals with dilated cardiomyopathy after active first degree familial screening. The true percentage of genetic forms of dilated cardiomyopathy may be even higher due to incomplete age-dependent penetrance in relatives and the occurrence of *de novo* mutations. Most of the familial dilated cardiomyopathies have an autosomal dominant inheritance pattern, although all other inheritance patterns have been identified (autosomal recessive, X-linked, and mitochondrial). During the past decades disease-causing mutations have been identified in more than 30 different genes [5]. Despite this high number of genes that are related to dilated cardiomyopathy, until now only in one third of the individuals with familial dilated cardiomyopathy a disease-causing mutation is found. Most of the disease-causing mutations are found in genes encoding cytoskeletal and sarcomeric proteins. The low yield of DNA diagnostics can partly be explained by a heterogenic phenotype with incomplete penetrance, in often quite small pedigrees with premature death in the most severely affected carriers. This low yield of DNA-analysis in dilated cardiomyopathy may however change in the near future, when strategies switch from single gene testing by classic Sanger sequencing to whole exome or even genome sequencing.

In case there is a familial form of dilated cardiomyopathy, familial and genetic counselling is recommended [6]. However, it is unsettled whether or not genetic testing is indicated in forms of sporadic dilated cardiomyopathy.

Risk of Sudden Cardiac Death in Dilated Cardiomyopathy

Sudden cardiac death accounts for 15–20 % of all natural deaths [7, 8]. The proportions differ due to different used definitions of sudden cardiac death. The definition of sudden cardiac death used in the ACC/AHA/ESC guideline is: "death from an unexpected circulatory arrest, usually due to cardiac arrhythmia occurring within an hour of the onset of symptoms" [9].

The proportion of sudden cardiac death in dilated cardiomyopathy is even higher; around one third of all deaths in individuals with dilated cardiomyopathy are sudden. The prevention of sudden cardiac death in individuals with dilated cardiomyopathy is of major importance, because 10 % of the total population with dilated cardiomyopathy die suddenly [10]. A major problem in the prevention of sudden cardiac death in dilated cardiomyopathy is that the cause of the sudden cardiac death is not always well established. Most of the sudden cardiac deaths are due to malignant ventricular arrhythmias, although still a major portion is due to other causes such as bradyarrhythmias, pulmonary or systemic embolization, or pulseless electrical activity.

The prevention of sudden cardiac death requires accurate risk stratification with a good sensitivity, specificity, and predictive accuracy for malignant ventricular arrhythmias. Most of the risk stratifications available for dilated cardiomyopathy are based on studies with individuals with non-ischemic dilated left ventricular impairment. Another important problem is that most of the predictors for sudden cardiac death are also predictors for all-cause mortality, due to the general poor prognosis in individuals with dilated cardiomyopathy. Different possible predictors for sudden cardiac death have been suggested, like syncope, non-sustained ventricular tachycardia and induction of ventricular tachycardia by electrophysiology testing. Although they are associated with a higher risk of sudden cardiac death, there is no evidence that they are useful for the selecting individuals who will benefit from implantable cardioverter defibrillator (ICD) implantation. The ACC/AHA/ESC guideline from 2006 recommends to use the following criteria for prophylactic ICD implantation*: left ventricular ejection fraction 30–35 % or lower in combination with a New York Heart Association classification II or III, in individuals with dilated cardiomyopathy who received optimal medical therapy and have an expected survival for more than 1 year* [9]. This recommendation is based on major selection criteria used in the randomised controlled trials that showed that ICD implantation reduced mortality (the trials are discussed further on). The Marburg Cardiomyopathy Study, a prospective study with 343 individuals with dilated cardiomyopathy, evaluated multiple potential risk factors for malignant ventricular arrhythmias. After a follow-up of 52 months, only a reduced left ventricular ejection fraction remained as an independent risk factor for malignant ventricular arrhythmias [11].

Due to the heterogenic background of dilated cardiomyopathy it would probably be of additional value to add genetic information to the risk stratification for predicting malignant ventricular arrhythmias. Unfortunately, there are only few studies that assess the additional value of genetic testing in this respect. One example is a study where multivariate analysis did identify four risk factors associated with malignant ventricular arrhythmias in 269 individuals carrying disease-causing mutations in the gene encoding lamin A/C. These four risk factors included non-missense mutations (ins-del/truncating or mutations affecting splicing) and male gender in addition to non-sustained ventricular tachycardia, left ventricular ejection fraction <45 % [12].

Prevention of Sudden Cardiac Death in Dilated Cardiomyopathy

The general treatment of individuals with dilated cardiomyopathy depends on clinical presentation and most of the time depends on experience of the physician. The implementation of therapies like beta blockers and ACE inhibitors has reduced mortality and also the occurrence of sudden cardiac death

in individuals with heart failure. Amiodarone and sotalol is indicated as adjunct to an ICD; in individuals with frequent arrhythmias and an ICD. But is not indicated as an alternative to ICD implantation.

The efficiency of ICD implantation as secondary prevention after resuscitation is well established; however ICD implantation as primary prophylaxis is less clearly established. Primary prevention of sudden cardiac death was tested in different randomized controlled trials in individuals with non-ischemic dilated left ventricular impairment. The first trials comparing ICD implantation versus placebo/amiodarone were unable to show a statistically significant survival benefit for ICD implantation. Indeed, two trials were terminated prematurely due to futility (because of a lower than expected all-cause mortality) and another trial was underpowered [13–15]. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), trial in 2,521 individuals with congestive heart failure, was the first trial that showed a benefit of ICD implantation on all-cause mortality [16]. When these randomized controlled trials were combined in a meta-analysis, a significant reduced mortality of 31 % was found in favour of ICD implantation. ICD implantation in individuals with non-ischemic left ventricular impairment prevents (each 2 years) one dead for every 25 implantations [17]. Due to relative low mortality rates in the control group, the absolute benefit of ICD implantation is low. This further emphasizes the importance of an improved identification of individuals with an increased risk of malignant ventricular arrhythmias.

In conclusion, the risk of sudden cardiac death in individuals with dilated cardiomyopathy is high and selected individuals might benefit from ICD implantation for primary prevention of sudden cardiac death. The difficulty is to predict which individuals will benefit most from ICD implantation. The implantation strategy that is available at the moment is effective, but includes also a high number is individuals that may later turn out not to have needed an ICD so that the current selection strategy can be improved particularly in cases of genetic dilated cardiomyopathy.

Skeletal Muscular Dystrophy

Dystrophinopathies

Dystrophinopathies are caused by mutations in the dystrophin gene and are categorized as Duchenne and Becker muscular dystrophy. Dystrophinopathies have an X-linked recessive inherited pattern, in around one third of the cases the dystrophinopathy is caused by a *de novo* mutation. Progressive skeletal muscle weakness is the principal symptom, cause by muscle fiber degeneration. Duchenne muscular dystrophy is associated with the most severe clinical symptoms. Becker muscular dystrophy is associated with the same symptoms as Duchenne muscular dystrophy, but the symptoms are milder and the age of onset in later. Both phenotypes are most of the time caused by deletions in the dystrophin gene, but can also be caused by partial gene duplications and point mutation in the coding sequence or the splicing site. The phenotypic differences between Duchenne and Becker muscular dystrophy can be explained by whether or not the reading frame for dystrophin is preserved. In most of the cases of Duchenne muscular dystrophy the reading frame is disrupted, which leads to a total absence of dystrophin at the sarcolemma.

Dystrophin is a component of the glycoprotein complex of muscle fibers, and is important for mechanical reinforcement of the sarcolemma and the stability of the glycoprotein complex.

Duchenne Muscular Dystrophy

General

Duchenne muscular dystrophy is the most common and severe form of muscular dystrophy. The incidence of Duchenne muscular dystrophy is 1.7–2.1 per 10,000 live male births [18, 19]. The first clinical symptoms are progressive muscle weakness of the lower extremities, starting at the age of 2–3 years. Later, also the upper extremities and distal limb muscles loose strength. Physical examination reveals pseudohypertrophy of the calf muscles, lumbar lordosis, a waddling gait, shortening of the Achilles tendons, and hypo- or areflexia. Serum creatine kinase (CK) activity is highly elevated, even

before the appearance of any clinical signs of disease. Mild cognitive impairment is frequently found. The diagnosis Duchenne muscular dystrophy needs to be confirmed by DNA-testing, and muscular biopsy can be useful to distinguish between Duchenne muscular dystrophy and other phenotypes. The dystrophy is highly progressive and most of the individuals are wheelchair bound by the age of 12. Most of the individuals develop progressive scoliosis. Respiratory insufficiency occurs around the age of 20, necessitation the use of assisted ventilation.

Cardiac Involvement

Most of the individuals with Duchenne muscular dystrophy develop cardiac abnormalities during the teenage years, although only half of them will complain of any symptoms [20]. The symptoms are most of the time not typical for cardiac abnormalities, like sleep disturbances and anorexia. The lack of symptoms can be explained by the inability to exercise due to the severe skeletal muscle abnormalities.

The cardiac abnormalities are characterised by dilated cardiomyopathy with extensive fibrosis, mitral regurgitation due to involvement of the posterior papillary muscle, conduction disorders en (primarily supraventricular) arrhythmias.

The electrocardiogram (ECG) shows typical features, tall right precordial R waves and left precordial Q waves [21]. These ECG features can be explained by the typical fibrosis of the posterobasal portion of the left ventricle. Up to 95 % of boys have signs of cardiac disease at the end of their lives. Diagnostic evaluation of the cardiac function is important, because of the high prevalence of dilated cardiomyopathy and absent of clinical symptoms. However, barrel-shaped chest, increased adiposity of the chest walls, scoliosis and respiratory problems can make conventional echocardiography challenging and sometimes impossible. Cardiac magnetic resonance is a good alternative. Cardiac evaluation is advised at time of diagnosis, at least ones in the 2 years before the age of 10 and annually after the age of 10 [22].

Prognosis

The survival of individuals with Duchenne muscular dystrophy has improved the last decade from a survival up to an age of 14–20 years, which now has been extended to an age of 26–35 years. This is probably due to initiation of assisted ventilation, improved therapy and more awareness of the comorbidities among the caregivers [23, 24]. Improved treatment of respiratory failure allows individuals to live longer, due to this longer lifespan cardiac failure has become a major cause of death. Severe skeletal muscle abnormalities are not related to severe cardiac abnormalities. There are some hypotheses that the opposite is true; that less severe muscle abnormalities are related to more exercise with increased workload of the heart, which could lead to earlier cardiac failure [25]. Ten to twenty percent of the deaths are sudden, although it is not know whether this is due to malignant ventricular arrhythmias. However, on Holter monitoring ventricular ectopy and ventricular arrhythmias are frequently found [26]. Ventricular arrhythmias are most of the time related to severe cardiac dysfunction and are suggested to predict all-cause mortality. Further studies need to evaluate the cardiac cause of death and to define the influence of malignant ventricular arrhythmias as a cause of death in individuals with Duchenne muscular dystrophy.

Becker Muscular Dystrophy

General

Individuals with Becker muscular dystrophy have in general the same clinical symptoms as individuals with Duchenne muscular dystrophy, but with a later age of onset and less severe disease progression. The age of onset is most of the time after the age of 12 years. The clinical presentation of Becker muscular dystrophy is more heterogeneous, and can vary from asymptomatic to symptoms due to muscular and/or cardiac abnormalities. The variable phenotype is (partly) dependent on the type and site of the mutation in dystrophin gene. In a recent described population of 115 individuals with Becker muscular dystrophy with

duplications in dystrophin gene were less severe affected than individuals with deletions in the same gene. Further on, the onset of muscular and cardiac abnormalities was earlier in individuals with proximal deletions than in individuals with a deletion in the distal part of the gene [27].

In case of muscular weakness, similar muscle groups are affected as in Duchenne muscular dystrophy. However, the first presentation can also be dominated by muscular cramps, fatigue, myalgia. The disability in this group of individuals is less severe than in individuals with Duchenne muscular dystrophy. Only part of the individuals becomes wheelchair bound; the age at which this occurs varies from adolescence onward. Respiratory involvement is in general mild or moderate [27]. Mental retardation can be present in these individuals, but is less frequently and less severe than in individuals with Duchenne muscular dystrophy. In more than half of the individuals dilated cardiomyopathy is present and can dominates the phenotype in some individuals.

Cardiac Involvement

Although neuromuscular phenotype is less severe in individuals with Becker muscular dystrophy than in individuals with Duchenne muscular dystrophy, the cardiac involvement is often more evident. Some individuals may present with cardiac abnormalities before the development of a skeletal muscular phenotype, or even with pure cardiac disease without muscular weakness. Most of the individuals develop symptoms due to cardiac abnormalities in their third decade, however mild abnormalities could be observed earlier. Most of the individuals with cardiac abnormalities are asymptomatic; up to one-third of the individuals develop severe heart failure due to dilated cardiomyopathy [25]. Also, conduction disorders and both atrial and ventricular arrhythmias could be present. Comparable with Duchenne muscular dystrophy there is no relation between severity of the skeletal muscular abnormalities and the severity of the cardiac abnormalities.

ECG abnormalities are frequently found, including sinus tachycardia, atrial fibrillation and conduction disorders. A high frequency of decreased R waves or prominent Q waves in lateral leads (90 %) and prominent R waves in right precordial leads (47 %) have been described and are possible related to myocardial damage in the lateral and posterior wall [25].

Echocardiographic evaluation is important to identify asymptomatic individuals at early stage of the cardiac disease. Myocardial thickening is described in a few case reports in the early stage of the disease, and could develop into dilated cardiomyopathy [28]. Dilated cardiomyopathy is characterised in individuals with Becker muscular dystrophy by severe dilatation of the left ventricle with secondary mitral regurgitation and wall motion abnormalities. Left ventricular function may be severe depressed, which could lead to heart failure with heart transplantation requirement. Right ventricle is often involved, and could be dilated at an early stage of the disease [29].

Cardiac evaluation is advised at the moment of diagnosis and at least every 5 years in individuals whose heart is not (yet) affected [30]. When there are cardiac abnormalities the intervals of cardiological evaluation needs to be shorter. Dilated cardiomyopathy can remain asymptomatic and stable for many years, but can also evolves rapidly to cardiac failure and sometimes leading to sudden cardiac death [31].

Prognosis

Due to the milder muscular involvement in Becker muscular dystrophy, individuals are more likely to be limited by cardiac complaints than individuals with Duchenne muscular dystrophy. Dilated cardiomyopathy is in most of the individuals asymptomatic, but can lead to end-stage heart failure with heart transplantation requirement. Individuals with Becker muscular dystrophy have a better prognosis than individuals with Duchenne muscular dystrophy, death occurred usually in the fourth or fifth decade [1]. More than half of the individuals who died, died due to their cardiac abnormalities; most of the time due to congestive heart failure, but some individuals die suddenly [30, 31]. It is not known whether or not this is due to malignant ventricular arrhythmias. On Holter monitoring

ventricular arrhythmias are documented, but are most of the time related to a reduced left ventricular function [32, 33].

Female Carriers of Duchenne Muscular Dystrophy and Becker Muscular Dystrophy

Female carriers of both Duchenne and Becker muscular dystrophy can develop muscular weakness and cardiac abnormalities. The abnormalities are most of the time, when found, mild and less progressive. This can be explained by the fact that in female carriers there is a mosaic pattern in the skeletal and heart muscle with both dystrophin-negative as well as dystrophin-positive fibers.

A couple of decennia ago it was already known the female mutation carriers of Duchenne or Becker muscular dystrophy have frequently abnormal ECG parameters (18–61 %) [34–36]. Years later, research was published about the occurrence of dilated cardiomyopathy in female carriers. The prevalence of dilated cardiomyopathy among female carriers varies from 7–75 %, and depends on the used definition of dilated cardiomyopathy, but penetrance is also age-dependent [37]. Most of the carriers with dilated cardiomyopathy have no symptoms, but the cardiac disease can be progressive and even lethal. Also, sudden cardiac death has been described in female carriers. This might be suggestive of arrhythmias in carriers with asymptomatic dilated cardiomyopathy. Clinical evaluation is advised at the time of diagnosis or at the age of 16 years, and every 5 years, or more frequently in individuals with abnormalities [30]. There is some doubt whether female carriers have a reduced life expectancy compared with the life expectancy in the normal population [37, 38].

Myotonic Dystrophy

General

Myotonic dystrophy is a multisystem heterogeneous disorder, divided into two major forms. Myotonic dystrophy is most of the time inherited in an autosomal dominant manner and has a prevalence of 1 in 8,000 in the general population. The disorder is not only characterised by muscular dystrophy, but it also affects other systems. Affected individuals may also show cataracts, cardiac abnormalities, infertility, and insulin resistance.

Myotonic dystrophy type 1, also known as Steinert's disease, is the most prevalent form and results from an expansion of more than 50 CTG trinucleotide repeats in the 3'-untranslated region of the dystrophia myotonica protein kinase gene (*DMPK*). The number of repeats differs per individual; more repeats are associated with an earlier age of onset and more severe clinical phenotype. The repeat expansion in children of parents with myotonic dystrophy is most of the time longer, due to instability of the repeat. The repeat may expand in length during meiosis and mitosis.

Myotonic dystrophy type 2, also known as proximal myothonic myopathy, is less severe than myotonic dystrophy type 1 and results from CCTG tetranucleotide repeat expansion in intron 1 of the zinc finger protein 9 gene (*ZNF9*). Genetically, the diagnosis of myotonic dystrophy type 2 is fulfilled in the presence more than 75 tetranucleotide repeats in intron 1 of *ZNF9*. There is no association between the number of repeats and the age of onset or disease severity [39].

Both in myotonic dystrophy type 1 and 2 the repeat expansion is transcribed to RNA, but is not translated. The repeat expansion is in an RNA transcribed region of functionally different genes, which suggests that the disorders are caused by the RNA itself, rather than the specific gene. It is thought that accumulated RNAs alter RNA binding protein activity, which in turn results in aberrant splicing and abnormal function of several other genes.

The clinical manifestation of both myotonic dystrophy type 1 and 2 are comparable, although myotonic dystrophy type 1 is most of the time more severe and presents at an earlier age. Myotonic dystrophy can present as a congenital, juvenile, and adult onset form.

The diagnosis of myotonic dystrophy is based on DNA testing in an individual who is clinically suspected to have myotonic dystrophy. The clinical manifestation of the classic form is characterised by slowly progressive facial, neck and distal muscle weakness, most of the time in

combination with myotonia (slow relaxation following a normal muscle contraction). Most of the individuals have major complaints of muscle pain, which can start before the occurrence of muscular weakness. Myotonic dystrophy is a multisystem disorder, and besides the muscular disorders there is also ocular, endocrinal, gastrointestinal, respiratory and cardiac involvement.

Congenital myotonic dystrophy, only seen as part of myotonic dystrophy type 1, is the most severe subtype with neonatal hypotonia, motor and mental retardation, and facial diplegia. Respiratory difficulties are common in neonates and are the leading cause of death during the neonatal period. If newborns survive this period, most turn out to have mental retardation (50–60 %) [40]. Eventually these children develop myotonia and the characteristics of classical myotonic dystrophy.

Cardiac Involvement

Cardiac abnormalities are rather common in myotonic dystrophy, and are characterised by both cardiac conduction disorders and structural cardiac abnormalities. The cardiac abnormalities can be manifested before the onset of the neuromuscular symptoms. Cardiac abnormalities are considered to be a less frequent complication in myotonic dystrophy type 2 than in myotonic dystrophy type 1 [41]. On the ECG both atrioventricular and intraventricular conduction disorders are frequently found and are slowly progressive over time, a pacemaker may become necessary in up to 15 % of individuals. Conduction disorders are related to myocyte hypertrophy and disarray, fibrosis, focal fatty infiltration, all identified in autopsy studies and which can be present anywhere along the conduction system including the His-Purkinje fibers [42]. Arrhythmias can be present, mostly atrial tachyarrhythmias but ventricular arrhythmias can occur.

Structural abnormalities are can be found on echocardiography, but are rarely symptomatic. The structural abnormalities are characterised by left ventricular hypertrophy, dilatation and reduced ejection fraction [43].

Annual cardiological ECG evaluation is advised in individuals with myotonic dystrophy. In case of ECG abnormalities Holter monitoring is advised [30].

Prognosis

Life expectancy is reduced in individuals with myotonic dystrophy type 1, with a mean age of death around 53 years. The age of death is related to the age at onset of symptoms [44–46]. Most of the individuals die due to their respiratory and cardiac abnormalities. A high number of individuals die suddenly, in the majority of the cases due to malignant ventricular arrhythmias and progressive conduction disorders. Groh et al. found an association between a prolonged PR interval, widening of the QRS complex, atrial tachyarrhythmias and an increased risk of sudden cardiac death in individuals with myotonic dystrophy type 1, even when the individuals were asymptomatic [45]. It has become common practice to implant a prophylactic pacemaker in both symptomatic and asymptomatic individuals with myotonic dystrophy when they have severe ECG abnormalities [47]. It is not yet settled, whether or not an ICD should be preferred when a pacemaker is indicated and individuals have an increased risk of sudden cardiac death [48, 49]. Further research needs to be done, whether or not implantation of an ICD is effective. The life expectancy is individuals with myotonic dystrophy type 2 is less reduced than in individuals with myotonic dystrophy type 1, due to the absence of a congenital form and the less severe clinical manifestation [44, 50, 51].

Emery–Dreifuss Muscular Dystrophy

General

Emery–Dreifuss muscular dystrophy, also known as humeroperoneal muscular dystrophy, is a rather uncommon type of muscular dystrophy [1]. The clinical manifestation of Emery-Dreifuss muscular dystrophy is characterised by the triad of early contractures, muscular weakness/wasting and cardiac abnormalities [52]. The first symptoms occur usually in the first or second decade of life. The contractures, often are present before there are symptoms of muscular weakness, and are localized in the elbows, entire spine and Achilles tendons. The muscular

weakness and wasting is most of the time slowly progressive and have a humero-peroneal distribution. Later on, also the proximal limb girdle musculature could become weakened. The cardiac abnormalities are characterised by conduction disorders. Inheritance patterns can be X-linked, autosomal dominant, or rarely autosomal recessive. The X-linked subtype can be caused by mutations in the *STA* gene encoding emerin, localized to the nuclear membrane. In most of the cases there is a complete loss of emerin expression in the muscles. Both the autosomal dominant and recessive forms are related to mutations in the *LMNA* gene. *LMNA* encodes for lamin A/C, also nuclear membrane proteins. Mutations in *LMNA* can cause several other phenotypes, including limb-girdle muscular dystrophy type 1B and isolated dilated cardiomyopathy with conduction disorders. Mutations in the genes encode for Nesprin-1 and -2, proteins that bind both emerin and lamin A/C, can also cause Emery-Dreifuss muscular dystrophy.

The diagnosis can be based on the typically clinical manifestation in combination with a positive family history and a disease-causing mutation. In some cases additional diagnostic research is indicated to make the diagnosis, EMG and muscle biopsy may be helpful.

Cardiac Involvement

Cardiac involvement is common in Emery-Dreifuss muscular dystrophy, and is present in majority of the individuals by the third decade. The ECG may show conduction disorders, (sinus-)bradycardia and atrial fibrillation with a slow ventricular response. The conduction disorders are characterized by progressive atrioventricular conduction abnormalities. The bradycardia can be caused by atrial paralysis, which is often seen in individuals with Emery-Dreifuss muscular dystrophy. Treatment with a pacemaker is often indicated [53, 54]. Structural abnormalities can also occur in these individuals, with on echocardiography signs of dilated cardiomyopathy and dilated atria. The dilated cardiomyopathy can be highly progressive and can result in end-stage heart failure. Mutations in *LMNA* are often found in individuals undergoing heart transplantation [55, 56].

Prognosis

Although progression the muscular dystrophy is slow and considered to be benign, the cardiac consequences are often severe [54]. The principal concern in these individuals is death resulting from the cardiac abnormalities. Sudden cardiac death may occur, even in individuals with mild or no skeletal muscular abnormalities and without any cardiac symptoms [57]. It is hypnotized that the sudden cardiac death can be the result of either malignant ventricular arrhythmias or bradyarrhythmias (sinus arrest or severe atrioventricular conduction disorders). In a meta-analysis the risk of dying suddenly was not alleviated by pacemaker implantation in *LMNA* mutation carriers, which suggest that malignant ventricular arrhythmias play a major role in sudden cardiac death in *LMNA* mutation carriers [58]. Analyses of *LMNA* mutation carriers, both in individuals with or without skeletal muscular involvement, show a high prevalence of malignant ventricular arrhythmias. The prevalence of malignant ventricular arrhythmias was equal in individuals with or without skeletal muscular involvement [12, 59, 60]. It is not clear whether the high prevalence of sudden cardiac death in individuals with mutations *STA* gene are also caused by a high prevalence of malignant ventricular arrhythmias, it even is suggested that in these individuals bradyarrhythmias are a more prevalent cause [57].

Limb-Girdle Muscular Dystrophy

General

Limb-girdle muscular dystrophies (LGMD) combines a number of disorders with heterogeneous aetiologies, in which muscular weakness in the pelvic and shoulder girdle are present [61]. Twenty-two different subtypes have been described, with both an autosomal dominant and autosomal recessive inherited pattern. However, in some individuals the inheritance pattern cannot be determined.

Most of the subtypes are autosomal recessive, and these subtypes have a more severe disease expression. The clinical phenotypes are heterogenic and differ per subtype; the age of onset

varies from early childhood to the fourth decade. The first clinical presentation is characterised by muscular weakness of shoulder girdle, the pelvic girdle or both. The progression is usually slowly, and will gradually affect the limb muscles. In severe cases this could lead to wheelchair dependency. The distinction between the different subtypes requires protein analysis in muscle biopsy and genetic testing.

Only in a part of the subtypes cardiac abnormalities have been described. However, it is not possible to exclude cardiac abnormalities in all other subtypes, because of the rareness of some subtypes. The subtypes with cardiac involvement are LGMD1B caused by mutations in *LMNA* gene, LGMD1E caused by mutations in desmin gene, sarcoglycanopathies (LGMD2C-F) caused by mutations sarcoglycan genes and LGMD21 caused by mutations in fukutin-related protein (*FKRP)* gene [41, 62].

Cardiac Involvement

The cardiac involvement in LGMD1B and LGMD1E is comparable, although cardiac involvement has been reported in only one family with LGMD1E to date [63]. Cardiac involvement in LGMD1B is common, and characterised by conduction disorder, both atrial and ventricular arrhythmias and cardiomyopathy [64]. The type of cardiac abnormalities is equal to the cardiac abnormalities in Emery-Dreifuss muscular dystrophy caused by mutation in *LMNA* gene.

Sarcoglycanopathies comprise four subtypes of autosomal recessive LGMD that are the result of mutations in the transmembrane proteins of the sarcoglycan complex. Mild cardiac abnormalities have been described in all four subtypes; however in some cases also severe ventricular arrhythmias and heart failure have been described. Whether there are clear differences in cardiac involvement between the sarcoglycanopathies is not known [65].

Cardiac abnormalities are often found in individuals with LGMD2I, and range from mere ECG abnormalities to severe heart failure. The first structural abnormalities, left ventricular wall motion abnormalities and dilated cardiomyopathy, can be detected in the second decade [66]. Severe ventricular arrhythmias are to our knowledge not noticed in individuals with LGMD2I [66].

Prognosis

The muscular and cardiac involvement in LGMD can be quite variable, and differ per subtype. In some subtypes the muscular dystrophy is the most prominent, for example in sarcoglycanopathies (LGDM2C-F), which were previously called Duchenne-like muscular dystrophy. In the case of predominant muscular involvement the respiratory status should be monitored, because of possibility of the development of respiratory failure. As described above in some other subtypes there is a high prevalence of cardiac abnormalities, which could lead to end-stage heart failure and in some cases to sudden cardiac death. Routine cardiac evaluation is advised in individuals with a subtype of LGMD that is associated with cardiac abnormalities [30].

Myofibrillar Myopathies

General

Myofibrillar myopathies represent variety of disorders with a similar morphological phenotype. The symptoms are characterised by progressive muscle weakness often beginning in the distal muscles, peripheral neuropathy and cardiac abnormality. The diagnosis needs to be confirmed with muscle biopsy. Myofibrillar Myopathies are associated with mutations in different genes, for example in genes encoding Z band alternatively PDZ-containing protein, desmin and filamin C [67]. However, only in a minority of the cases a genetic cause is found. Despite this genetic heterogeneity, the clinical and morphologic neurological phenotypes are remarkably homogeneous [67].

We will focus on desminopathies, a subset of myofibrillar myopathies that is caused by mutations in the desmin gene. Individuals with desminopathy can present with isolated neurological or cardiological symptoms, but in most of the cases there is an overlap between both [68]. The age of onset varies from childhood to sixth decade [69].

Cardiac Involvement

In half of the individuals a different cardiomyopathy subtype is identified, including restrictive, hypertrophic, arrhythmogenic right ventricular and dilated cardiomyopathy. Dilated cardiomyopathy is most often found. The cardiomyopathy can lead to severe heart failure. Both conduction disorders and arrhythmias are often found and are most of the time combined with structural cardiac abnormalities, pacemaker and/or ICD can be necessary in some individuals. Most of the found arrhythmias are supraventricular, but ventricular arrhythmias are regularly described [68].

Prognosis

The life expectancy of individuals with desminopathy is reduced especially due to the cardiac abnormalities, with a mean age of death around 50 years. Most of the individuals die due to heart failure (48 %) or sudden cardiac death (26 %). It is not known whether these sudden cardiac deaths are, due to malignant ventricular arrhythmias per se or also due to conduction disorders. In around a fourth of the patients respiratory insufficiency is reported, only a minority of the individuals die due to respiratory failure. Yearly cardiological evaluation is proposed starting at the age of 10 years, so that the cardiac abnormalities can be detect in an early stage and can be treated [68].

Congenital Muscular Dystrophies

General

Congenital muscular dystrophy (MDC) is a heterogeneous group of disorders, characterized by the presence of muscle weakness and hypotonia at birth or within the first 6 months of life and muscular dystrophy on muscle biopsy. Originally MDC is classified into two different groups based upon the presence or absence of structural brain defects, namely a classic and a syndromic group. Cognitive impairment is often present, particularly in individuals with structural brain defects.

A whole range of genes is associated with different subtypes of congenital muscular dystrophy and nearly all subtypes inherited in an autosomal recessive pattern.

MDCs have a heterogenic disease manifestation; most of the subtypes are not or slowly progressive and frequently more organ systems are involved.

Due to its variety in phenotype we will discuss only the most relevant subtypes in this chapter. MDC1A is a severe subtype, accounts for about 30 % of the MDC in Europe, and is caused by a deficiency of alpha-2 chain of laminin (also known as merosin) [70]. Individuals with MDC1A disabled due to muscle weakness and contractures, respiratory insufficiency could require tracheotomy. Fukuyama MDC, is mostly found in Japan and is caused by mutations in fukutin gene, which leads to reduced glycosylation of alpha-dystroglycan [71]. This subtype is characterised by severe generalized muscle weakness in combination with structural brain damage. MDC1C is caused by mutations the same gene as in LGMD21, namely *FKRP*. Individuals with MDC1C have most of the time not the ability to walk, due to severe general muscle weakness and hypotonia. MDC1C is also characterized by leg muscle hypertrophy, especially in the calf muscles. Also in these individuals severe respiratory insufficiency may occur [72].

Cardiac Involvement

The cardiac involvement varies per subtype, and can be complete absent. Cardiological evaluation is recommended at time of diagnosis and before surgery in each subtype. The need and the frequency of cardiological follow-up is dependent on the subtype [30]. Cardiac involvement in MDC1A is characterized by right bundle branch block and dilated cardiomyopathy. Although in one third of the individuals cardiac abnormalities are present during cardiological evaluation, only a minority of the individuals are symptomatic [73]. Cardiac abnormalities are often found in dystroglycanopathies, including Fukuyama MDC. Structural abnormalities are regular described, including dilated cardiomyopathy, systolic dysfunction and myocardial fibrosis. Individuals could develop severe heart failure after their second decade [41].

Mild structural heart changes have been described in MDC1C. However it is unknown whether this could lead to end-stage heart failure, probably because the respiratory impairment in more prominent present [72].

Prognosis

The prognosis of congenital muscular dystrophy is dependent on the subtype; some of the individuals die shortly after birth, whereas other can live into adulthood with only minimal disability. The cause of death in congenital muscular dystrophies is usually respiratory insufficiency. In MDC1A the prognosis is in the majority of the individuals determined by recurrent aspirations and respiratory insufficiency, although the prognosis has been improved due to better treatment strategies [70]. Premature death due to the cardiac abnormalities is sporadically described [73].

In Fukuyama MDC most of the individuals die due to respiratory or cardiac failure at a mean age of 17 years. Due to better treatment strategies for respiratory insufficiency it is possible that severe cardiac abnormalities become more prevalent [74].

In individuals with MDC1C respiratory insufficiency is prominent complication, in the second decade of life. Mild cardiac impairment are found, but not described as cause of death [72].

Facioscapulohumeral Muscular Dystrophy

General

Facioscapulohumeral muscular dystrophy is an autosomal dominant disorder and most of the time associated with reduced copies (≤10) of the D4Z4 repeat sequences in the subtelomeric region of chromosome 4q35. The dystrophy derives its name from the muscle groups that are first affected—facial and shoulder girdle [1]. It is the third most common muscular dystrophy, after Duchenne and myotonic dystrophy, with an estimated prevalence of 1:22,000 [75]. Clinical signs are highly variable. The age of onset varies from infancy to advanced age, and typically start in the second decade. Also the progressing of the disease is highly variable, even within families, the progression of the disease is most of the time slowly, but may progress rapidly and leads to significant disability. Although the disorder can be associated with severe disabilities, there is a normal life span in these individuals.

When the diagnosis facioscapulohumeral muscular dystrophy is suspected, based on clinical characteristics, molecular diagnostic testing is appropriate to confirm the diagnosis without the need for muscle biopsy.

Cardiac Involvement

Severe cardiac abnormalities are uncommon in individuals with facioscapulohumeral muscular dystrophy [41]. However mild cardiac abnormalities have been noted, characterised by supraventricular arrhythmias and mild conduction disorders [76, 77].

Prognosis

In other muscular dystrophies the life span is most of the time reduced due to severe respiratory and cardiac insufficiency. In individuals with facioscapulohumeral muscular dystrophy both the respiratory and cardiac abnormalities are mild, and so the life span is not limited [75]. Cardiological evaluation is recommended at the moment of diagnosis, further cardiological follow-up should be dictated by the clinical situation [30].

Conclusions

Both dilated cardiomyopathy and skeletal muscular dystrophy are rare disorders, with major impact on the quality of life and with most of the time severe disabilities and reduced life expectancy. The last decades, knowledge about these disorders has grown steeply, however due to the rareness of these disorders most knowledge is based on series with low numbers of individuals.

We showed the overlap between dilated cardiomyopathy and skeletal muscular dystrophy. A majority of the skeletal muscular dystrophies are accompanied by cardiac abnormalities. The severity of these cardiac abnormalities differs per type of skeletal muscular dystrophy and ranges from only ECG abnormalities to severe heart

failure and malignant ventricular arrhythmias. The survival of individuals with skeletal myopathies can be dramatically reduced by these cardiac abnormalities. Fortunately there is more awareness of the occurrence of cardiac abnormalities in individuals with skeletal muscular dystrophy, and cardiac abnormalities can be detected at an earlier stage of the disease so that early measures may prevent or slow progression of the disease.

The genetic cause of these diseases is more often identified in individuals where dilated cardiomyopathy accompanies skeletal muscular dystrophy. This gives the opportunity to improve the diagnostic and treatment strategies specified on the genetic background. However, most of this knowledge is still scarce, due to lack of understanding of the pathophysiology of the mutations and due to small number of individuals affected.

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4
Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Hugh Calkins and Frank Marcus

Abstract

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) is an inherited cardiomyopathy characterized clinically by ventricular arrhythmias, sudden death, and structural abnormalities of the right ventricle. Although structural involvement of the right ventricle predominates, a left dominant form (LDAC) has been described. Structural involvement of both ventricles is common in advanced disease. Due to significant heterogeneity in its manifestation, the diagnosis of ARVC/D is challenging and requires a multifaceted approach to patient evaluation. The recently published Revised Task Force Criteria provide clinicians with a validated model to improve the diagnosis of ARVC/D. The management of ARVC/D is primarily aimed at reducing the burden of symptomatic arrhythmias and decreasing the incidence of sudden cardiac death. Automatic implantable cardioverter-defibrillators (AICDs) significantly reduce mortality in patients with ARVC/D. However, accurate risk assessment is needed to avoid exposing low-risk patients to the long-term complications of AICDs. Strenuous exertion increases the rate of disease progression and increases the risk of sudden death.

Keywords

Arrhythmogenic Right Ventricular Dysplasia (ARVD) • Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC/D) • Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) • Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) • Arrhythmogenic Cardiomyopathy

H. Calkins, MD (✉)
Department of Cardiology,
School of Medicine, Johns Hopkins
University School of Medicine,
Baltimore, MD, USA

Department of Cardiology,
The Johns Hopkins Hospital,
1800 Orleans Street, Baltimore 21287, MD, USA
e-mail: hcalkins@jhmi.edu, www.arvd.com

F. Marcus, MD
Division of Cardiology,
The University of Arizona,
Sarver Heart Center, Tucson, AZ, USA
e-mail: fmarcus@u.arizona.edu

Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) is an inherited cardiomyopathy that is characterized by ventricular arrhythmias, an increased risk of sudden death, and abnormalities of right ventricular structure and function [1–9]. Although structural involvement of the right ventricle predominates, a left dominant form of ARVC/D has been described [9]. In most patients structural abnormalities of the right ventricle

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predominate. The pathologic hallmark of ARVC/D is right ventricular myocyte loss with fibrofatty replacement. Since the first detailed clinical description of the disorder in 1982 [1], significant advances have been made in our understanding of all aspects of this disease. Over the last decade, mutations in several desmosomal proteins have been identified as the genetic basis of ARVC/D. Since a pathogenic mutation can be identified in 30–50 % of affected individuals, genetic testing has emerged as an important diagnostic tool [10, 11]. The purpose of this article is to provide a concise and up-to-date review of the current state of knowledge regarding the natural history, clinical presentation, pathogenesis, diagnosis, and treatment of ARVC/D. Specific emphasis is placed on discussing the characteristics and therapeutic approaches to ventricular arrhythmias that occur in patients ARVC/D.

Natural History and Clinical Presentation

ARVC/D is an unusual condition with an estimated prevalence in the general population of 1 per 5,000 [1, 2]. This is roughly tenfold less common than hypertrophic cardiomyopathy which occurs in about 1 per 500 of the general population.

Four stages of ARVC/D have been described. The first is the "concealed phase" during which time patients are asymptomatic and have no clinical manifestations of ARVC/D. It may not be possible to diagnose ARVC/D during this early "concealed phase". The next phase is an overt clinical disorder characterized by ventricular arrhythmias. Patients in this phase often present with palpitations, syncope ventricular tachycardia or sudden cardiac death. In some patients ventricular arrhythmias may develop before overt evidence of structural heart disease is present. In our experience this is extremely rare. Establishment of a correct diagnosis of ARVC/D is particularly challenging in this situation. However, in the next phase, the overt electrical stage of ARVC/D occurs in the presence of structural heart disease as assessed by the ECG, echocardiogram, and cardiac MRI. The third phase is characterized by progressive RV dysfunction often with subtle left ventricular (LV) involvement. This is followed by the final phase in which the myocardial degenerative process results in severe global dilation with biventricular involvement [1, 2]. Patients usually present during the second to fifth decade of life with palpitations, lightheadedness, syncope, or sudden death [6, 11]. In our experience it is extremely rare to manifest clinical signs or symptoms of ARVD/C prior to the age of 12 years and after the age of 60 years.

Although ARVC/D is predominantly a disease of the right ventricle [7], it is now well established that involvement of the left ventricle is common in patients with advanced disease. Left-dominant arrhythmogenic cardiomyopathy (LDAC) also occurs and is defined by early disease of the LV, often affecting the posterolateral wall, in the absence of significant RV systolic dysfunction [5, 9]. Clinically, patients with LDAC present with VT primarily with a right bundle branch block morphology with evidence of structural abnormalities of the LV myocardium, Global LV dilation can progress to left ventricular systolic failure. The most common ECG features of LDAC are T wave inversions in the lateral chest leads (leads V3 through V6). Although ARVC/D may affect either or both ventricles, our experience is that most ARVC/D patients have little or no LV involvement in the early stages of disease. It is possible that LDAC may be more prevalent than is appreciated since patients with LDAC may be diagnosed as having idiopathic cardiomyopathy. When present, left-dominant disease is more commonly seen in patients with desmoplakin mutations [5, 10].

Histopathology

Post-mortem examination of patients with ARVC/D often shows RV myocardial atrophy with wall thinning, aneurysms and global dilation of the RV. Initial studies evaluating the histology of ARVC/D in autopsy cases described two possible pathologic patterns: fatty and fibrofatty replacement of the myocardium [7]. However, it has been shown that the clinical

profile of patients with purely fatty replacement of the myocardium did not fit the diagnosis of ARVC/D [8]. In fact, fatty infiltration of the heart occurs physiologically and increases with age and body weight. Thus, replacement fibrosis and myocyte loss are now considered the pathologic hallmarks of ARVC/D and fatty replacement is not required for diagnosis. Another common histological finding includes patchy lymphocytic inflammatory infiltrates surrounding areas of myocyte necrosis [7].

Etiology

In most cases, ARVC/D is inherited in an autosomal dominant pattern with significantly variable penetrance and expressivity. Among probands diagnosed with this disease, screening of first degree relatives identifies other affected individuals in approximately 50 % of cases [1, 10–13]. In a minority of cases, ARVC/D is inherited in an autosomal recessive pattern as part of a cardiocutaneous syndrome such as Naxos disease or Carvajal syndrome which is also characterized by woolly hair and palmoplantar keratodermia.

Linkage mapping and candidate gene evaluation studies performed on patients with the autosomal dominant form of ARVC/D initially was not productive due to significant variability in the penetrance and expressivity of the disease. It was the evaluation of patients with Naxos syndrome, a disease with 100 % penetrance by adolescence, that identified a disease causing mutation: a homozygous deletion of two base pairs found in the plakoglobin gene located in the 17q21 locus [14, 15]. The gene encodes a key component of desmosomes, which are complex intercellular adhesion structures found in stratified epithelial cells of the skin as well as in myocytes. Desmosomes are composed of three major groups of proteins: Cadherins are transmembrane proteins which provide the actual mechanical coupling between individual cells and include desmogleins and desmocollins. Desmoplakin is a plakin-family protein which serves to anchor the desmosomal structure to the intermediate filaments of the cell. Lastly, Armadillo proteins including plakoglobin and plakophillin link desmoplakin and the cadherin tails.

The identification of defective desmosomal proteins in Naxos syndrome led to studies investigating their role in other arrhythmogenic cardiomyopathies. The Carvajal syndrome, another cardio-cutaneous syndrome that has left-dominant arryhthmogenic cardiomyopathy, was shown to be associated with a recessive mutation in desmoplakin. Other genetic mutations were subsequently identified in the autosomal-dominant form of ARVC/D and include desmoplakin, desmoglein-2, desmocollin-2 and plakophillin-2 genes [13, 16–20]. Mutations in several extra-desmosomal genes such as those encoding transforming growth factor β3 (TGFβ3), cardiac ryanodine receptor (RyR2) and transmembrane protein 43 (TMEM43) have also been implicated in specific types of atypical forms of ARVC/D [21, 22]. In the United States, a desmosomal protein mutation can be identified in 30–50 % of ARVC/D patients [10, 11]. The most commonly mutated genes are plakophillin-2 (45 %) and desmoglein-2 (9 %). Importantly, while 86 % of patients had a single heterozygous gene mutation, 7 % showed compound heterozygosity and another 7 % showed digenic heterozygosity. This is important as clinicians need to be aware that some individuals with ARVC/D may have more than one mutation in one or more of the many desmosomal proteins. Other candidate genes are likely to be identified in the future. Thus it is possible for the affected individual (the proband) will have more than one defective gene. Since all the genetic abnormalities have not yet been identified, the first degree relatives may not have the known gene but could have inherited the unknown gene mutation. Therefore, finding a pathogenic gender mutation in the proband but not in the first degree relative does not completely exclude the possibility of desmosal mutation in the first degree relative.

It should be mentioned here that not all identified variants are causal mutations [23]. This recent study compared the results of genetic testing in 93 ARVD/C probands, 82 ARVD/C probands from published reports, and 427 healthy controls [12]. Mutations were found in 58 % of ARVD/C cases versus 16 % of controls. Radical mutations were observed in 43 % of

ARVD/C cases versus 0.5 % of controls. In contrast 21 % of ARVD/C cases demonstrated missense mutations versus 16 % of controls. The authors concluded that radical mutations are high probability ARVD/C associated mutations, whereas rare missense mutations need to be interpreted with caution. Recently variants in TITIN have been associated with a ARVC like phenotype [24].

Pathogenesis

Initial attempts to explain the pathogenesis of ARVC/D produced several hypotheses including the dysplastic theory which held that the atrophy and fibrofatty replacement of the RV myocardium in ARVC/D was a congenital, developmental defect. This led to the original description of the syndrome as arrhythmogenic right ventricular dysplasia. It is now clear, however, that the structural defects in ARVC/D are not present at birth but actually develop progressively throughout childhood and early adulthood. Thus the dysplastic theory is only partially correct. "Arrhythmogenic Right Ventricular Dysplasia" or Right Ventricular Cardiomyopathy is still used due to name recognition with this disease.

The genetics of ARVC/D has provided support for the hypothesis that the disease may be caused by desmosomal dysfunction. The pathogenic mechanisms are not fully clear, but several theories have been advanced. Defective desmosomal proteins may lead to impaired mechanical coupling between individual cells, leading to myocyte uncoupling especially under conditions that increase myocardial strain [13, 25–27]. The resulting inflammation, fibrosis and adipocytosis may be a non-specific response to injury similar to that seen in other forms of myocardial damage. This pathogenic model can explain the observation that prolonged strenuous exertion, which increases myocardial strain, significantly increases the risk of an earlier clinical onset of the disease and augments the risk of sudden death [13, 25]. It also explains why the RV, which is more distensible than the LV due to its thinner wall and asymmetric shape, is more often involved in ARVC/D especially in its early stages. Furthermore, defects in mechanical coupling of myocytes may also lead to impairment in electrical coupling. Ultrastructural evaluation of the myocardium of patients with ARVC/D has shown reduced expression of several intercalated disc proteins, including Connexin-43, a key component of gap junctions [26, 27]. This finding may account for the development of conduction delay and arrhythmias even in the absence of significant structural defects in the early "concealed" phase of the disease.

The mechanisms that lead to the variability in penetrance and expressivity of disease are still not fully understood. Family members with identical genotypes and even monozygotic twins show significant differences in symptomatology, presence and distribution of structural changes, and rate of disease progression [28]. This observation has led to the "second hit" hypothesis which suggests that modifier genes and/or environmental factors are likely responsible for phenotypic heterogeneity. Xu et al. recently showed that compound and digenic hetrozygosity was associated with more severe disease in plakophillin-2 mutants [29]. Other such disease modifying genes are likely to be identified in the future. Furthermore, viral genome has been found at a higher rate in myocardial biopsies from ARVC/D patients compared to controls suggesting that viral myocarditis may precipitate or exacerbate disease in patients with desmosomal dysfunction [30].

Diagnostic Approach

Due to the significant heterogeneity in the manifestation of disease, there is no single gold-standard diagnostic test for ARVC/D [31, 32]. Instead, the diagnosis relies upon the demonstration of a combination of defects in RV morphology and systolic function, depolarization/repolarization abnormalities on electrocardiogram (ECG), characteristic tissue pathology, typical arrhythmias and family history. Thus the initial evaluation of all patients suspected of having ARVC/D should include a physical exam and clinical history including family history of arrhythmias or sudden death, ECG, signal averaged-ECG (SAECG), 24-h Holter monitoring and comprehensive non-invasive imaging of both ventricles. If this non-invasive workup is

suggestive but not diagnostic of ARVC/D, further testing should be considered to establish the diagnosis including contrast ventriculography, endomyocardial biopsy with or without electroanatomic mapping, and electrophysiologic testing.

The standard 12-lead ECG is abnormal in the majority of patients with ARVC/D [6, 11]. Because of this observation, the finding of a normal ECG in a patient with ARVC/D renders the diagnosis of ARVC/D less likely. T wave inversion (TWI) in the right precordial leads (V1–V3) is the most common ECG manifestation of ARVC/D [33, 34]. TWI in leads V1 through V3 is now considered major criteria for ARVC/D and TWI in leads V1 and V2 is considered minor criteria [33]. A recent study demonstrated that TWI through V3 was the ECG feature with the optimal sensitivity and specificity for the diagnosis of ARVC/D in patients without a right bundle branch block (RBBB). RBBB is a common finding in ARVC/D patients, especially in those with severe structural disease, and its presence obscures the interpretation of the known depolarization abnormalities. In patients with incomplete RBBB, TWIs through V3 still appear to be the feature with the optimal sensitivity and specificity. However, in patients with complete RBBB, R/S ratio < 1 in V1 seems to provide the optimal sensitivity and specificity (88 and 86 %, respectively) in diagnosing ARVC/D [33]. T wave inversion beyond V3 in patients with complete RBBB is also a feature of ARVC/D [33]. Epsilon waves, which are distinct low frequency deflections in the ECG that occur following the QRS and before the T wave are far less common and are a marker of advanced ARVC/D. Terminal activation delay, which is defined as a prolonged upstroke of the S wave until the QRS returns to baseline (>55 ms) is a more recently described marker of ARVC/D [32].

A signal-averaged ECG (SAECG) provides increased sensitivity in the detection of activation delay [35]. The technique involves obtaining an arithmetic mean of sequential ECG complexes over time which increases the signal-to-noise ratio, thereby allowing detection of very low-amplitude "late potentials". These microvolt potentials may be manifest as epsilon waves on a 12-lead ECG. The standard protocol involves recording a SAECG using three band-pass filters (25–250 Hz, 40–250 Hz, and 80–250 Hz). The SAECG is defined as abnormal if one or more of the following criteria are present: (1) filtered QRS duration (fQRS) >114 ms. (2) terminal low amplitude (<40 μV) signal duration ≥38 ms. (3) root mean square voltage of the terminal 40 ms of the filtered QRS complex (RMS40) <20 μV [35]. The likelihood of an abnormal result seems to be correlated with the degree of structural abnormalities. Thus, the SAECG may be normal in the early concealed phase of the disease.

Ambulatory Holter monitoring is a valuable test for the evaluation of patients with suspected ARVC/D. The presence of frequent ventricular ectopic beats or sustained/non-sustained ventricular tachycardias (VT), particularly of LBBB morphology, is consistent with the diagnosis of ARVC/D. If a 24-h Holter monitor does not capture any arrhythmias, further options include extending the duration of Holter monitoring, implanting a loop recorder or exercise testing to induce VTs. It is generally accepted that less than 200 PVCs per 24 h is within normal limits. The presence of 1,000 PVCs or more per 24 h is commonly observed in patients with ARVC/D. Recently, we have reported that the number of PVCs on a 24 h Holter is directly proportional to a patient's chance of developing appropriate ICD therapy for VT or VF in patients with an ICD implanted for primary prevention [36]. This observation is important since Holter monitoring is widely available and the results can be clearly interpreted. Holter monitoring can also be done on a yearly basis to assist in evaluating a patient's arrhythmic risk.

Assessment of ventricular structure and function is critical for the diagnosis of ARVC/D. Echocardiography provides the least expensive and most widely available non-invasive method of imaging the RV. Findings on a transthoracic echocardiogram (TTE) that are suggestive of ARVC/D include global or segmental wall motion abnormalities (akinesis/dyskinesis) with cavity dilation, hypertrophic RV trabeculation and systolic dysfunction. RVOT dilation (diameter > 30 mm) has been reported to have the highest sensitivity and specificity (89 and 86 %, respectively) of echocardiographic parameters in diagnosing ARVC/D [32]. Table 4.1 lists the echo parameters which have been incorporated into the revised Task Force criteria [32].

Table 4–1. 2012 Task Force Criteria for ARVD/C

1. Global or regional dysfunction and structural alterations
   - *Major*
     - 2d echo criteria
       - Regional RV akinesia, dyskinesia, or aneurysm AND 1 of the following measured at end diastole
         - PLAX RVOT >32 mm or
         - PSAX RVOT >36,
         - Fractional area change <33 %
     - MRI criteria
       - Regional RV akinesia or dyskinesia or dyssynchronous RV contraction AND 1 of the following
         - Ratio of RV end-diastolic volume to BSA >100, <110 ml/m2 (male) or >100 mL/m2
         - RV ejection fraction > 40 % < 45 %
     - RV angiography criteria
       - Regional RV akinesia, dyskinesia, or aneurysm
   - *Minor*
     - 2d echo criteria
       - Regional RV akinesia or dyskinesia or dyssynchronous RV contraction AND 1 of the following measured at end diastole
         - PLAX RVOT > 29 < 32 mm or
         - PSAX RVOT > 32 < 36
         - Fractional area change > 33 % < 40 %
     - MRI criteria
       - Regional RV akinesia or dyskinesia or dyssynchronous RV contraction AND 1 of the following
         - Ratio of RV end-diastolic volume to BSA >110 ml/m^2 (male) or >100 mL/m^2
         - RV ejection fraction <40 %
2. Tissue characterization of wall
   - *Major*
     - Residual myocytes <60 % by morphometric analysis (or <50 % if estimated), with fibrous replacement of the RV free wall myocardium in >1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
   - *Minor*
     - Residual myocytes 60–75 % by morphometric analysis (or 50–65 % if estimated), with fibrous replacement of the RV free wall myocardium in >1 sample with or without fatty replacement of tissue on endomyocardial biopsy
3. Repolarization abnormalities
   - *Major*
     - Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS >120 ms)
   - *Minor*
     - Inverted T waves in V1 and V2 in individuals >14 years of age (in the absence of complete RBBB) or in V4, V5, and V6
     - Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of a complete RBBB
4. Depolarization/conduction abnormalities
   - *Major*
     - Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of T wave) in the right precordial leads (V1–V3)
   - *Minor*
     - Late potentials by SAECG in >1 of 3 parameters in the absence of a QRSd of >110 ms on standard ECG
     - Filtered QRS duration (fQRS) >114 ms
     - Duration of terminal QRS < 40 μV >38 ms
     - Root-mean-square voltage of terminal 40 ms < μV
     - Terminal activation duration >55 ms measured from the nadir of the end of the QRS, including R′, in V1, V2, or V3 in absence of complete RBBB
5. Arrhythmias
   - *Major*
     - Nonsustained or sustained VT of LBBB morph with superior axis
   - *Minor*
     - Nonsustained or sustained VT of RVOT configuration, LBBB morph with inferior axis or of unknown axis
     - >500 PVCs per 24 h (Holter)
6. Family history
   - *Major*
     - ARVD/C in first degree relative who meets Task Force Criteria
     - ARVD/C confirmed pathologically at autopsy or surgery in first degree relative
     - Identification of pathogenic mutation categorized as associated or probably associated with ARVD/C in the patient under evaluation
   - *Minor*
     - History of ARVD/C in first degree relative in whom it is not possible to determine whether the family member meets Task Force Criteria
     - Premature sudden death (<35 years of age) due to suspected ARVD/C in a first degree relative
     - ARVD/C confirmed pathologically or by current Task Force Criteria in second-degree relative

Adapted from Ref. [8]

Cardiac MRI (CMR) is an imaging modality which has the benefit of providing tissue characterization and identification of intra-myocardial fat and fibrosis in addition to assessment of ventricular structure and function. However, there appears to be significant inter-reader variability in the interpretation of CMR, possibly due to the limited experience with this imaging modality for the diagnosis of ARVC/D in many centers. Furthermore, intramyocardial fat occurs physiologically in older, obese patients and is not specific for ARVC/D in the absence of functional abnormalities. Table 4.1 shows the MRI parameters which have been incorporated into the revised Task Force criteria [32].

Endomyocardial biopsy may be obtained to demonstrate the characteristic histopathology if the diagnosis is unclear or to rule out a competing diagnosis. However, the test appears to have low diagnostic sensitivity for several reasons including patchy distribution of disease and high rate of sampling error [33]. The thin, dyskinetic areas of the RV free wall are the most likely sites to provide an optimal specimen, but targeting these areas may carry a higher risk of perforation and tamponade. A recent small study

showed that immunohistochemical analysis of desmosomal protein distribution in endomyocardial biopsy specimens can provide high sensitivity and specificity (91 and 82 %, respectively) for the diagnosis of ARVC/D [37]. Sarcoidosis and giant cell myocarditis can cause patterns similar to that observed in ARVC/D [38]. Table 4.1 contains the pathological parameters which have been incorporated into the revised Task Force criteria [32]. Despite the potential value of endomyocardial biopsy, it is our impression that it is rarely performed in the United States. This is a reflection of the fact that invasive cardiologist are wary of biopsying the RV free wall since the septum is usually unaffected in ARVC/D. Furthermore, the function and structure abnormalties of the RV can usually be ascertained with non-invasive imaging techniques, such as CMR, which usually obviates the need for a biopsy. However, it is important to note that sarcoidosis can often mimic ARVC/D, making it necessary to obtain a biopsy to distinguish between the two conditions in select patients. In this case, a septal biopsy may be sufficient for differential diagnosis since the septum is not spared in sarcoidosis.

The role of genetic testing in the diagnosis of ARVC/D is increasing in importance. Identification of a known or suspected disease-causing mutation in patients undergoing evaluation for ARVC/D is now considered a major diagnostic criterion [32]. However, currently only 30–50 % of ARVC/D probands are found to have a pathogenic mutation [10, 11] possibly due to the high incidence of rare mutations in many patients. Thus, while genetic testing can be used to confirm ARVC/D in index cases, lack of an identifiable mutation does not exclude the disease. The sensitivity of mutation analysis may improve as other new candidate genes are discovered. However, at present the most important utility of this test is in the screening of asymptomatic family members of probands who have a pathological genetic abnormality. Theoretically these family members have a 50 % chance of inheriting the disease-causing mutation. Asymptomatic gene carriers are likely to require life-long monitoring due to age-dependent penetrance, while non-carriers are unlikely to have the disease. However, as mentioned previously, the non-carrier of the known genetic defect may still be a carrier of a still yet undiscovered gene and still needs serial evaluation.

Differential Diagnosis

The diagnosis of ARVC/D should be considered in any patient who does not have known heart disease and who presents with frequent PVCs or symptomatic ventricular tachycardia especially if there is left bundle branch block (LBBB) morphology with superior axis. The most common conditions that must be considered in the differential diagnosis include idiopathic right ventricular outflow tract ventricular tachycardia (RVOT-VT) and cardiac sarcoidosis. Of note, ARVC/D can be very difficult to distinguish from RVOT-VT in the absence of structural changes during early disease. They can both present with LBBB-type VT with inferior axis. The differential diagnosis is based on the fact that RVOT-VT is non-familial, and patients do not have the characteristic ECG/SAECG abnormalities of ARVC/D and do not usually have inducible arrhythmias on programmed electrical stimulation. This diagnostic distinction is important to make because RVOT-VT carries a benign prognosis and generally can be effectively treated with antiarrhythmic drugs or catheter ablation. Several studies have recently compared the morphology of VT or PVCs with a LBBB inferior axis morphology in patients with idiopathic RVOT VT with patients with ARVC/D [39, 40]. Krahn et al. reported that an algorithm combining lead I QRS duration for sensitivity and axis for specificity is useful for differentiating the two tachycardia substrates [39]. A lead I QRS duration $\geq$120 ms had a sensitivity of 100 %, specificity 46 %, positive predictive value of 61 %, and negative predictive value of 100 % for ARVC/D. The addition of a mean QRS axis <30° (R < S in lead III) to the above criterion increased specificity for ARVD/C to 100 % [39]. A more recent study examining patients with PVCs or VT with a LBBB inferior axis morphology confirmed that a QRSd >120 ms in lead V1 during VT or with PVCs favors the diagnosis of ARVC/D as compared with idiopathic RVOT VT [40].

Cardiac sarcoidosis should be suspected in patients who have evidence of conduction

system abnormalities, especially in the presence of other extracardiac symptoms. In some situations, an endomyocardial biopsy may become necessary to differentiate between the two disorders.

A minority of ARVC/D patients first present with symptoms of RV systolic heart failure. The differential diagnosis in such patients includes RV infarction or pulmonary hypertension. Dilated cardiomyopathy must be considered if there is evidence of biventricular failure. Patients with dilated cardiomyopathy who have early significant ventricular ectopy should be evaluated for possible biventricular arrhythmogenic cardiomyopathy (BVAC).

Diagnostic Criteria

In 1994, an international group of experts created the Task Force (TF) Criteria for the diagnosis of ARVC/D based on the initial experience with symptomatic probands at major referral centers [1]. They established major and minor criteria in six categories including structural changes/ systolic dysfunction, tissue pathology, repolarization and depolarization abnormalities, arrhythmias and family history. In that publication the diagnosis of ARVC/D was based on the presence of two major, one major and two minor or four minor criteria. Despite being quite specific, these TF criteria lacked sensitivity for diagnosis especially in presymptomatic patients. Recently, the TF criteria were revised to improve upon the subjectivity of some of the original criteria and to increase sensitivity by integrating new knowledge and technology [32] (Table 4.1). Although these new criteria have only been published recently, they are being enthusiastically adopted for the diagnosis of ARVC/D since they are based on extensive experience and were established based on comparison of the sensitivity and specifically of the parameters in a large number of patients with ARVC/D compared with data from normal controls.

I do consider the weight of genetic variants in the scoring system overvalued (major criterium) given the observation discussed above. You may consider to add that here as a warning.

Management

Implantable Cardioverter Defibrillators

Prevention of sudden cardiac death is the primary goal of management. Several studies of ARVC/D probands who received an ICD showed appropriate interventions in 48–78 % of patients over a period of 3–7 years [41–43]. Of these, 25–40 % were considered life-saving based on the presence of rapid VT/VF with a rate of ≥240 BPM over a period of 3–7 years [41–43]. Predictors of appropriate therapy included prior VF arrest, syncope, severe RV dilation, LV dysfunction, young age and definite disease by TF criteria. However, in one study even patients with probable ARVC/D received appropriate ICD intervention in 33 % of cases. Furthermore, the incidence of these rapid ventricular arrhythmias appeared to be similar in patients receiving ICD for primary versus secondary prevention. There remains debate regarding the predictive ability of EP testing in stratifying arrhythmia risk.

We recently reported the results of a study which investigated the incidence of appropriate ICD therapy among 84 patients who had an ICD implanted for primary prevention of VT or VF [36]. Over a mean follow up of 4.7 ± 3.4 years, appropriate ICD therapy was seen in 40 (48 %) patients of which 16 (19 %) received interventions for rapid VT/VF. Proband status ($p < 0.001$), inducibility at electrophysiological (EP) study ($p = 0.005$), presence of nonsustained ventricular tachycardia (NSVT) ($p < 0.001$) and Holter PVC count >1,000/24 h ($p = 0.024$) were identified as significant predictors of appropriate ICD therapy. The 5 year survival free from appropriate ICD therapy for patients with one, two, three and four risk factors was 100, 83, 21 and 15 %, respectively. Inducibility at EP study (HR 4.5, 95 % CI 1.4–15, $p = 0.013$) and NSVT (HR 10.5, 95 % CI 2.4–46.2, $p = 0.002$) remained as significant predictors on multivariable analysis. These findings are important as they demonstrate that nearly half of the ARVC/D patients treated with an ICD for primary prevention experienced appropriate ICD interventions. Inducibility at EP study and NSVT are independent strong predictors of appropriate ICD therapy. More frequent

ventricular ectopy is associated with progressively more common ICD therapy. Incremental risk of ventricular arrhythmias and ICD therapy was observed in the presence of multiple risk factors. In considering these results it is important to recognize that the use of rapid VT/VFL as a surrogate for sudden death results in an overestimation of this endpoint.

The issue of which patients with ICD require ICD implantation remains an area of uncertainty. At present we generally recommend ICD placement in all probands who meet Task Force criteria. With each discussion the risks and benefits of ICD implantation are reviewed in detail so an informed decision can be made. However, we are more circumspect about recommending implantation of an ICD in a family member of a proband who has been diagnosed with ARVC/D. These individuals are now being identified at a much earlier stage in their disease than was possible previously due to genetic testing and improved cardiac imaging. With exercise restriction and the use of a beta blocker their risk of sudden death appears to be reduced to a level below which placement of an ICD is justified by risk assessment. If a decision is made not to implant an ICD we emphasize close monitoring and serial follow-up to promptly identify those individuals who become symptomatic and would clearly benefit from an ICD. It is worth noting that the threshold for implanting an ICD for primary prevention of sudden death in ARVC/D patients is considerably higher in Europe than in the United States.

Catheter Ablation of VT

Catheter ablation is another option for treatment of patients with ARVC/D who have ventricular tachycardia. Although several studies have been published which have reported good results, data collected by the Johns Hopkins ARVC/D Registry which follows ARVC/D patients from around the United States has been less encouraging [44–50]. We recently reported on a cohort of 24 patients who underwent ARVC/D for ventricular tachycardia [46]. These 24 patients underwent 48 ablation procedures at 29 different electrophysiology centers in the United States. The cumulative VT free survival was 75 % at 1.5 months, 50 % at 5 months, and 25 % at 14 months. The immediate success of the procedure had no bearing on recurrence; nor did the use of assisted mapping techniques, or repetition of the procedure [46]. Although the absolute recurrence rate of VT or the development of new VTs following VT ablation is substantial over time, catheter ablation has been shown in many studies to reduce the frequency of VT episodes and the need for ICD therapies. This has important implications for quality of life. More recently there have been several studies which have reported favorable results with epicardial ablation of VT in patients with ARVC/D [49]. The observation that VT can only be ablated with an epicardial approach in some patients is consistent with the observation that ARVC/D generally begins in the epicardium of the right ventricle and progresses towards the endocardium [1]. We are currently gathering data on a large number of patients who have had an epicardial ablation procedure for ARVC/D in the United States.

It is clear that catheter ablation of VT is of value in reducing the frequency of VT episodes and appropriate ICD therapies in patients with ARVC/D. This in turn results in improved quality of life. It is important to bear in mind however, that VT ablation is not curative and these patients remain at risk of VT recurrence or sudden death. Because of this VT ablation should not be viewed as an alternative to ICD implantation. We generally consider catheter ablation in patients with an ICD who have experienced recurrent VT and have failed or been intolerant to pharmacologic therapy. Whether catheter ablation should be employed prior to or after failure of antiarrhythmic drug therapy including sotalol or amiodarone is a decision that must be discussed fully with patients so that an informed decision can be made.

Pharmacologic Therapy

Pharmacologic treatments such as beta-blockers and class III antiarrhythmic agents (sotalol, amioadrone) are commonly used to reduce the

burden of arrhythmias. Sotalol appears to be the most effective AAD to prevent inducible VT in patients with ARVC/D [51, 52]. Amiodarone alone or in combination with β-blocking drugs may be an alternative in nonresponders, but frequent side effects of amiodarone during long-term therapy in young patients limit this pharmacological strategy.

However, evidence to support their use is not definitive. A recent retrospective analysis of 95 ARVC/D patients with ICDs reported no improvement in arrhythmias with beta-blockers or sotalol, but there was a significant improvement with amiodarone in a small number of patients [53]. Larger studies are needed to validate the use of amiodarone to reduce appropriate ICD interventions. Beta-blockers and ACE-Inhibitors are also used due to their proven benefit in reducing mortality and slowing disease progression in other cardiomyopathies, but evidence for their efficacy in ARVC/D is lacking. One study from Japan reported that carvedilol therapy improved LV function in patients with ARVC/D [54].

Exercise Restriction

An important recommendation for patients with ARVC/D is exercise restriction. Evidence to support the value of exercise restriction includes the well-established observation that many patients who develop ARVC/D are competitive athletes. Furthermore, ventricular arrhythmias commonly occur during exercise. A study by Kirchof et al. in a heterozygous plakoglobin murine model of ARVC/D subjected to endurance training provide additional support the value of exercise restriction [55]. Thus, it is currently recommended that competitive athletics and endurance sports should be restricted in patients with ARVC/D. Whether lower levels of exercise are "safe" remains uncertain. Our current advice to patients is to limit exercise to walking and golf. If higher levels of exercise are performed such as jogging or bicycle riding we recommend that it be limited in duration and intensity as much as possible. These recommendations need to be balanced with quality of life considerations [56].

Cardiac Transplantation

Cardiac transplantation is considered in patients with progressive heart failure and/or intractable recurrent ventricular arrhythmias [57]. Few patients with ARVC/D require cardiac transplantation [6]. We recently reported the details of 18 ARVC/D patients who underwent cardiac transplantation for ARVC/D. The average age of first ARVC/D symptoms was 24 ± 13 years (median age 18 years) and the average age at cardiac transplant was 40 ± 14 years (median age 44 years). Thirteen patients were transplanted predominately because of HF symptoms and 5 were transplanted predominately for VT. The results of this study provided new insight into the population of patients that will ultimately require cardiac transplantation for ARVC/D. These patients often had clinical onsets of the disease at a relatively young age, and most commonly with VT or HF symptoms. One year after transplantation, survival was 94 and 88 % were alive at an average post-transplant follow-up of 6.2 ± 4.8 years (median 4.5 years).

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5
The Wolff-Parkinson-White Syndrome and the Risk of Sudden Death

Michael H. Gollob, Rafeeq Samie, David H. Birnie, Martin S. Green, and Robert M. Gow

Abstract

Over 80 years ago, Drs. Wolff, Parkinson and White described the ECG characteristics and arrhythmia vulnerability of a young cohort of individuals. The condition would soon bear their names, and through subsequent decades of clinical, anatomical and physiological observations, the Wolff-Parkinson-White syndrome fascinated the cardiology field.

In more recent years, the condition has become recognized as a potential cause of sudden cardiac death in previously well individuals. The genetic basis of a complex form of Wolff-Parkinson-White syndrome associated with metabolic storage disease has now been recognized. Lastly, the advent of catheter ablation therapy in the last 20 years has allowed for cure of this condition. This chapter will review the history of this common condition, the variants in anatomy and physiology, genetics, and association with sudden cardiac death.

Keywords

WPW • Sudden death • PRKAG2 • Preexcitation • Re-entry arrhythmia

History

In 1930, Drs. Wolff, Parkinson and White described a series of patients with the electrocardiographic (ECG) features of a short PR interval and "bundle-branch block" QRS pattern, who also had frequent paroxysms of supraventricular tachycardia [1]. The condition would soon bear their name and be termed the Wolff-Parkinson-White (WPW) syndrome. The ECG description would be refined, and the widened QRS described to depict a slurred upstroke or delta wave, and alternatively noted to represent ventricular preexcitation.

Some 15 years following their original clinical description, the anatomic basis for a short PR interval and delta wave was identified through

M.H. Gollob, MD (✉)
Arrhythmia Research Laboratory,
Division of Cardiology, Department of Medicine,
University of Ottawa Heart Institute,
Rm. H350, 40 Ruskin St., Ottawa, ON K1Y 4W7, Canada
e-mail: mgollob@ottawaheart.ca

R. Samie, MD • D.H. Birnie, MD • M.S. Green, MD
Division of Cardiology, Department of Medicine,
University of Ottawa Heart Institute,
Ottawa, ON K1Y 4W7, Canada
e-mail: dbirnie@ottawaheart.ca

R.M. Gow, MD
Division of Cardiology, Department of Medicine,
Children's Hospital of Eastern Ontario,
University of Ottawa,
Ottawa, ON, Canada
e-mail: rgow@cheo.on.ca

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histologic examination of hearts from deceased patients with WPW. Wood [2] and Ohnell [3] both described the existence of accessory muscular connections (accessory pathways) between atrial and ventricular myocardium. However, debate continued over the role of these observations in relation to the physiologic mechanism of ventricular preexcitation and supraventricular tachycardia in the WPW syndrome [4, 5].

The physiologic basis of WPW and the mechanism of tachycardia were firmly established by the seminal work of Drs Durrer and Wellens [6, 7]. Through the technique of programmed electrical stimulation and intracardiac catheters recording atrial and ventricular signals, they demonstrated the inducibility of reciprocating tachycardia utilizing the normal atrio-ventricular (A-V) conduction axis and an accessory conducting circuit (the accessory pathway) in WPW patients. The reciprocating or 're-entry' mechanism of tachycardia was consistent with the initial hypothesis of tachycardia mechanisms proposed by Ralph Mines in 1914 [8]. These landmark studies set the stage for curative therapy, first by an open-heart surgical procedure [9]. In 1984, Morady and Scheinman developed the technique of catheter ablation [10]. The use of this method for eradicating accessory pathway tissue responsible for WPW became routine with the use of radiofrequency energy, and provided a safe, minimally invasive procedure for the cure of WPW [11–13]. The latest advance in the history of this fascinating syndrome has been the identification of a genetic cause for a familial form of WPW [14], providing the opportunity to now understand the molecular basis and embryologic development of the substrate for WPW, the accessory AV connection, some patients with a familial form of the condition.

Since the pioneering work of these leaders in the arrhythmia field, much has been learned about variations that exist in the physiology and anatomic basis of the WPW syndrome (Fig. 5.1).

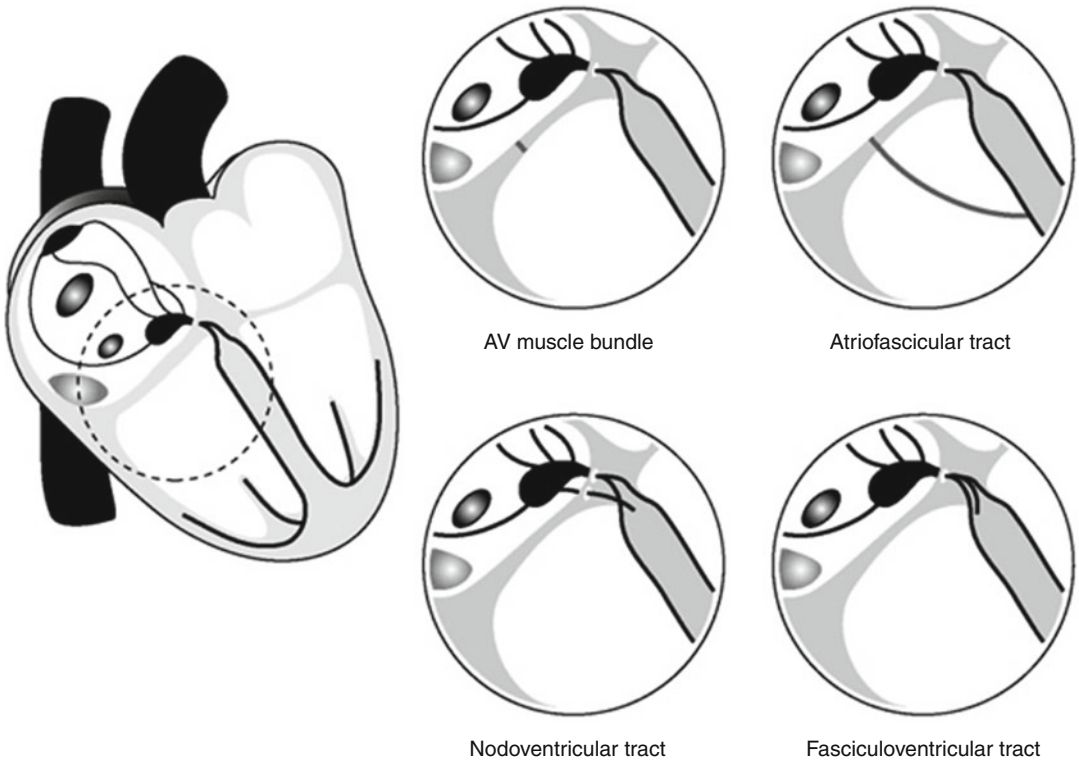

Figure 5–1. Graphic illustration of the anatomic variants for ventricular preexcitation. The most common AV accessory connection is a muscle bundle crossing the AV annulus, giving rise to the accessory pathway responsible for most cases of WPW. Variant AV connections may exist, including the atriofascicular pathway that connects atrial musculature into the distal right bundle branch. True Mahaim fibers, nodoventricular and fasciculoventricular tracts, arise from the normal AV conduction axis and insert into the summit of the interventricular septum

In addition, it is now recognized that the arrhythmias associated with WPW may present more than just a symptomatic nuisance, and lead to sudden cardiac death in a minority of patients.

Unusual Variations of Accessory A-V Connections in WPW Syndrome

WPW is relatively common arrhythmia condition, with an estimated prevalence of 1/500 [15]. Although the vast majority of patients have a common form of A-V connections, commonly referred to as a 'Kent bundle', many variations of accessory A-V connections exist. These variations may be related to unusual accessory pathway anatomic locations, distal connections to portions of the conduction system rather than ventricular myocardium, or unusual conduction properties of the accessory connections.

Some of these variations may be present in patients at risk for sudden arrhythmic death and in some cases these variations may confuse the diagnosis or management. In general, sudden arrhythmic death associated with WPW syndrome is thought to be mainly due to preexcited atrial fibrillation or flutter with extremely rapid A-V conduction over the accessory pathway, and subsequent degeneration to ventricular fibrillation or flutter (VF) [16]. Since these accessory pathways must be capable of rapid antegrade conduction, it has been assumed that manifest preexcitation must be a marker of those with a risk of arrhythmic death. However, in occasional patients the preexcitation may not be manifest during sinus rhythm despite the ability of the accessory pathway to sustain rapid antegrade conduction (The *Wolff* in Sheep's Clothing*)*. What are the references to back up this statement? This phenomenon is usually related to either accessory pathway location or decremental conduction within the pathway.

The Wolff in Sheep's Clothing

Manifest preexcitation during sinus rhythm occurs when activation from the atria reaches the ventricle via the accessory pathway before the competitive activation via the A-V node and His-Purkinje system. However, when accessory pathway conduction is slow (such as is seen with decremental accessory pathways) or when conduction via the A-V node is more rapid, ventricular preexcitation on the 12-lead ECG may be minimal during sinus rhythm despite the ability of the pathway to sustain rapid tachycardia (Fig. 5.2). Thus, the degree of preexcitation observed on resting ECG is not a predictor for the risk of malignant arrhythmias.

Unusual Accessory A-V Pathway Locations

Several unusual accessory pathway locations have been described. These include ventricular insertions in the RV outflow tract [17], and atrial insertions at the RA and/or LA appendage [17, 18]. In addition, accessory connections may terminate in portions of specialized conduction system. Typically these are atriofascicular accessory pathways with distal termination in the distal ramifications of the right bundle branch and often with decremental A-V node-like properties [19–22]. Atriofascicular accessory connections are potentially troublesome since the ECG during sinus rhythm shows little or no evidence of preexcitation. Once again, the absence of manifest preexcitation does not preclude rapid and potentially life-threatening tachycardia that uses the accessory pathway in the antegrade direction (Fig. 5.3). Although there may be clues in the sinus rhythm ECG to the presence of these pathways, these are not universally present [23]. In view of the often normal appearing resting ECG, regular, wide-complex, antedromic tachycardia mediated through these accessory connections are frequently incorrectly diagnosed as ventricular tachycardia by the non-arrhythmia specialist.

Unusual accessory A-V connections have also been described in the coronary sinus musculature [24]. In these cases, the lattice-work array of coronary sinus musculature may connect to the left ventricle via the middle cardiac vein or other posterior coronary vein. In addition, accessory pathways may be associated with a diverticulum at the mouth of the coronary sinus [25]. A characteristic ECG pattern of ventricular

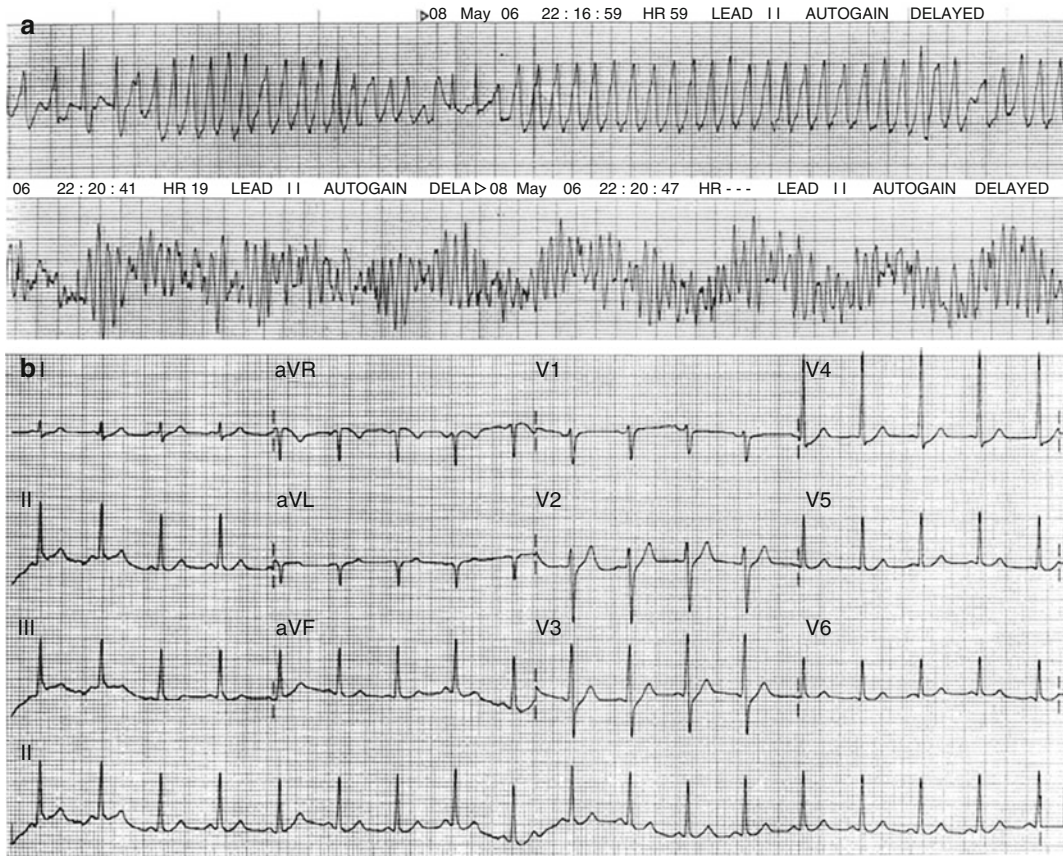

Figure 5–2. (Panel **a**) This shows a monitor lead from a 27 year old man who presented to the emergency department with rapid palpitation. The *top strip* shows preexcited atrial fibrillation. The *bottom strip* recorded about 3–4 min later after degeneration to ventricular fibrillation. (Panel **b**) This shows the 12 lead ECG from the same patient recorded after successful defibrillation. Note the absence of manifest preexcitation despite the fact that the accessory pathway was capable of rapid A-V conduction. The accessory pathway was successfully ablated on the lateral mitral annulus

preexcitation with QS complexes of the inferior leads is a clue to this unusual connection (Fig. 5.4).

Other unusual accessory AV connections exist but are rarely seen to participate in tachycardia. These include fasciculoventricular connections, which represent fibres originating from the His or bundle-branch fascicles and connecting to the summit of the interventricular septum, as originally described by the pathologist Ivan Mahaim [26]. These accessory connections do not participate in reentrant tachycardia, but may have antegrade conduction and produce some degree of ventricular preexcitation on ECG. Occasionally, these connections may coexist with other arrhythmic substrates [27–29].

WPW and Congenital Heart Disease

It is recognized that accessory pathways occur more frequently in patients with congenital heart disease than in the general population. A prevalence of between 2.7 and 8.6 per 1,000 has been found. More specifically, accessory pathways and the WPW syndrome occur more frequently in some forms of congenital heart disease than others. Ebstein's anomaly of the tricuspid valve is the most common anomaly associated with WPW (10–30 %), followed by the various forms of single ventricle, atrial septal defects, and congenitally corrected transposition (L-TGV) among others [30]. The WPW pattern on the electrocardiogram is seen in between 4 and 26 % of patients with Ebstein's anomaly. Importantly,

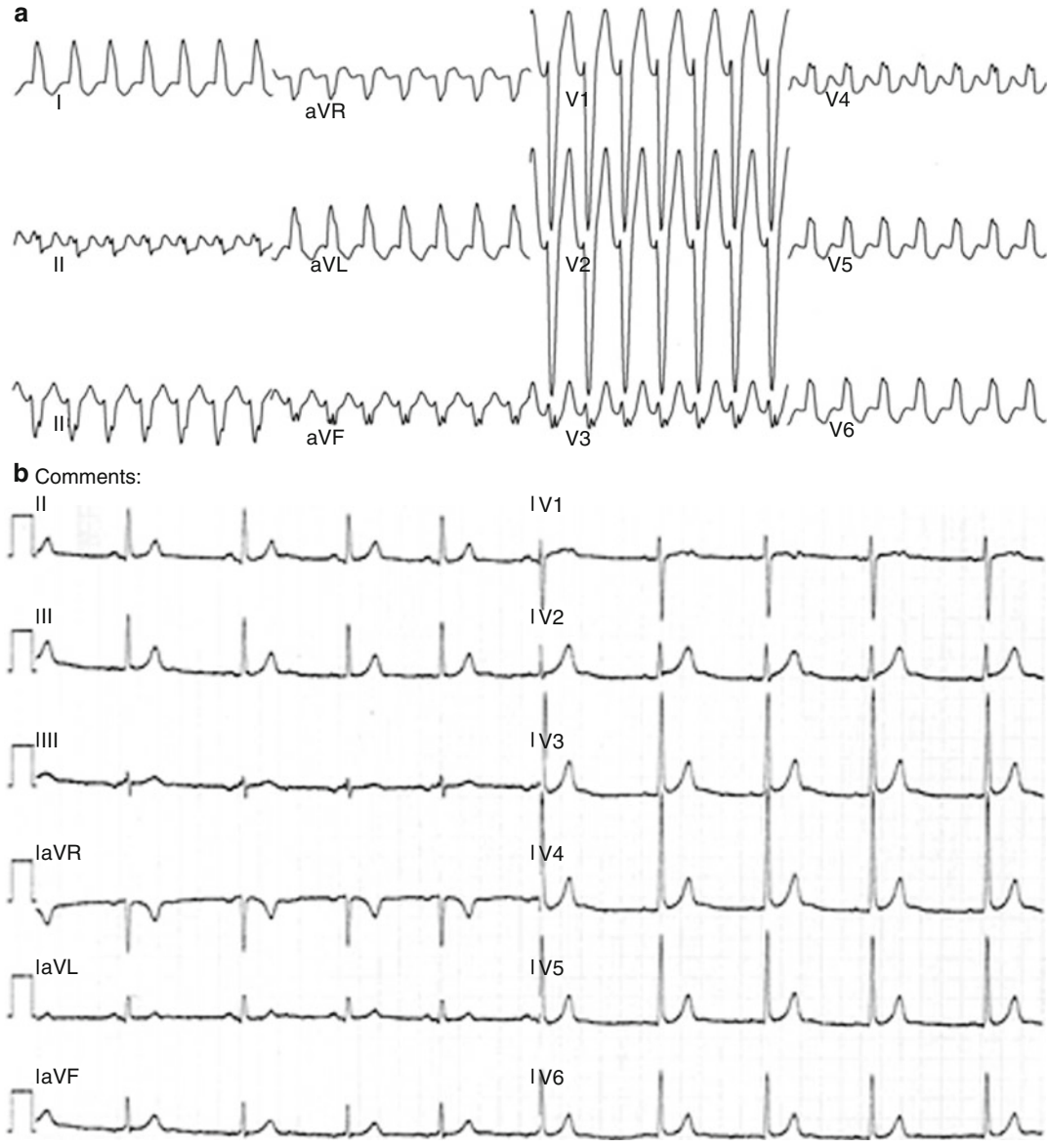

Figure 5–3. (Panel **a**) This shows a wide QRS tachycardia induced in the electrophysiology laboratory. The tachycardia has LBBB-like morphology with left axis deviation. This was shown to be an antidromic tachycardia using a right anterior atriofascicular accessory pathway in the antegrade direction and the A-V node retrogradely. (Panel **b**) This is the 12 lead ECG from the same patient showing no evident preexcitation. The accessory pathway had decremental conduction properties such that the normal sequence of ventricular activation was preserved. The atriofascicular accessory pathway was successfully ablated in the right anterior region in close proximity to the A-V node

multiple pathways are found in about one half of patients, and the pathways are predominantly right sided. Rarely, an accessory pathway may be created during surgical anastomosis of atrial tissue to the ventricular myocardium in the Bjork modification of the Fontan operation [31].

Uncontrolled arrhythmias causing death in patients with WPW have been described following cardiac surgery to correct congenital abnormalities. Consequently, it has been recommended that accessory pathways be ablated prior to surgery, especially if vascular or cardiac chamber

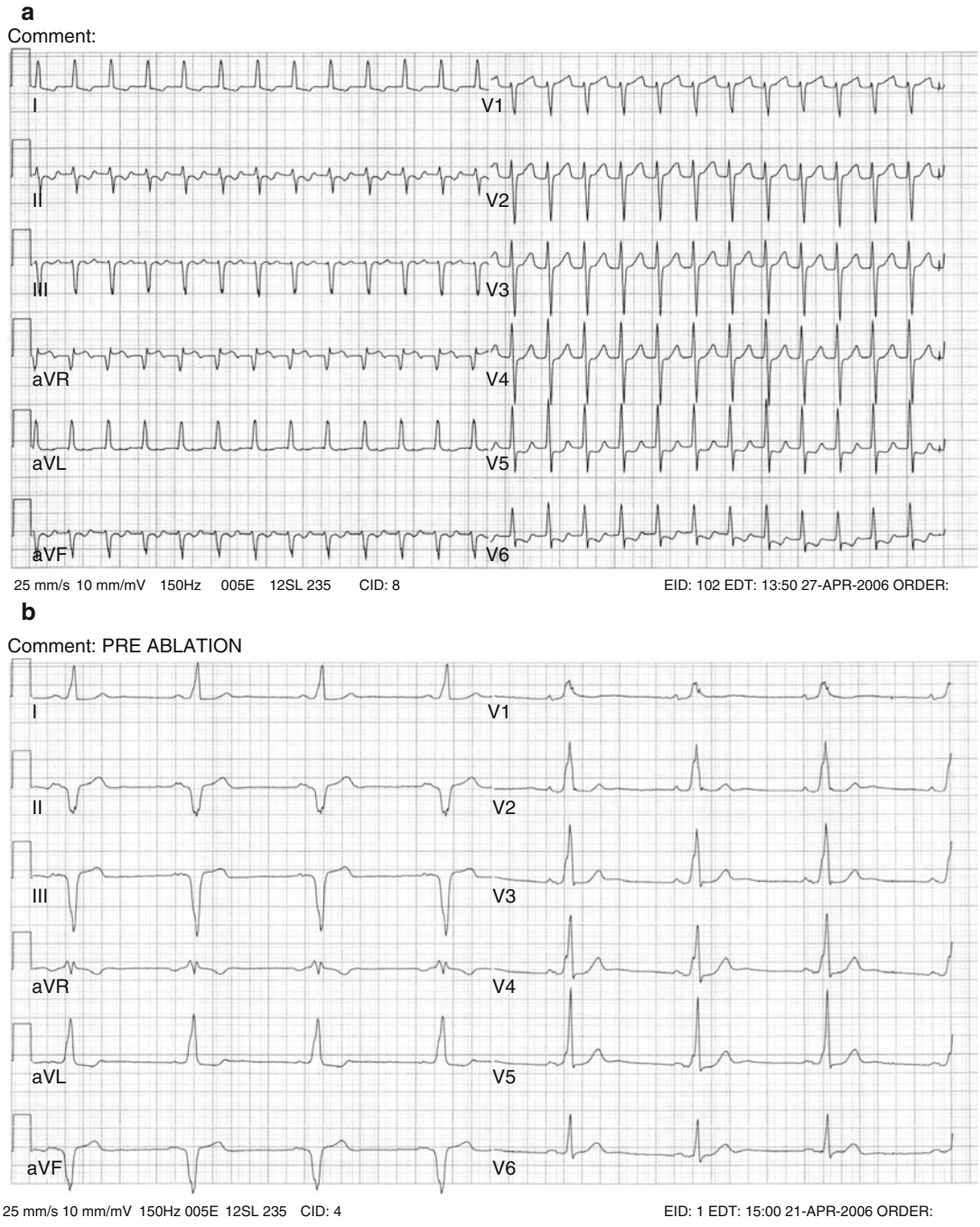

Figure 5–4. (Panel **a**) A rapid, narrow complex tachycardia in a patient proven to have a coronary sinus mediated accessory AV connection inserting into the posterior left ventricle. (Panel **b**) Characteristic ECG features of a coronary sinus connection, with negative delta waves and QS complexes in all three inferior leads. (Panel **c**) Coronary sinus angiography reveals two diverticuli branches. The accessory connection was mapped within the smaller diverticulum, and radiofrequency ablation from with the diverticulum (*arrow*) successfully eradicated conduction of the accessory connection

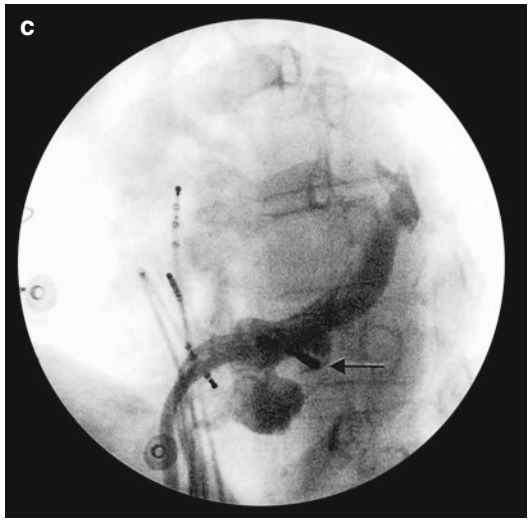

Figure 5–4. (continued)

access may be restricted following surgery (Class I recommendation) [32].

In general, studies examining sudden death in patients with congenital heart disease have not identified WPW as a significant risk factor. For example, in a population based prospective study over 45,857 patient years none of the 41 patients that died were reported as having associated WPW [33]. Similarly, in patients with Ebstein's anomaly who died suddenly, WPW was not noted as a predisposing factor [34]. It would seem reasonable, however, to be concerned about a potential risk in patients whose underlying congenital heart disease makes them particularly prone to having atrial tachycardia and atrial fibrillation if they are also found to have WPW. Such patient groups clearly include those with previous Mustard operation, Senning operation, Ebstein's anomaly and Fontan operations, however, individual patients with a wide range of previously operated congenital heart disease may be at risk for atrial arrhythmias.

Genetics and WPW

A familial occurrence of WPW has been described as early as 1959 [35]. In 1987, Vidaillet et al. reported that a family history of WPW was apparent in 3.4 % of patients, and noted a higher incidence of multiple accessory pathways in familial WPW [36]. These observations provided the impetus to identify genes responsible for WPW.

To date, only a single gene has been reported to be responsible for a familial form of WPW [14]. First reported in 1986, a large French-Canadian family demonstrated an autosomal dominant mode of inheritance with a high degree of disease penetrance and variable clinical expressivity [37, 38]. The predominant clinical phenotype observed in approximately 50 % of patients is that of the classic ventricular preexcitation pattern of WPW (Fig. 5.5). ECG variants of preexcitation are commonly observed, including a short PR interval without a delta wave. Clearly distinguishing this familial form of WPW from the more common sporadic variety is the co-existence of cardiac hypertrophy in 30–50 % of patients [14, 37]. In addition, progressive cardiac conduction system disease, including sinus node dysfunction is common. Development of paroxysmal and eventual chronic atrial fibrillation is seen in 80 % of patients by the sixth decade of life [39].

Electrophysiologic studies in affected individuals of the French-Canadian family have identified typical accessory pathways to be responsible for preexcitation and to participate in re-entry arrhythmias. These observations are consistent with the EP findings of other investigators who have assessed unrelated families with the identical genetic syndrome [40, 41]. Fasciculoventricular tracts (see Fig. 5.1), in addition to typical accessory pathways, have been observed at EP study in some affected members of the Canadian family. This finding is consistent with the observation of a short PR interval and no delta wave on resting ECG and the presence of preexcited atrial tachycardia in some patients (Fig. 5.6).

The disease-causing gene was identified to be *PRKAG2*, a gene coding for the gamma-2 regulatory subunit of AMP-activated protein kinase (AMPK). AMPK is known to have a critical role in the preservation of cellular 'energy homeostasis' in the heart by regulating key lipid and glucose metabolic pathways. Thus, it was hypothesized that the pathologic basis of the cardiac hypertrophy seen in this genetic syndrome in humans may be secondary to

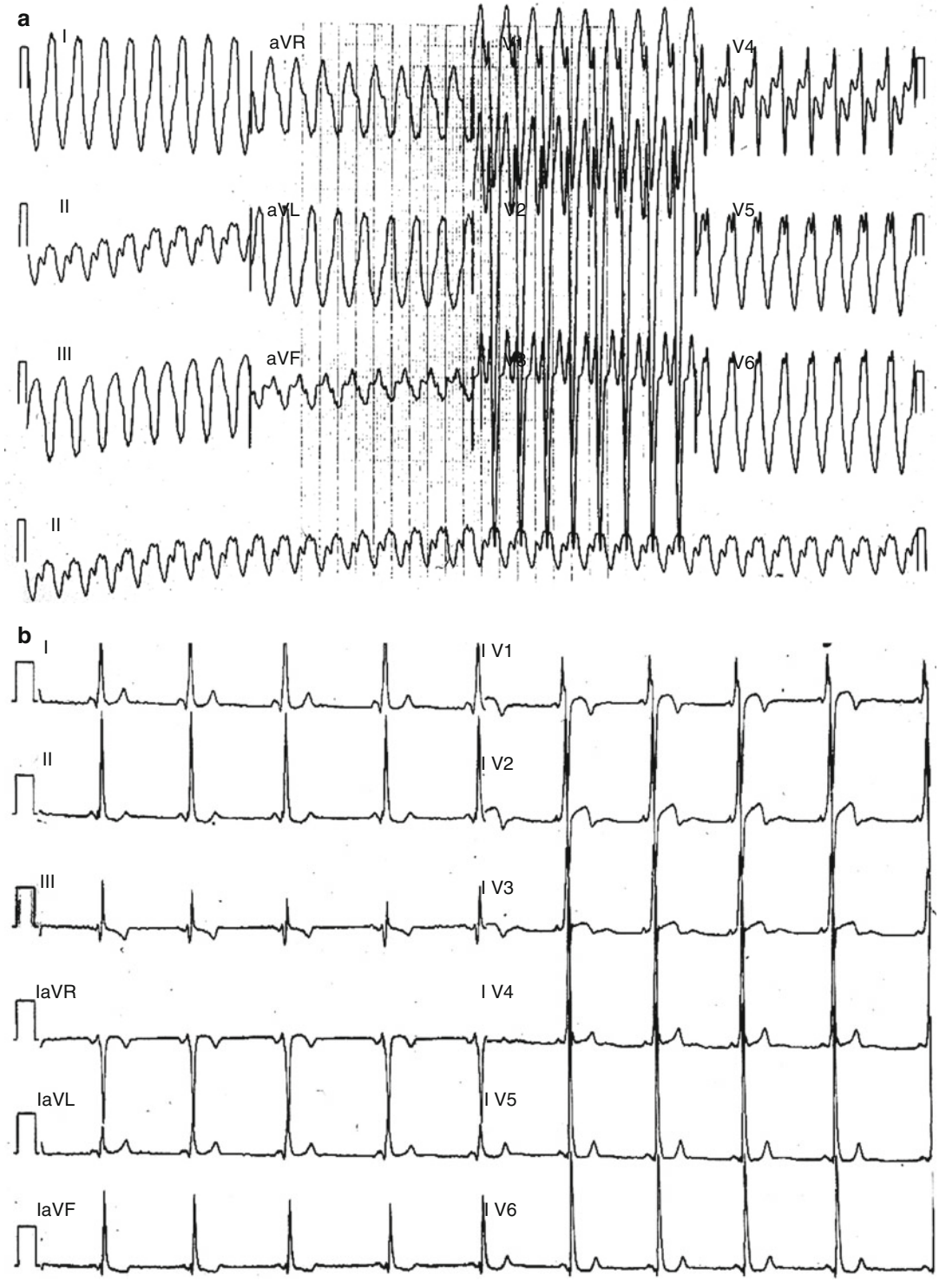

Figure 5–5. (Panel **a**) Presenting 12-lead ECG of a 20 year old male proven to harbor a PRKAG2 mutation (Arg302Gln) responsible for familial WPW. This patient had frequent episodes of presyncope. Electrophysiologic study identified the mechanism of this tachycardia to be antedromic AVRT utilizing a right free-wall accessory pathway. Following ablation of the right sided pathway, ventricular preexcitation persisted and a left sided accessory pathway was evident. (Panel **b**) Resting ECG of the same patient following cardioversion. A classic pattern of WPW is evident, in this case a composite of right and left sided antegrade-conducting accessory pathways

abnormal glycogen storage in the heart [42]. This was confirmed by the development of transgenic mice models with cardiac expression of human *PRKAG2* mutant genes [43, 44]. These mice were found to have a glycogen storage disease of the heart, which has now also been confirmed in affected humans [45, 46]. In addition, these mice developed the classic ECG features of WPW, including the inducibility of AVRT and accessory pathway block with normalization of the ECG during procainamide infusion [44].

Although the link between accumulation of cellular glycogen and accessory pathways remains to be elucidated, the present hypothesis considers the effect of excessive glycogen on normal heart development [42]. During early cardiac development, the heart exists as a tubular structure with muscular continuity between atrial and ventricular myocardium [47]. Atrioventricular septation occurs between 7 and 12 weeks of fetal life, with myocardial continuity between atrial and ventricular myocardium now occurring primarily via the developed normal conduction axis [47]. However, it has been well established by histologic study that remnants of A-V muscle continuity outside of the normal conduction axis are still observed in normal neonatal hearts [47]. The observed accessory fibres connecting atrial and ventricular myocardium in neonatal hearts are described as thin in nature and would therefore not be expected to have the 'cable' capacity to conduct a depolarizing electrical wavefront from atrial to ventricular tissue. In this respect, these accessory fibres may be considered quiescent or subclinical and are a normal finding in newborn hearts. The effect of glycogen accumulation may be postulated to promote conduction through these otherwise quiescent accessory fibres. First, the enlargement of these accessory fibres due to glycogen accumulation may improve their 'cable' capacity and ability to conduct a depolarizing wavefront. This concept is consistent with the histological finding of abnormally enlarged accessory fibres giving rise to WPW in a patient with glycogen storage disease due to Pompe Disease [48]. The effect of

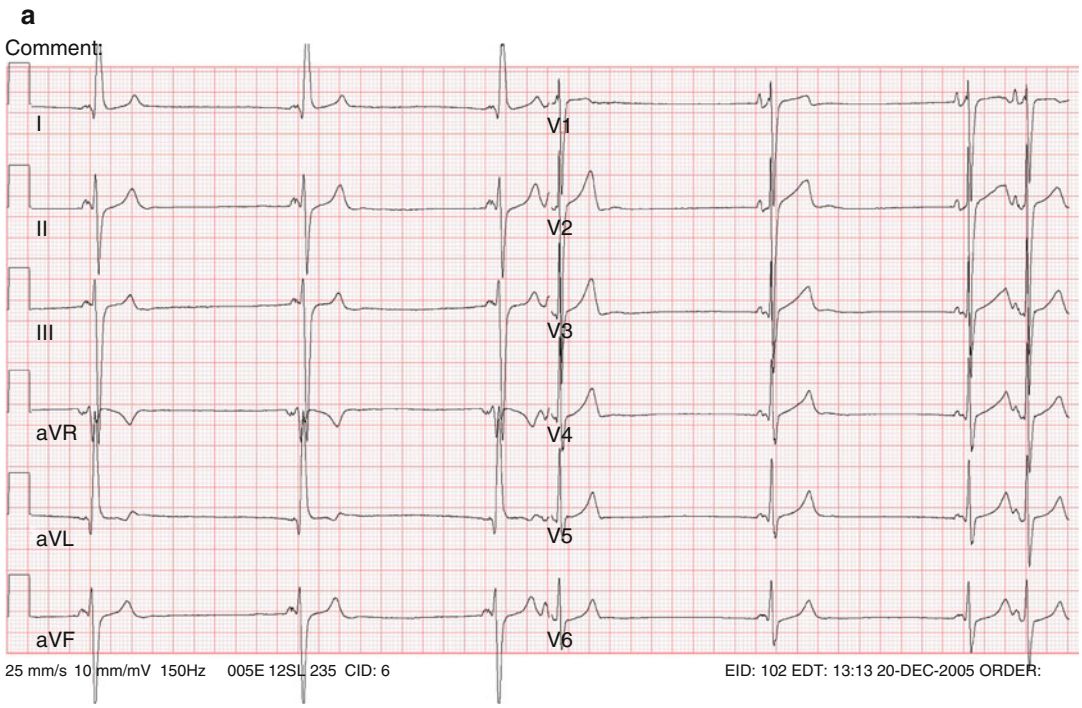

Figure 5–6. (Panel **a**) A resting 12-lead ECG in a 26 year old female cousin of the patient illustrated in Fig. 5.5, proven to have the same PRKAG2 mutation. This patient had severe sinus bradycardia, and short PR interval without a delta wave. Electrophysiologic study showed no evidence of a typical accessory pathway. However, characteristics of a fasciculoventricular pathway were seen. (Panel **b**) Frequent atrial tachycardias with significant pauses upon termination eventually resulted in permanent pacemaker placement

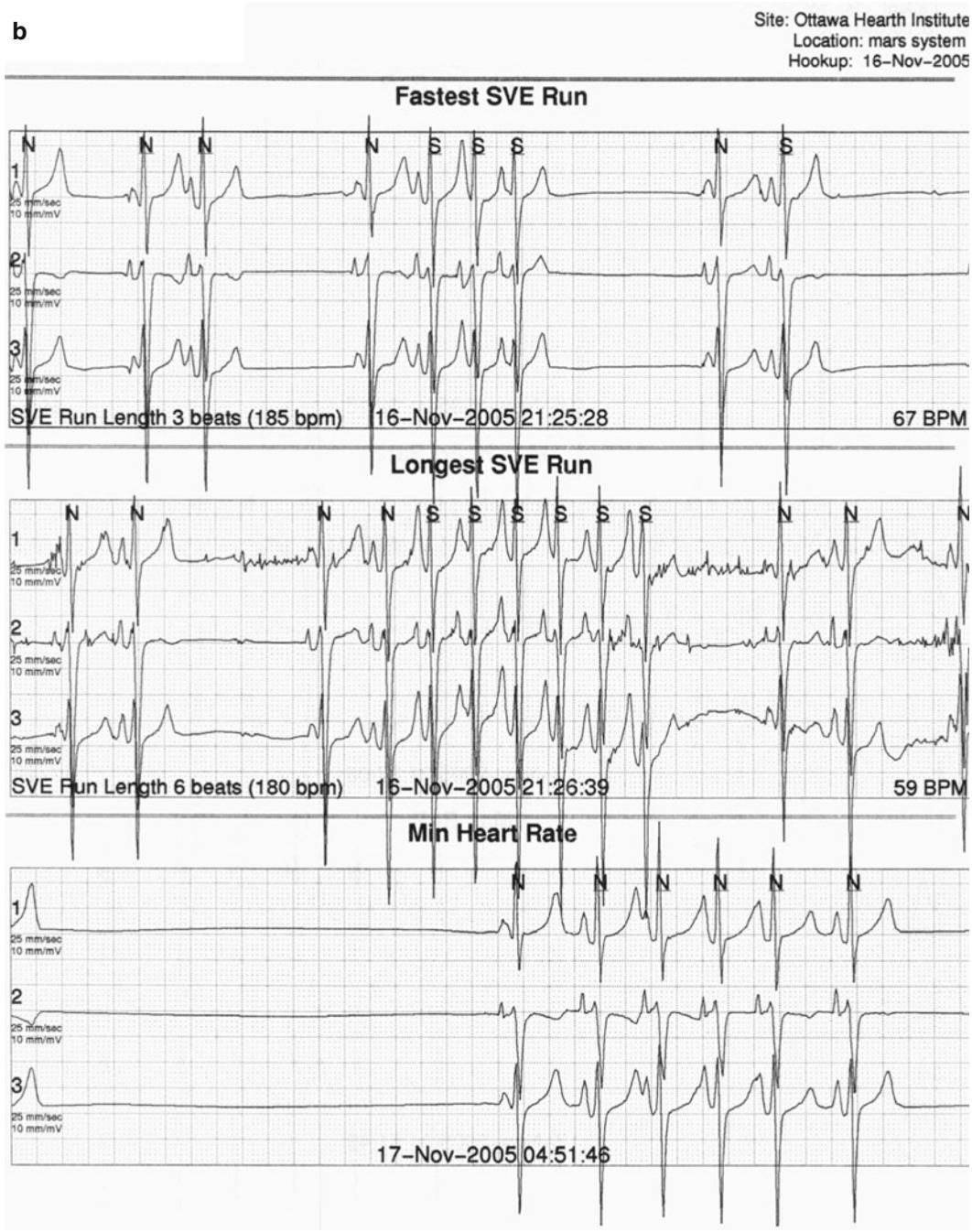

Figure 5–6. (continued)

increased glycogen in myoctes may further alter electrical properties by other mechanisms. The relationship between decreased cellular pH due to glycogen accumulation and the effect on myocyte conduction properties is unknown. However, given the known sensitivity of ion channel gating and current to intracellular pH [49, 50], a change in kinetics favoring conduction would not be unexpected. The hypothesis presented to account for the presence of WPW in the PRKAG2

cardiac syndrome suggests that this phenotype is secondary to the effects of glycogen on naturally occurring, quiescent, accessory fibres. The progression to conduction disease and left ventricular dysfunction in a significant number of affected patients by their 4th decade of life likely reflects a myopathic effect from the long-term cellular glycogen excess.

In recent years, a rare form of WPW associated with dysmorphic facial features and neurocognitive delay has been observed in patients with microdeletions at chromosomal region 20p12.3 [51].

WPW and the Risk of Sudden Cardiac Death

The Risk of SCD in WPW Patients Followed Prospectively

In most long-term, population-based follow-up studies, the risk of sudden cardiac death in WPW has been reported to be very low. In 1993, Munger et al. reported on the natural history of 113 patients with WPW in a population based study in Olmsted County, Minnesota [52]. They reported two cases of premature SCD over an average patient follow-up of 12 years, suggesting a 1.9 % risk of SCD over a 12 year follow-up (0.15 %/year risk). Fitzsimmons et al. obtained follow-up on 238 consecutive military aviators with WPW over an average of 21.8 year and found that SCD occurred in only 1 of 228 patients (0.4 %) [53]. However, limitations in accurately determining the rate of SCD in both studies arises from the consistent finding of patients lost to follow-up. In the Olmsted County cohort, six patients could not be located for follow-up. Assuming the worse case scenario of sudden death in these cases, the estimated range of SCD rate from this cohort would be 0.15–0.58 %/year risk (SCD in 2–8 of 113 patients over 12 years). Similarly, in the study of Fitzsimmons et al., follow-up on ten patients could not be ascertained, raising the possible range of SCD risk from 0.4 to 4.6 % over a 21.8 year follow-up.

As the above studies suggested a very low risk of sudden cardiac death, the recommendation by most "experts" and professional bodies has been that WPW patients whom are asymptomatic should not be considered for potential curative therapy via catheter ablation. These recommendations have been challenged by a study by Pappone et al. [54]. In a follow-up study of 162 WPW patients over an average of 3.1 years, these authors reported sudden cardiac arrest in 3 patients, indicating a 0.61 %/year risk of SCD. Further, previous EP studies in these asymptomatic patients had induced preexcited atrial fibrillation, suggesting EP study may have risk-stratified these previously asymptomatic patients for catheter ablation to reduce the risk of cardiac arrest.

Sudden Cardiac Death in the Young and the Incidence of WPW

In early autopsy series assessing the cause of SCD in previously healthy, young patient cohorts, WPW as an etiology for SCD was not routinely reported [55, 56]. Similarly, in these early retrospective studies, other electrical diseases of the heart such as Long QT syndrome (LQTS), Brugada syndrome or catecholaminergic polymorphic ventricular tachycardia (CPVT), for example, were never reported. The absence of these diagnostic possibilities reflects the limitations of routine autopsy procedures. Pathologists do no routinely assess for the histologic evidence of accessory pathways responsible for WPW, nor can routine autopsy detect purely electrical disease, such as LQTS. In WPW, histologic assessment would require thousands of sections across both AV annuli and an extraordinary time commitment for review. Thus, the possibility of WPW in a grossly structurally normal heart is not addressed as a possibility in the sudden death of a young patient.

In a unique study, Topaz et al. clinically evaluated 22 consecutive young survivors of sudden cardiac death, providing the opportunity to assess for both gross structural and non-structural causes for cardiac arrest in resuscitated patients [57]. The most common identifiable causes were dilated cardiomyopathy and WPW, each considered responsible for three cases (13.3 %). In two of three WPW patients, AF was induced during EP study. LQTS, and the most commonly attributed cause of SCD in the young,

hypertrophic cardiomyopathy, were each found in one case. This data is supported by a study from Basso and colleagues who retrieved prior ECGs on 93 patients aged <35 years who experienced sudden cardiac death. Ten patients (10.5 %) had ECG documented ventricular preexcitation, and detailed histologic examination of their hearts confirmed the presence of accessory pathways [58]. Importantly, 40 % of these patients were asymptomatic prior to their sudden death.

Risk Stratification for SCD in WPW

The objective of risk stratifying patients for the risk of sudden death in WPW is motivated by the tragedy of losing an otherwise healthy, young individual to a condition that is most often curable. Unfortunately, significant limitations exist in the development of a protocol with a high predictive accuracy in determining risk. These limitations arise due to the relatively low incidence of sudden death in WPW cohorts and the relatively small number of survivors of sudden death that have been subsequently evaluated. Nevertheless, a number of non-invasive and invasive electrophysiologic observations have been proposed to be associated with either a higher or lower estimated risk. These observed variables traditionally endeavor to predict whether or not an accessory pathway is capable of sustaining rapid conduction to the ventricles during atrial fibrillation.

Non-invasive observations such as the presence of intermittent preexcitation on resting ECG has been suggested to predict a low risk of sudden death and to represent a longer ERP of the accessory pathway. Similarly, the apparent block of accessory pathway conduction and loss of preexcitation during exercise has been used to conclude that some WPW patients are at low risk of SCD [59, 60]. However, Critelli et al. have demonstrated that such patients may be still be capable of sustaining atrial fibrillation with rapid ventricular responses despite this observation [61]. Further, Sharma et al. described two of six patients with WPW who survived SCD but yet demonstrated loss of preexcitation on exercise treadmill [62]. Thus, robust data supporting non-invasive markers to predict a high or low risk of SCD in WPW do not currently exist.

Invasive electrophysiologic testing has also been proposed to stratify for the risk of SCD in patients with WPW. The antegrade ERP of the accessory pathway, the shortest preexcited RR interval (SPRR) during atrial fibrillation, and the inducibility of AVRT or atrial fibrillation have all been used to stratify the risk of sudden cardiac death. The most consistent observation in WPW patients who have survived SCD or who underwent EP study prior to SCD, is the ability to induce AF during EP study and the observation of a SPRR of <250 ms [55, 62, 63]. In 25 patients studied by Gallagher and colleagues, 24 patients had inducible AF and all had an observed SPRR of 250 ms or less [63]. In three patients subsequently found to develop SCD studied by Pappone et al., all had prior inducibility of AF and a SPRR of <250 ms [54]. Although the sensitivity of a SPRR of <250 ms during AF is high, the specificity is not, as many patients without SCD have been noted to meet this criteria within these studies. In addition, a further study by Sharma et al. noted two of nine WPW survivors of SCD who had relatively high SPRR during AF (396 and 295 ms) [62], highlighting the lack of complete reassurance that may be provided to young patients. Other electrophysiologic measures that have been considered for risk stratifying include the accessory pathway antegrade ERP, shortest preexcited RR interval during atrial pacing, presence of multiple pathways, or pathway location. Bromberg and colleagues reported a cohort of 60 children with WPW who underwent invasive electrophysiologic assessment, including 10 with documented VF or asystole [64]. Again, only the SPRR during AF significantly differed between high-risk and low risk groups. No difference existed in accessory pathway antegrade refractory period, shortest pre-excited RR interval during atrial pacing, presence of multiple pathways, or pathway location. Interestingly, clinical history also did not differentiate the high risk patients.

Despite the limitations in the interpretation of electrophysiologic data, transesophageal electrophysiology studies are used as part of the clinical management strategies in children by 50 % of practicing pediatric electrophysiologists [65]. However, there is very little data that indicates the information that is provided is useful

Table 5–1. Guidelines for drug therapy for WPW

Arrhythmia	Recommendation	Classification	Level of evidence
WPW syndrome (pre-excitation and symptomatic arrhythmias), well tolerated	Flecainide, propafenone	IIa	C
	Sotalol, amiodarone, beta blockers	IIa	C
	Verapamil, diltiazem, digoxin	III	C
Single or infrequent AVRT episode(s) (no pre-excitation)	No therapy	I	C
	Vagal maneuvers	I	B
	Pill-in-the-pocket-verapamil	I	B
	Diltiazem, beta blockers	IIb	B
	Sotalol, amiodarone, flecainide, propafenone Digoxin	III	C
Pre-excitation, asymptomatic	No Therapy	I	C

WPW Wolff-Parkinson-White, *AVRT* atrioventricular reentrant tachycardia

for risk stratification using standard markers. Physiologic parameters that can be measured by transesophageal study (antegrade accessory pathway refractory period and the shortest RR interval during atrial burst pacing) may not distinguish high risk pediatric patients from those who are low risk [64]. As well, it has been shown that there is poor agreement between the intervals measured at invasive electrophysiology with those measured by the transesophageal approach [66].

Overall, the traditionally accepted indicator for increased risk of sudden death in WPW is an observed SPRR during AF of <250 ms. However, exceptions to this rule exist [62]. Conversely, the inability to induce AF during EP study using an aggressive pacing protocol may identify a lower risk population. The small number of studies and patients evaluated preclude definitive risk stratification recommendations.

Clinical Management of WPW

Pharmacologic Therapy

Chronic anti-arrhythmic drug therapy is one option in the management of patients with symptomatic WPW. However, there are no randomized studies comparing drug therapy with radiofrequency ablation. Similarly, no evidence exists that drug therapy reduces the risk of sudden cardiac death, although it is presumed that such therapy will minimize the risk for developing atrial fibrillation. Furthermore, it should be clearly discussed with patients that drug therapy is an arrhythmia reduction strategy and is not a cure for the condition. There are some data from the electrophysiology lab and observational studies about a number of anti-arrhythmic drugs. A summary of guidelines of drug therapy for WPW is shown in Table 5.1. Of critical importance is the avoidance of drugs exerting a predominant A-V nodal blocking effect in patients with manifest preexcitation. The use of drugs like digoxin and verapamil preferentially block A-V nodal conduction without a significant effect on accessory pathway conduction, increasing the risk of rapid conduction of atrial activity via the accessory pathway in the presence of atrial fibrillation, with subsequent degeneration to ventricular fibrillation.

Class IC Anti-Arrhythmic Drugs

Propafenone and flecainide have been shown to block accessory pathway conduction and render supraventricular tachycardia (SVT) to be non-inducible during electrophysiology (EP) procedures [67, 68]. In addition, both propafenone and flecainide have been studied in small, randomized control studies comparing these Class IC agents with placebo in patients with paroxysmal, narrow complex SVT [69, 70]. In these studies it is likely that some patients had accessory pathway mediated tachycardia. The results consistently demonstrated that both drug agents are generally better than placebo; however even on active therapy up to 25 % of patients had recurrent SVT within 2 months, indicating the limitations of drug therapy in patient management.

Table 5–2. Recommendations for catheter ablation for WPW in adults

Arrhythmia	Recommendation	Classification	Level of evidence
WPW syndrome (pre-excitation and symptomatic arrhythmias), well tolerated	Catheter ablation	I	B
WPW syndrome (with AF and rapid-conduction or poorly tolerated ARVT)	Catheter ablation	I	B
AVRT, poorly tolerated (no pre-excitation)	Catheter ablation	I	B
Pre-excitation, asymptomatic	Do nothing	I	C
	Catheter ablation	IIa	B

WPW Wolff-Parkinson-White, *AF* atriofibrillation, *AVRT* atrioventricular reentrant tachycardia

Table 5–3. Recommendations for catheter ablation for WPW in children

Arrhythmia	Recommendation	Classification	Level of evidence
WPW syndrome (pre-excitation and symptomatic arrhythmias), well tolerated	Catheter ablation	I	B
WPW syndrome (with AF and rapid-conduction or poorly tolerated ARVT)	Catheter ablation	I	B
AVRT, poorly tolerated (no pre-excitation)	Catheter ablation	I	B
Pre-excitation, asymptomatic	Do nothing	I	C
	Catheter ablation	IIa	B

WPW Wolff-Parkinson-White, *AF* atriofibrillation, *AVRT* atrioventricular reentrant tachycardia

In pediatrics, successful use of flecainide has been described in case series of recurrent SVT, fetal and neonatal arrhythmias [71]. In older children, flecainide at doses between 2.2 and 5 mg/kg/day has been efficacious in symptomatic WPW [72].

Class II Anti-Arrhythmic Drugs

There are no studies looking at the efficiency of beta blockers for WPW; however, despite this paucity of data recent consensus guidelines have given beta blockers a Class IIa recommendation [32].

Class III Anti-Arrhythmic Drugs

Intravenous sotalol has been assessed for its ability to render SVT non-inducible in the EP lab, and proven to be highly successful [73], suggesting oral sotalol may be efficacious in arrhythmia management. Anecdotal reports suggest moderate efficacy of chronic amiodarone in reducing arrhythmia burden in WPW [74], however in view of the relative toxicity of this drug it is seldom recommended for long-term arrhythmia management in young patients.

Ablation for WPW

In the current era, catheter ablation for the cure of WPW is usually performed as a day case procedure and under local anesthetic. Venous access is primarily via the femoral vein with some operators also using the internal jugular vein or a subclavian vein. Access for left sided accessory pathways is achieved either using a retrograde aortic approach using femoral artery access or transseptally from right to left atrium. The accessory pathway is localized by mapping the site of earliest ventricular activation during sinus rhythm or atrial pacing and/or mapping the earliest atrial activation during ventricular pacing. A successful ablation is seen by loss of delta waves during radio frequency application.

Indications for ablation of WPW are detailed in Tables 5.2 and 5.3 [32, 75]. Current guidelines consider that the risks of the actual ablation procedure may outweigh the potential benefits. In 2002, the North American Society for Pacing and Electrophysiology (NASPE), now the Heart Rhythm Society, developed a position statement for the use of radiofrequency catheter ablation in children with arrhythmias [75]. Class 1 indications for ablation were: (1) a history of aborted sudden death and (2) syncope in a patient with WPW where there is (a) a short pre-excited RR

interval during atrial fibrillation (<250 ms) or (b) an antegrade effective refractory period of the accessory pathway less than 250 ms at electrophysiologic testing. Asymptomatic WPW was considered to be a Class II indication in children older than 5 years and there was agreement that ablation should not be performed in the asymptomatic child with WPW who is younger than 5 years of age (i.e. a Class III recommendation). Despite these recommendations, a survey of practicing pediatric electrophysiologists showed that 84 % use electrophysiology studies to risk stratify asymptomatic children with some stratifying patients as young as 1 year of age [65]. In children older than 5 years, catheter ablation is considered a class IIB indication [75].

Invasive risk stratification or empiric catheter ablation in an informed patient with asymptomatic WPW remains controversial, but appears to be supported by the recent data of Pappone et al. [54]. The major potential benefit is the elimination of the small risk of sudden cardiac death associated with WPW. In the case of asymptomatic WPW, the pros and cons of the procedure should be discussed very carefully with the patient/family and a decision should be individualized based on the wishes of an informed patient. Some high risk occupations (pilots, bus drivers, military personnel) have mandatory requirements for ablation of asymptomatic WPW. However these requirements are also controversial and vary from jurisdiction to jurisdiction.

In most experienced hands the acute success rate for ablation of WPW is in the range of 95 %. The rates are higher in left sided accessory pathways. There is a small recurrence rate of 1–2 % in subsequent weeks. Most complications associated with the procedure are minor and relate to venous or arterial access. Significant complications of heart block, cardiac tamponade, pneumothorax, myocardial infarction, venous and arterial embolism, vascular injury, and death have been reported. In a European study published in 1993 the complication rate was 4.4 % with 3 deaths in 2,222 patients (0.14 %) [76]. These data were accumulated in the early era of catheter ablation. In 2002, it was reported that the complication rate from ablation procedures in the U.S. had decreased from 4.2 % in the early experience to 3.0 % in more recent years [77], suggesting the knowledge gained through the early experience has resulted in a reduction of complication risk.

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6
Acquired (Drug-Induced) Long and Short QT Syndromes

Rashmi R. Shah and Ihor Gussak

Abstract

This chapter is presented in two parts – QT interval prolongation and QT interval shortening. Part 1 begins with a historical perspective on the consequences of drug-induced QT prolongation and its frequency in patient population at large. There is in depth discussion of various molecular and electrophysiological mechanisms that underpin induction of torsade de pointes, the relationship between QT interval and the proarrhythmic risk it poses and how this relationship is modulated by a number of ancillary properties of a drug. The authors also summarize some of the novel markers of clinical risk in a setting of QT interval prolongation. Regulatory initiatives, including the studies required and their interpretation with regard to clinical risk, are covered in great detail with reference to the two guidelines (ICHS7B and ICH E14) from International Conference on Harmonization. Risk factors for drug-induced QT prolongation and torsade de pointes and the potential mechanisms underpinning each risk factor are discussed in detail, together with a balanced discussion of evidence on why females are at a greater risk. Pharmacogenetic factors and the available evidence concerning potential inter-ethnic differences in drug-related QT response are discussed at length. The authors highlight how drug-induced prolongation of QT interval fits into overall risk/benefit assessment of a drug and its labeling implications. Part 2 is comparatively shorter and begins with the rationale for drugs as a cause of QT shortening and discusses the diagnostic dilemmas and defining normal lower values of QTc interval and the threshold value for diagnosing short QT interval. It then summarizes the epidemiological evidence linking short QT interval with potentially fatal ventricular arrhythmias. Nonclinical data on drugs implicated in QT shortening are reviewed followed by clinical evidence and industry experience, especially taking account of drugs such as the anticonvulsants lamotrigine, rufinamide and BAY-79, a highly selective tyrosine kinase inhibitor. This is followed by a summary of regulatory perspectives in the context of ICH E14 and risk/benefit of drugs that may be found to shorten QT interval

R.R. Shah, BSc, MBBS, MD, FRCP, FFPM (✉)
Rashmi Shah Consultancy Ltd,
Gerrards Cross, UK
e-mail: clinical.safety@hotmail.co.uk

I. Gussak, MD, PhD, FACC
Ono Pharmaceutical USA, Lawrenceville, NJ, USA

Department of Internal Medicine,
University of Medicine and Dentistry of New Jersey,
Robert Wood Johnson Medical School,
New Brunswick, NJ, USA
e-mail: igussak@hotmail.com

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Introduction

The QT interval of the surface electrocardiogram (ECG) represents the interval from the beginning of ventricular depolarization (Q wave) to the end of its repolarization (T wave). This interval represents the summation of the duration of action potentials (APD) of the ventricular myocytes. Figure 6.1 shows the principal ion currents involved in the genesis of APD.

Whereas it was believed at one time that only the prolongation of QT interval is harmful, gradually accumulating evidence shows that shortening of this interval is just as harmful. The evidence for harmful effects of significant changes in the duration of QT interval comes from adverse clinical outcomes associated with congenital and acquired forms of long QT syndromes (frequently referred to as cLQTS and aLQTS, respectively) and with congenital forms of short QT syndromes (SQTS). For further information on congenital LQTS and SQTS, the reader is referred to the corresponding chapters in this book. This chapter is concerned with acquired forms of QT interval changes, both prolongation as well as shortening, with a focus on drugs as their cause.

Drug-Induced QT Interval Prolongation

QT interval prolongation *per se* is not harmful but in the presence of appropriate risk factors, or when it is excessively prolonged, the cardiac rhythm typically changes to a unique form of polymorphic ventricular tachycardia known as torsade de pointes (TdP) [2]. Although usually a transient tachyarrhythmia associated with a brief episode of palpitation, the clinical manifestations of sustained TdP include symptoms arising from impaired cerebral circulation such as dizziness, syncope and/or seizures. TdP subsequently degenerates into ventricular fibrillation (VF) in about 20 % of cases [3] and, not uncommonly, cardiac arrest and sudden death may be the outcome [4]. The overall mortality from TdP is of the order of 10–20 % [3, 5, 6]. De Bruin et al. have reported significantly increased odds ratios (for the risk of cardiac arrest) of 2.1 in patients who received QTc-prolonging drugs [7].

The acquired form of LQTS is by far the more common compared to its congenital counterpart. Drugs used clinically, both cardiac and non-cardiac, account for a vast majority of the acquired form of LQTS.

Historical Perspective on Drug-Induced QT Interval Prolongation

One of the first scientific meetings on QT interval prolongation, convened in 1993 in the aftermath of terfenadine-induced QT interval prolongation and TdP, questioned whether QT interval prolongation was beneficial or harmful [8]. Clinical experience with a wide range of drugs, including class III antiarrhythmic drugs which primarily exert their therapeutic effect by prolonging the QT interval, over the subsequent

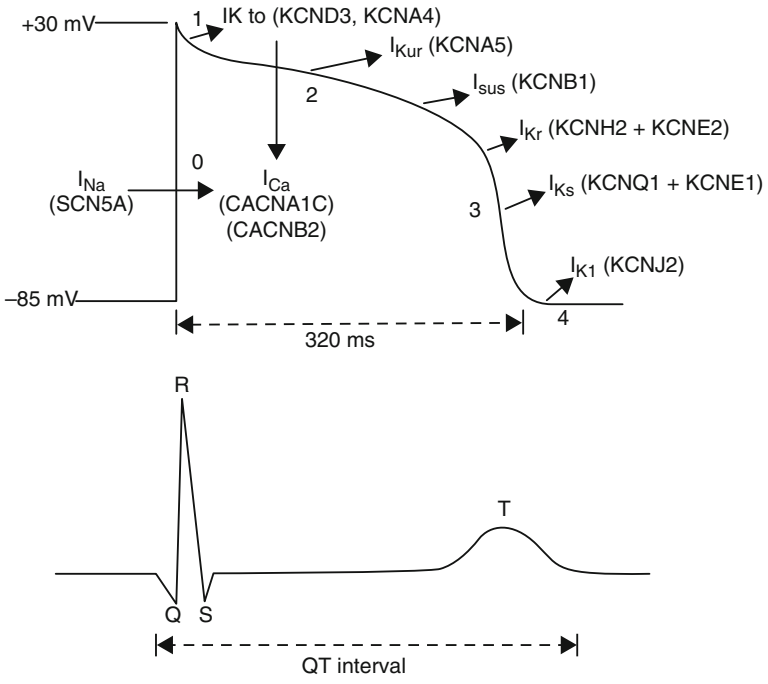

Figure 6–1. QT interval of the ECG, five sequential phases (numbers 0–4) of the human cardiac ventricular action potential and the main currents involved (with genes encoding these current channels). I_{Ca} calcium current, I_{K1} inward rectifier potassium current, I_{Kr} rapidly activating delayed rectifier potassium current, I_{Ks} slowly activating delayed rectifier potassium current, I_{Kto} transient potassium current, I_{Na} sodium current, I_{Kur} ultra-rapidly activating delayed rectifier potassium current, I_{sus} sustained current (Reproduced from Shah and Morganroth [1]. With permission from Adis, a Wolters Kluwer business (© Adis Data Information BV 2008. All rights reserved.))

4–5 years provided a fairly compelling evidence that prolongation of this interval is potentially harmful and any apparently beneficial effects associated with class III antiarrhythmic drugs are incidental and almost certainly outweighed by the unquantified risk associated with their use. For example, in November 1994, the Survival With Oral d-Sotalol (SWORD) study, set up to compare (+)-(S)-sotalol (also known as *d*-sotalol) with placebo in preventing sudden arrhythmic deaths, had to be terminated prematurely because of a 65 % greater mortality associated with the active treatment relative to placebo [9]. Although both enantiomers of sotalol are equipotent with respect to their class III activity [10], (+)-(S)-sotalol is devoid of the β-adrenoreceptor blocking activity possessed by its (−)-(R)-isomer (*l*-sotalol) that is present in the racemic drug on the market. The incidence of TdP in association with racemic *d,l*-sotalol is variously estimated to be 2.6–4.1 % [11].

The impact and the magnitude of drugs as a clinical cause of QT interval prolongation are hard to overestimate. Until the introduction of thioridazine in 1958, quinidine was the only drug known to be associated with this undesirable effect. Introduction of thioridazine for the treatment of schizophrenia was to herald the beginning of a large number of non-cardiac drugs found to be associated with QT interval prolongation [12]. A list of major QT-prolonging drugs with their torsadogenic potential can be accessed at www.torsades.org. An extensive literature search by one of the authors (RS) in 2008 identified just over 160 drugs capable of prolonging QT interval. The list includes a wide range of therapeutic, pharmacologic or chemical classes as shown in Table 6.1. The list has since increased considerably.

Prenylamine and lidoflazine, both antianginal agents, were withdrawn from the market in 1988 and 1989, respectively because of their torsadogenic potential. During the period 1990–2010, 53 drugs had been withdrawn from the major markets of the world and of these, 12 (23 %) were withdrawn due to their potential to prolong QT interval and/or induce TdP (Table 6.2). Sotazide, a proprietary fixed combination product of 160 mg sotalol with 25 mg hydrochlorthiazide and indicated for hypertension, proved to be highly proarrhythmic (because of the contribution of hypokalaemia induced by the thiazide component) [14]. Needless to say, this product was also removed from the market in 1996.

Table 6–1. A selection of drug classes involved in acquired QT interval prolongation[a]

Pharmaco-therapeutic or chemical drug class	Reported representative examples
α-adrenoreceptor antagonists	Alfuzosin, indoramin, ketanserin, lofexidine
Anesthetics	Desflurane, enflurane, halothane, isoflurane, propofol, sevoflurane
Analgesics and opiate agonists	Levacetylmethadone, methadone, oxycodone, propoxyphene
Antianginal drugs	Lidoflazine, prenylamine, ranolazine, (terodiline)
Antiarrhythmic drugs	Ajmaline, almokalant, amiodarone, aprindine, azimilide, bepridil, disopyramide, dofetilide, dronedarone, ibutilide, lorcainide, nifekalant, procainamide, quinidine, semitilide, sotalol, tedisamil, terikalant
Antibacterials	Azithromycin, clarithromycin, clindamycin, erythromycin, roxithromycin, spiramycin, telithromycin
Antidepressants	Amitriptyline, citalopram, desipramine, fluoxetine, nortriptyline, protriptyline, trazodone, venlafaxine
Antifungal agents	Fluconazole, ketoconazole, posaconazole, voriconazole
Antihistamines	Astemizole, diphenhydramine, hydroxyzine, mizolastine, terfenadine
Antimalarials	Choloroquine, halofantrine
Antitussive agent	Clobutinol
Cytotoxic drugs	Aclarubicin, acodazole, arsenic trioxide, depsipeptide, vorinostat
Fluoroquinolones	Ciprofloxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin
Lipid lowering agent	Probucol
Neuroleptic agents	Chlorpromazine, droperidol, haloperidol, melperone, mesoridazine, pimozide, quetiapine, risperidone, sertindole, thioridazine, ziprasidone
Non-nucleoside reverse transcriptase inhibitor	Efavirenz
Estrogen receptor modulator	Tamoxifen, toremifene,
Phosphodiesterase inhibitors	Sildenafil, tadalafil, vardenafil
Protease inhibitors	Atazanavir, nelfinavir, saquinavir
Serotonin antagonists	Cisapride, dolasetron, domperidone, granisetron, ondansetron
Tyrosine kinase inhibitors	Crizotinib, lapatinib, nilotinib, sunitinib, vandetanib

[a]This list is alphabetical in order and not all-inclusive

Table 6–2. Drugs with QT-liability withdrawn from the market due to adverse risk/benefit assessment

Drug	Therapeutic use	Year withdrawn
Prenylamine	Antianginal	1988
Lidoflazine	Antianginal	1989
Terodiline	Urinary incontinence	1991
Terfenadine	Antihistamine	1998
Sertindole[a]	Antipsychotic	1998
Astemizole	Antihistamine	1999
Grepafloxacin	Antibiotic	1999
Cisapride	Gastric prokinetic	2000
Droperidol	Tranquillizer/analgesic	2001
Levacetylmethadol	Methadone substitution	2001
Dofetilide	Atrial fibrillation	2004
Thioridazine	Antipsychotic	2005
Clobutinol	Antitussive	2007
Propoxyphene	Analgesic	2009

[a]Re-introduced in 2005 following re-evaluation of risk–benefit
Updated from Shah [13]

QT-related proarrhythmic toxicity is only second to drug-induced hepatotoxicity which, during the same period, accounted for the withdrawal of 16 (30 %) drugs. Ten (19 %) other drugs were withdrawn due to other non-QT related cardiac safety issues such as valvulopathy and cardiac-related mortality.

Regulatory approval for marketing has been delayed or denied to a number of new drugs because of their potential to prolong QT interval [15]. In addition, countless new and established medicines now have prescribing restrictions placed on them as a result of their QT-liability. It has now also become routine for regulatory authorities to include substantial descriptive data on the effect of new drugs on QT interval in their prescribing information.

There is much concern regarding the unregulated use of alternative medicines (e.g. the consequences that follow the induction of CYP3A4 by St John's Wort). Therefore, it is salutary to record that even now, more than nine decades after the proarrhythmic toxicity of the alkaloid quinidine was first described, another alkaloid has recently been reported to be associated with QT interval prolongation and TdP. Ibogaine is a psychoactive alkaloid derived from the root bark of a West African plant, *Tabernanthe iboga*. It is metabolized by CYP2D6 [16] and in recent years, it has been increasingly used in the treatment of various forms of addictions. The extent of its use is not precisely known but among 11 deaths within

72 h of ingesting ibogaine during 1990 and 2006, there were six individuals between the ages of 24 and 28 years [17]. In these relatively young subjects, the cause of death remained unclear, in some even after autopsy. Without necessarily implying TdP as the cause of these deaths, it is worth recording that a well documented case of TdP has been reported in association with the use of ibogaine [18]. It seems that even the allegedly most innocuous substances may carry hidden unexpected risks of QT interval prolongation.

Epidemiological Aspects of Drug-Induced QT Prolongation

The available data on the prevalence of acquired form of QT prolongation are highly heterogeneous, depending on the population studied, QT correction formula applied and the cut-off values used to define prolongation. Whereas congenital LQTS is estimated to affect 1 in about 2,000 individuals [19], estimates of the prevalence of QTc interval ≥500 ms in hospital setting range from 3.5 to 16.2 %, depending on the population studied [20–22]. In a study of 537 medical inpatients, 22.3 % had a prolonged QTc based on the Bazett formula [23]. The adjusted odds for QTc prolongation based on the Bazett correction were significantly higher in patients who had liver disease, hypokalaemia and who were taking ≥1 QT-prolonging drug at admission. Astonishingly, an overall 50.8 % of patients with QTc prolongation received additional QT-prolonging drugs during hospitalization, thus further increasing the risk of potentially fatal TdP.

By all accounts, despite progressive but modest improvement in pharmacovigilance methodology, it seems that drug-induced QT interval prolongation is a modern epidemic. A search of the safety database of US Food and Drug Administration (FDA) from 1969 to 1998 for all adverse events mapped to QT interval prolongation and TdP retrieved 2,194 cases, of which 0.6 % were from 1969 to 1978, 6.6 % from 1979 to 1988 and 92.8 % from 1989 to 1998 [5]. The Centre for Pharmacovigilance of Swissmedic (the Swiss drug regulatory authority) has also reported an increase in the number of reports of drug-induced TdP and prolonged QT interval from 6 in 1997 to 22 in 2003 [24]. Many of the cases reported in 2002 and 2003 were related to the use of methadone. QT-prolonging drugs are widely used (or more appropriately stated, misused) [25]. Often, there is co-prescription of a QT-prolonging drug with its metabolic inhibitor or another QT-prolonging drug [6, 26, 27]. Perhaps more worrying is the concern not so much about the QT-prolonging property of a drug but the prescribing patterns of physicians and dispensing diligence of the pharmacists [28–32]. The risk of drug-induced QT prolongation with all its potentially serious consequences can be greatly mitigated by a more considerate approach to risk/benefit evaluation and prescribing on a case-by-case basis.

Molecular Basis of Drug-Induced QT Interval Prolongation

Our understanding of how drugs prolong the QT interval owes much to our understanding of the mechanisms that underpin various types of cLQTS.

In principle, QT interval can lengthen as a result of increased duration of either the depolarization phase (increased sodium or calcium currents) or the repolarization phase (decreased potassium current) of the ventricular action potential. However, the phase almost always affected by drugs is the repolarization phase, which represents a net balance between small inward depolarizing current mediated by calcium ions and an overwhelming outward repolarizing current mediated by potassium ions. As shown in Fig. 6.1, there are multiple forms of potassium channels, each with different activation and deactivation kinetics, which mediate this repolarizing current during phases 1–3 of the ventricular action potential.

The rapidly and slowly activating components of the delayed rectifier potassium current, IKr and IKs respectively, are the dominant currents responsible for the duration of phases 2 and 3 of the action potential, and therefore, the QT interval. The most common mechanism by which drugs prolong the QT interval is a direct inhibition of the potassium channel that is responsible for the IKr current.

IKr/hERG Potassium Channel

The channel conducting the IKr current (known as Kv11.1) is composed of the pore-forming α-subunits encoded by *KCNH2* gene and the β-subunits named miRP1 encoded by *KCNE2* gene [33]. The α-subunit is referred to as the hERG (human ether-a-go-go related gene) channel. Four hERG subunits co-assemble with MiRP1 subunits to form IKr channel. When expressed in heterologous systems, the hERG channel recapitulates faithfully the function of IKr channel and a vast majority of drugs that reduce IKr current and prolong the QT interval do so by their inhibitory effect on the hERG channel [34–37]. hERG channel proteins are synthesized in the endoplasmic reticulum and matured in the Golgi apparatus before being transported to the cell surface.

Mechanisms of Drug-hERG Interactions

Drug trapping studies indicate that the inner cavity of hERG is larger than that of other voltage-gated K^+ channels. Majority of hERG channel blockers appear to cross the cell membrane and enter the channel from the cytosolic side when the channel opens. The unique susceptibility of the hERG channel to a drug-induced block is the result of two aromatic amino acids (Tyr652 and Phe656) with side chains oriented toward the large central cavity of the pore region. These aromatic residues are unique to the EAG channel family and provide high-affinity binding sites for a wide range of compounds, a vast majority of which have in common a central basic nitrogen group together with several hydrophobic/aromatic groups. Mutations at these two sites reduce hERG binding of a number of drugs. Three polar residues, Thr623, Ser624 and Val625, at the base of the pore helices are also critical for high-affinity binding for some compounds (e.g. methanesulfonanilides) but not others (cisapride, terfenadine, propafenone). Equally important factor explaining the promiscuous block of hERG channel by a large number of drugs is that unlike other potassium channels, hERG lacks two specific proline residues that distort and limit the volume of the inner cavity. For more detailed information, the reader is referred to other reviews [38–40].

The *KCNH2* gene encodes at least two transcripts of hERG – hERG 1a, the original isolate, and hERG b, an alternate transcript in which the first five exons of 1a are substituted with a single, distinct exon [41, 42]. Although it was previously believed that hERG 1b is not expressed at the protein level in human heart [43], recent immunocytochemical studies using isoform-specific antibodies have, however, shown that hERG 1b subunits also contribute to native IKr channels *in vivo*, most likely in heteromeric assemblies with hERG 1a [44, 45]. In heterologous systems, transfection forms hERG 1a/1b heteromeric channels with properties distinct from the hERG 1a homomeric channels [42, 46]. Further studies have now revealed that (a) heteromeric hERG 1a/1b currents are much larger than hERG 1a currents and conduct 80 % more charge during an action potential and (b) hERG 1a/1b heteromeric channels have differential drug sensitivity compared with 1a homomeric channels [45]. In a study of 50 compounds comparing the sensitivities of hERG 1a and 1a/1b channels stably expressed in human embryonic kidney (HEK-293) cells, the potency of most compounds was similar for the two targets. However, significant differences were observed for a few compounds. Whereas fluoxetine was more potent at blocking hERG 1a/1b compared to 1a channels, converse was true for E-4031 and dofetilide [47]. This observation may partly explain the observed discrepancy of results from hERG studies and other electrophysiological studies for some drugs. Studies with N588K mutation of *KCNH2* gene indicates that the study of co-expressed hERG1a/1b channels should be considered when investigating clinically relevant hERG channel mutations, even if these reside outside of the N-terminus region [48].

Provided the concentration of the drug is high enough, it seems that almost any drug may inhibit the hERG channel *in vitro*. It is not surprising therefore that data from three major pharmaceutical companies have shown a large proportion of drugs to be 'active' at hERG channels. Although this may simply reflect the nature of new drugs being developed, it is noteworthy that one company reported 86 % of compounds to be active at 10 mM while another reported that 76 (70 %) of the 109 compounds tested were active at hERG. Of the 76 hERG inhibitors, 17 %

displayed an IC_{50} value <1 μM, 51 % had an IC_{50} value between 1 and 10 μM and 32 % had an IC_{50} value >10 μM. The third company reported that 25 % of compounds were active at 1 μM and expected about 75 % to be active at 10 μM (Shah, personal communication from various companies, 2003). Drugs with hERG IC_{50} values in low nM (moderate to high risk) or high μM (no risk) concentrations rarely present problems when evaluating their potential clinical significance.

Although most drugs that prolong the QT interval have been shown to do so by a direct block of the normal hERG channel on the cell surface as discussed above, drug-induced QT interval prolongation may also result from other forms of drug-hERG interactions. Some mutations of genes encoding for ion channels are associated with abnormal channel protein that have intrinsically defective trafficking property and cannot reach the cell surface. Most of the *KCNH2* gene-related mutations that have been studied have been shown to cause loss-of-function by generating trafficking-deficient channels [49, 50]. Disruption of trafficking of hERG protein from the endoplasmic reticulum to the cell membrane is now emerging as another major mechanism. For details, the reader is referred to other reviews on this subject [49, 51–53]. Drugs known to disrupt hERG trafficking include geldanamycin, arsenic trioxide, pentamidine, cardiac glycosides and probucol [54–57]. There are other drugs such as fluoxetine, ketoconazole and fluconazole that have been shown to block hERG current by both the mechanisms; directly by blocking the channel and indirectly by disrupting the trafficking of hERG channel protein [58–60]. As for fluoxetine, its metabolite also exerts both the effects at similar concentrations [58]. Depletion of intracellular potassium disrupts hERG trafficking which can be restored by permeating potassium or rubidium ions [61].

It is often assumed that the effect on QTc interval due to impaired trafficking may not become manifest until the culprit drug is administered chronically over a protracted period of many days or weeks. There are no conclusive data that lead to this assumption but as illustrated below by two drugs which prolong QT interval predominantly by inhibition of hERG trafficking, this would seem not to be the case, especially given the cellular cycling kinetics of hERG channel. About 50 % of initially synthesized immature hERG channel protein is converted into the mature form within the first 4 h, which decays with a half-life of about 11 h [62]. Cordes et al. have reported that 48-h treatment with 3 and 10 μM of pentamidine results 44 and 81 % reductions, respectively, of the hERG polypeptide [55]. Kuryshev et al. reported a concentration-dependent reduction of surface expression of hERG protein by pentamidine in concentrations of 0.01 – 10 μM, with an IC_{50} of 7.8 μM (4.8 μg/mL) and in isolated guinea pig ventricular myocytes, 10 μM pentamidine prolonged APD_{90} (that is, repolarization to 90 % of the resting potential) by approximately 140 % on overnight incubation [63]. Although drug-induced inhibition of trafficking or turnover of hERG-channel protein has not been studied *in vivo*, clinical data on pentamidine suggest that full trafficking-mediated effect on QT interval in man is already achieved by day 4, if not earlier [64–66] and the effect may persist well after discontinuation of the drug in view of the pharmacokinetic properties of pentamidine [67]. These findings are further supported by nonclinical *in vivo* studies [68]. With arsenic trioxide, another inhibitor of hERG trafficking, the peak effect on QTc interval (32.2 ms) was observed at 8 h after an injection although the peak serum concentration was reached at 4 h and the effect on QTc interval decreased gradually to 8.8 ms at 24 h following the injection [69].

Normal trafficking of some hERG mutants (e.g. T65P, N470D or G601S) can be restored by high-affinity hERG channel inhibitors such as E-4031, astemizole, terfenadine and cisapride whereas others (e.g. A561V, R752W, F805C or R823W) are resistant to a pharmacological rescue [70]. When trafficking is restored, many of these misprocessed channel proteins become functional upon incorporation into the plasma membrane. Therefore, depending on the ion channel blocking activity of the rescuing drug, prolongation of the QT interval may result when misprocessed channel proteins are rescued to promote their trafficking to surface membrane. Rescue of trafficking-defective LQT2 mutation N470D was studied using terfenadine (a drug with potent hERG blocking activity) and fexofenadine (a metabolite of terfenadine with no

appreciable hERG blocking activity) [71]. Whereas terfenadine rescued the channel and blocked it, fexofenadine rescued it without any appreciable channel block. The IC_{50} concentration of fexofenadine for block was approximately 350 times greater than that for rescue. It follows that QT prolongation will result following rescue by terfenadine but not by fexofenadine.

Caveolin-1, caveolin-2 and caveolin-3, encoded by *CAV1*, *CAV2* and *CAV3* genes respectively, are structural proteins of the cell membrane and are associated with cholesterol and sphingolipids in certain areas of the cell membrane. They lead to the formation of cave-like invaginations (caveolae) on the cell surface, which facilitate concentration of signaling molecules [72]. A number of cardiac ion channels and pumps (e.g. *SCN5A*-encoded Na^+ channel, *KCNA5*-encoded ultra-rapidly activating K^+ channel, *CACNA1C*-encoded L-type Ca^{++} channel and Na^+/Ca^{++} pump) are localized in these caveolae. Caveolin-1 has been reported to regulate hERG channels [73]. Recent studies have suggested a potential role for these caveolins in disrupting the function of the hERG channels. *In vitro* studies have shown that the lipid lowering drug probucol accelerates degradation of mature hERG channels which is associated with accelerated turnover of caveolin-1 [74].

Not only do cardiac glycosides disrupt hERG trafficking with high specificity and selectivity but they are also known to be potent inhibitors of Na^+/K^+ pumps. There is some evidence to suggest that inhibition of hERG trafficking by cardiac glycosides is initiated via direct block of Na^+/K^+ pumps and not via off-target interactions with hERG or any other protein [57]. Expression of surface ion channels is also regulated by a number of other factors such as hormones and electrolytes. Hypokalaemia is a frequent complication of prolonged and/or intensive diuretic therapy and is associated with QT interval prolongation and TdP. Extracellular potassium is required for hERG function and membrane stability. When extracellular potassium is very low, hERG channels very rapidly become dysfunctional and are subsequently internalized and degraded within hours [75, 76]. Caveolin is also believed to be involved in hypokalaemia-induced internalization of cell-surface hERG channels [77]. Increase in extracellular potassium or rubidium reduces hERG block by quinidine and cisapride [78]. Decrease in extracellular magnesium also exerts a direct action on hERG channels, resulting in suppression of outward repolarizing potassium current [79].

Apart from inhibition of IKr current, other potassium currents (I_{K1} and IKs), sodium and calcium currents as well as other factors such as autonomic nervous system modulation are involved in drug-induced TdP [80]. However, although ion channels conducting these other currents are involved in the genesis of action potential, drugs only rarely target any of them exclusively when prolonging QT interval.

Other Potassium Channels

Four KvLQT1 α-subunits (encoded by *KCNQ1)* assemble with minK β-subunits (encoded by *KCNE1)* to form the channel (known as Kv7.1) that conducts the slowly activating delayed rectifier potassium current (IKs). As the heart rate or adrenergic activity increases, this channel assumes progressively greater role in ventricular repolarization in order to adapt the APD to progressively shorter RR interval.

Drugs such as triamterene, indapamide, isoflurane, arsenic trioxide and azimilide have the potential to inhibit the IKs channel. Some drugs affect both IKr and IKs current (e.g. isoflurane, arsenic trioxide and azimilide) but their effect on QT interval is mediated predominantly via IKr inhibition.

The *KCNJ2* gene encodes the inward rectifier K^+ channel (known as Kir2.1), which is expressed in skeletal and cardiac muscle. Kir2.1 is an important contributor to the inward rectifier K^+ current (I_{K1}) which contributes to the terminal part of phase 3 of both atrial and ventricular action potentials. Studies using barium chloride and beagle Purkinje fibers have shown that inhibition of I_{K1} leads to prolongation of APD_{90} which is independent of gender [81]. A loss of function of I_{K1} secondary to genetic defects in *KCNJ2* leads to Andersen-Tawil syndrome, which is often but not always associated with prolongation of the QT interval. Although I_{K1} is generally not as sensitive to drug effects as is the IKr current, reduction of I_{K1} by low extracellular potassium

strongly promotes ventricular arrhythmias mediated by enhanced automaticity of the Purkinje system, and under conditions of acquired long QT syndrome caused by IKr blockade, the development of phase 3 early afterdepolarizations (EADs).

Role of Sodium Ion Channel

The *SCN5A* gene encodes for the cardiac sodium channel (known as Nav1.5). These channels consist of a highly processed α subunit, associated with auxiliary β subunits. Alternative splicing results in two transcript variants of α subunit and these two isoforms differ only by a single amino acid. Sodium channels in the adult central nervous system and heart contain β_1 through β_4 subunits. The pore-forming α subunit is sufficient for functional expression, but the kinetics and voltage dependence of channel gating are modified by the β subunits. Sodium channels generate large and very brief inward sodium current (INa) that causes the rapid upstroke of the action potential. This is accomplished by very brief channel openings with very short latency, meaning the channel is inactivated quickly. Late or "persistent" INa arises when sodium channels fail to completely inactivate. A possible mechanism for a sustained late current is an overlap in the relationships for channel activation and inactivation. Such an overlap has been referred to as a window current. Late INa may contribute to triggering arrhythmia in two ways: by lengthening repolarization phase and inducing EADs and by triggering late afterdepolarizations attributable to calcium oscillations in sodium–calcium overload conditions [82]. Late INa is reported to be increased in a number of cardiac diseases such as failing hearts, in post-myocardial infarction "remodeled" myocytes, and in hypoxic or ischemic hearts. An abnormal increase of late INa due to either heritable *SCN5A* mutations or organic heart disease is associated with a decrease of repolarization reserve and an increased susceptibility to TdP. Increase in late INa leads to APD prolongation which then promotes arrhythmias. Augmentation of late INa with ATX-II mimics LQT3 form of cLQTS (that results from gain-of-function mutations of *SCN5A*). Conditions leading to a reduction in IKr or augmentation of late INa also produce a preferential prolongation of the action potential of the M cells, present in the mid-myocardial layer of the ventricles. As a consequence, the QT interval prolongs and is associated with a dramatic increase in transmural dispersion of repolarization (TDR) radially across the ventricular wall. This creates a vulnerable window for the development of re-entry [83].

Amiodarone at therapeutic concentrations is able to inhibit late INa in human myocardium without large reductions in peak INa [84]. Not surprisingly, clinical use of amiodarone is associated with only occasional development of TdP. The presence of late INa also modulates the arrhythmogenicity of quinidine. Enhancement of late INa increased proarrhythmia caused by low but not high concentrations of quinidine. The proarrhythmic effects of quinidine were significantly greater in the presence than in the absence of ATX-II, suggesting the role of an increased level of late INa [85]. The biphasic proarrhythmic and antiarrhythmic effects of low and higher concentrations, respectively, of quinidine are associated with inhibitions of IKr and of INa (especially late INa), respectively [85]. Mexiletine dose-dependently reverses the ATX-II-induced prolongation of APD_{90} in all three cell types of the ventricular wall [86]. It also reverses *d*-sotalol-induced prolongation of the M cell APD, but had little effect on the action potential of epicardium and endocardium [87]. Due to its preferential effect on M cells, mexiletine reduces the TDR and is effective in the treatment of cLQT3. Mexiletine also antagonizes effects of sotalol on QT interval duration and its proarrhythmic effects in a canine model of TdP [86, 88]. Endogenous late INa contributes to the reverse rate dependence of IKr inhibitor-induced increases in APD and beat-to-beat variability of repolarization and to bradycardia-related ventricular arrhythmias. In a computational model, simulated reverse rate dependence of APD caused by E-4031 and *d*-sotalol was attenuated when late INa was inhibited [89].

Among the newer compounds, ranolazine (an antianginal agent) and RSD1235 (vernakalant) and AZD1305 (both antiarrhythmic agents) block the late INa current [90–93], in addition to both ranolazine and AZD1305 blocking the IKr current and RSD1305 blocking

the IKur current. These drugs are capable of attenuating IKr-induced APD prolongation and repolarization instability, thus suppressing EADs or TdP induced by class III agents [94]. It is interesting though that the development of AZD1305 has been discontinued because of its torsadogenic potential [95]. An increase in late INa, induced by ATX-II, has been shown to potentiate the proarrhythmic activities of low-risk QT-prolonging drugs in female rabbit hearts [96]. This suggests that even low-risk QT-prolonging drugs may be unsafe in patients in whom late INa is increased due to heritable (i.e., *SCN5A*) or acquired channelopathies. It has therefore also been suggested that this preparation can be useful in nonclinical studies to predict the risk that a drug candidate will cause TdP when late INa is increased. Assays with this preparation are able to detect the proarrhythmic potential of drugs that are known to have a very low proclivity to cause TdP.

Alfuzosin seems to be a rare example that prolongs cardiac repolarization by increasing the late sodium current [97].

Role of Calcium Ion Channel

Two types of voltage-gated calcium channels play critical roles in the cardiac tissue, namely L-type (long lasting) and T-type (transient). L-type channels respond to higher membrane potentials, open more slowly, and remain open longer than T-type channels. Because of these properties, L-type channels are important in *sustaining* an action potential. L-type channels are targeted and blocked by dihydropyridines. The calcium channel consists of a complex of α-1, α-2/δ, β, and γ subunits in a 1:1:1:1 ratio. The *CACNA1C* gene encodes for α-1c subunit (known as Cav1.2) in humans and this subunit is necessary for channel function. Mutations in the *CACNA1C* gene are associated with a variant of cLQTS called Timothy's syndrome and also with Brugada syndrome. There are four known isoforms of the β subunit but the one most relevant to cardiac tissue is β-2 subunit that in humans is encoded by the *CACNB2* gene. It is believed that the cytosolic β subunit has a major role in stabilizing the final α-1 subunit conformation and delivering it to the cell membrane by its ability to mask an endoplasmic reticulum retention signal in the α-1 subunit. Antimony-based drugs used to treat leishmaniasis prolong the cardiac action potential, and therefore the QT interval, by an increase in cardiac calcium currents [98, 99]. Arsenic trioxide also prolongs QT interval by increasing cardiac calcium current [54]. As discussed later, inhibition of calcium current appears to be protective.

Combined Blocks of Potassium Channels

Although *in vitro* data suggest that blockade of IKr and IKs simultaneously prolongs action potentials more than would be expected from simple summation of the two individual effects [100], this may not always be the case with QT interval *in vivo* despite the combination being more effective in inducing TdP [101]. Combined *in vitro* administration of two IKr blockers does not necessarily lead to potentiation of the drug effects [102]. Clinically, however, there are a number of anecdotal published reports of TdP occurring when another IKr blocker is administered to a patient already receiving one. As stated above, *in vitro* studies have shown that enhancement of late sodium current may potentiate the QT-liability of otherwise low-risk drugs by increasing the duration of the plateau phase of APD [96].

QT Interval Prolongation as a Marker of Drug-Induced Proarrhythmic Risk

Since the measured QT interval varies with heart rate, it requires correction for changes in heart rate to evaluate the effect of an intervention or an incurrent event. There are a large number of empirical formulas for this purpose described in the literature. Two widely used are Bazett's formula and Fridericia's formula, leading to rate-corrected intervals, referred to as QTcB interval and QTcF interval, respectively. However, any generic correction formula in general, particularly the Bazett's formula, has serious limitations since the QT/RR relation exhibits a very substantial inter-individual variability between subjects. The QT-prolonging effect of

amiodarone was confirmed by 31 previously published heart rate correction formulas but degree of prolongation differed from formula to formula and ranged from 13.6 to 30.9 ms [103]. When extreme precision if necessary to detect the effect of an intervention, the most widely used formula is that derived specifically for the study population (and referred to as QTcS interval) or preferably, for each individual study subject (and referred to as QTcI interval) [104]. This is often the preferred approach for drugs whose effect on QT interval is on the cusp of the threshold of regulatory concern (see later). However, in the majority of instances, the use of these study-specific or individual-specific formulas, compared to Fridericia's correction, does not appear to be resource-effective [105, 106]. Given the imperfection of QT interval as a marker of the risk of TdP, regulatory authorities are content with the use of Fridericia-corrected QTc interval (QTcF interval) in most instances.

One review in 1993 concluded, "At present, our knowledge base about the relation of the QT interval and torsades de pointes is grossly incomplete" [107]. Unfortunately, despite extensive research spanning over nearly two decades since then, our current knowledge base is not much better. Drugs that are equipotent as torsadogens do not induce the same increases in QT interval and conversely, equivalent increases in QT interval do not denote the same degree of proarrhythmic risk. The previously assumed link between QT prolongation and TdP is largely the result of the very definition of TdP. However, there is no clear (linear or otherwise) incremental relationship between QT prolongation and the risk of TdP, although the TdP risk tends to increase progressively as the degree of QT prolongation increases. There is unanimous agreement that QT interval, however corrected for heart rate, is an imperfect marker of the risk of TdP. This is hardly surprising since other properties of the drug and a number of patient-related factors modulate this risk. Nevertheless, it is at present the best and the simplest measure that is available as well as being the most readily accessible in routine clinical medicine. Potential to induce TdP is clearly determined by other factors that operate in tandem with a prolonged QT interval.

Delayed or prolonged ventricular repolarization also gives rise to the development of EADs at the levels of ventricular mid-myocardial M-cells and the Purkinje fibers. These EADs contribute to increasing TDR (see later). The amplitude of EADs is cycle length dependent, being greater during bradycardia, and there is a strong correlation between the preceding RR interval and the amplitude of EADs that follow [108]. When the amplitude of the EADs reaches a critical threshold, the resulting ectopic beat triggers a repetitive burst of electrical activity that forms the basis of TdP. In a comparison of ECG recordings with TdP from 15 congenital and 20 acquired LQTS patients with premature ventricular complexes from 40 patients with normal QT intervals and 24 of the 35 LQTS patients not related to TdP, abnormal giant T-U waves directly preceded TdP in 34 of 35 LQTS patients and were larger than T-wave amplitude in control patients and larger than the largest T-U-wave in LQTS without TdP. The TdP-initiating premature beat emerged from a T-U-wave in 27 of 35 LQTS patients and in none of 40 control patients. These ECG analyses suggest that EADs initiate TdP and, if present, may help to identify an imminent risk for TdP [109]. Whereas the phase 2 EADs are dependent on Ca^{++} current, phase 3 EADs are not and are believed to be dependent on low extracellular potassium which reduces the inwardly rectifying I_{K1} current. Phase 2 EAD generated from intact ventricular wall produce a trigger to initiate the onset of TdP under the conditions of QT prolongation [110]. Both phase 2 and phase 3 EADs occur in long QT syndromes although their respective roles in generating arrhythmias in intact cardiac tissue are not completely understood. In one study of 47 triggered activity episodes induced by exposure to IKr block and low extracellular potassium, the origins of these episodes were attributed to phase 2 EADs in 12 episodes (26 %) and phase 3 EADs in 35 episodes (74 %) [111].

Beat-to-Beat Variability in QT Interval as a Marker of Drug-Induced Proarrhythmic Risk

Beat-to-beat variability of repolarization duration, quantified as the short-term variability of the QT interval, is another novel marker being

investigated for differentiating the torsadogenic potentials of drugs that prolong QTc interval [112–114]. For example, although both intravenous doses of sertindole (1.0 and 0.2 mg/kg), an atypical antipsychotic drug, increased QT interval in the anesthetized dogs with chronic atrioventricular block, only the higher dose was associated with TdP in 10 of the 13 dogs. The beat-to-beat variability was the only parameter that predicted TdP outcome [112]. Similar observations have been made for amiodarone and bepridil [113]. In an anaesthetized methoxamine-sensitized rabbit, not only did increased beat-by-beat QT interval variability precede drug-induced TdP but it was also able to discriminate highly proarrhythmic compounds from compounds with a low proarrhythmic potential [114].

Transmural Dispersion of Repolarization as a Marker of Drug-Induced Proarrhythmic Risk

Studies with arterially perfused wedge preparations of canine left ventricle have revealed that drug-induced increases in APD, when localized to mid-myocardial M cells that are rich in IKr, increase APD in mid-myocardial cells but not in epicardial or endocardial cells which are relatively sparse in IKr channels. This induces an increase in (radial) transmural dispersion of repolarization (TDR) which serves as an electrophysiological substrate for TdP.

Increase in TDR and occurrence of EADs during phase 2 of the action potential are now recognized as important markers of the risk of QT interval degenerating into TdP. QT-prolonging drugs that suppress EADs or do not increase TDR have little or no potential to induce TdP. The value of TDR has been validated in a blinded evaluation of 13 agents with varying propensity for causing TdP, demonstrating both a high sensitivity and specificity [115]. Studies with drugs such as amiodarone, pentobarbital or ranolazine, have shown that they cause QT prolongations but are less likely to provoke TdP because their electrophysiological profiles lack these markers [116, 117]. They are typically drugs with multi-channel activities. For example, both ranolazine and amiodarone reduce not only IKr and IKs currents but also late Na^+ and Ca^{++} currents [90]. Vanoxerine, a new antiarrhythmic agent under investigation, is a potent hERG inhibitor as well as being sodium and calcium channels blocker. However, it does not affect TDR and therefore, although structurally different, resembles amiodarone in this respect [118]. A more recent study that compared two proarrhythmic to two non-proarrhythmic QT-prolonging drugs has also reported that TDR was enhanced only by the two proarrhythmic drugs and suggested that during drug development, TDR might be a superior nonclinical marker of the proarrhythmic risk [119].

Modulation of Proarrhythmic Risk by Ancillary Properties

Patch-clamp studies show that torsadogenic drugs can be divided into at least two groups. One group consists of pure IKr blockers whereas the other group includes drugs with ancillary effects on sodium and/or calcium channels which counterbalance the effects of IKr blockade [120]. Effects at both these ion channels are linked with TDR and EADs. Other pharmacological properties that are relevant to determining the proarrhythmic risk of a QT-prolonging drug are its activities at α-adrenoreceptors and β-adrenoreceptors. Modulation of α-adrenoreceptor activity seems to have greater effect than that of β-adrenoreceptor activity [121]. Evidence supporting the protective roles of these pharmacological activities is briefly summarized below.

The role of α-adrenoreceptor blocking activity is best exemplified by sertindole. Sertindole is sufficiently potent as an α-adrenoreceptor blocker that it frequently produces severe postural hypotension, requiring its dose to be increased gradually to reach therapeutic doses. Despite comparable QT prolongation, sertindole did not display the proarrhythmic electrophysiological profile (effect on TDR and appearance of EADs) typical of other torsadogenic blockers of IKr such as *d,l*-sotalol [122]. Although it is a potent QT interval prolonger, there are no well-documented reports of sertindole-induced TdP. First approved and marketed in the European Union in 1996, sertindole was removed from the market in 1998

because of concerns over its cardiac safety. Following an in-depth review of its electrophysiological and autonomic pharmacology, efficacy and safety in 2001, it was later re-introduced, albeit under carefully monitored post-marketing surveillance. Recurrent syncopal attacks with TdP despite β-blockade in a 7-year-old boy with cLQTS were completely abolished by changing the therapy to labetalol, a combined α- and β-adrenoreceptor blocking drug [123].

The role of β-adrenoreceptor blocking activity in modulating the risk of cardiac events (syncope, aborted cardiac arrest, and sudden cardiac death) in patients with LQT1 is evidenced by the high efficacy of β-blockers in these patients [124]. This is not altogether surprising since LQT1 is due to mutations in adrenergic-sensitive IKs current. However, consistent with the protective effect of β-adrenoreceptor blocking activity, racemic *d,l*-sotalol is predominantly antiarrhythmic whereas the *d*-isomer is predominantly proarrhythmic [9, 125–127]. In patients receiving bepridil, β-blockers have also been reported induce a statistically non-significant decrease in QTc interval but a significant decrease in TDR [128].

There is sufficient evidence to suggest that calcium channel blockade also appears to modulate torsadogenic risk in the setting of a prolonged QTc interval. Available data indicate that EADs can result from altered properties of the Na^+ channel as well as by the L-type Ca^{++} channel under the conditions of prolonged repolarization [87, 129, 130]. Failure to completely deactivate L-type Ca^{++} channels has been shown to be an essential mechanism underlying EADs caused by inhibition of both IKr and IKs channels [131]. Verapamil has long been shown to block *d*-sotalol-induced APD prolongation and EADs [132]. Verapamil and nifedipine have also been shown to reduce TDR and suppress EADs in models of LQT3 [133, 134]. Although citalopram is sufficiently potent at inhibiting hERG current and there are reports of TdP in association with its overdose, it is relatively safe at therapeutic concentrations and part of the explanation may be its ability to reduce L-type Ca^{++} current and the calcium "window" [135]. *In vitro* studies have shown that dofetilide has no effect on L-type Ca^{++} channel and is a potent torsadogen [136]. Interestingly, CPU228, a structural analogue of dofetilide, with significant IKr and L-type Ca^{++} channel blocking activities has been reported in nonclinical studies to be much safer [137]. It has been suggested that hERG blocking drugs could be made safer by incorporating compensating activities (hERG activation, calcium channel blockade or possibly β-blockade) [54, 138].

Other ECG Markers of Drug-Induced Proarrhythmic Risk

Since T wave represents cardiac repolarization, it is not surprising that drug effects on cardiac repolarization frequently manifest themselves early as *de novo* changes in T wave morphology or appearance of U waves. Whilst the significance of the later is still not fully established, the former is the subject of intense research. Together with QT interval, these additional T-wave related parameters appear very promising in improving the prediction of clinical risk.

The following is a brief summary of these potential T-wave related markers of proarrhythmic risk in the setting of drug-induced QT interval prolongation, although these require adequate validation.

T-Wave Morphology

In one study of 37 patients switched to sertindole, prominent T-wave morphology changes occurred during sertindole treatment and in some cases without concomitant prolongation of the QTcF interval. The mean effect size was higher for T-wave morphology combination score (MCS) compared to the mean effect size for QTcF interval [139]. MCS was defined as a computerized measure for T-wave morphology, based on its asymmetry, flatness and notching. In studies with two other IKr blockers (sotalol and a new antipsychotic agent), application of MCS was shown to be more discriminatory than QTc interval [140, 141]. In a study of 113 patients on bepridil therapy with and without ventricular arrhythmic events, QTc interval was prolonged in all patients but any type of T-U wave change (fused U, slurred, bifid, biphasic or negative) appeared in 73 % of event-free and 100 % of event groups. In multivariate analysis, only newly appeared negative

T-U wave exhibited a significant difference between the two groups [142]. As summarized earlier, abnormal giant T-U waves directly preceded TdP in 34 of 35 (15 congenital and 20 acquired) LQTS patients [109].

T-Wave Alternans (TWA)

T-wave alternans (TWA) is defined as beat-to-beat fluctuations in the morphology, amplitude and/or vector of electrocardiographic T-wave, and is associated with dispersion of repolarization. It is directly related to alternation of the M-cell APD, leading to exaggeration of TDR during alternate beats [143]. μ (micro)TWA represents very small beat-to-beat fluctuation in the amplitude of T-waves. There is a significant correlation between TWA or μ TWA and vulnerability to ventricular arrhythmias in individuals with or without organic heart disease and is a powerful marker for the risk of sudden cardiac death. Studies examining the effect of drugs on TWA are few and far between in the literature. Drug-induced TWA has been reported clinically following the use of almokalant [144], pentamidine [145] and amiodarone [146, 147] and it has been suggested that the magnitude of effect on TWA may allow the differentiation of proarrhythmic from non-proarrhythmic hERG blockers at clinically relevant concentrations [148–150]. For further information on the utility of TWA as a marker of proarrhythmic risk, the reader is referred more comprehensive reviews of the subject [151, 152].

Tpeak–Tend (Tp–Te) Interval

Often referred to as TPE, Tp–Te interval represents the time from the peak of the T wave to its return to baseline. The mean values of Tp–Te interval in lead V5 in healthy individuals have been reported as 94 ms in men and 92 ms in women [153]. Although there is some debate [154], it is generally believed that this interval on surface ECG best correlates with TDR but the prognostic significance of Tp–Te needs to be better documented [155]. Sertindole has been reported to significantly increase the QTcF interval but without any increase in the duration of Tp–Te from baseline [156], a property that may be associated with its α-adrenoreceptor blocking activity.

Tp–Te/QT Ratio

Recently, there is an interest in the utility of a new index – the ratio of Tp–Te interval to QT interval. In man, the mean value of this ratio is approximately 0.2 [157] and is relatively constant over a heart rate of 60–100 beats/min [158]. Tp–Te/QT ratio is significantly greater in patients at risk of arrhythmic event such as those with cLQTS, cSQTS, Brugada syndrome and also in patients with organic heart disease such as acute myocardial infarction. In the *in vitro* study of 13 agents with varying propensity for causing TdP referred to earlier [115], Tp–Te/QT ratio was able to distinguish torsadogenic from non-torsadogenic drugs. Agents that induced EADs, including cisapride, clarithromycin, sparfloxacin and erythromycin, tended to produce a greater prolongation of Tp–Te interval and increase in Tp–Te/QT ratio. In a study of 12 patients with and 15 without drug-induced TdP, mean Tp–Te intervals were 185 and 84 ms, respectively ($p < 0.001$) and the mean Tp–Te/QT ratios were 0.337 and 0.187, respectively ($p < 0.001$). This ratio did not correlate with the maximum QTc interval (mean 657 and 505 ms respectively, $p < 0.001$), but it was found to be a reliable predictor of TdP. The ratio was the best predictor and cumulative frequency distributions revealed that a ratio of 0.28 was a good cut-off point for risk of TdP [159].

Early and Late T-Wave Vectors

Based on their study of the effect of moxifloxacin, Couderc et al. have described two T-wave vectorcardiographic parameters, both indicative of ventricular repolarization heterogeneity, that appear to be very sensitive to subtle drug effects on cardiac repolarization current mediated by the IKr channel [160]. These parameters measure the time interval needed for the cardiac vector amplitude to change from its maximum value to a time when its amplitude has been reduced by 30, 50 or 70 %. These measurements are designated early repolarization duration (ERD_{30}, ERD_{50} or ERD_{70}) when they are measured before the T-wave apex and late repolarization duration (LRD_{30}, LRD_{50} or LRD_{70}) when measured after the apex. They depend on both the speed of the

repolarization process and the morphology of the T-loop. Using sotalol, these parameters were later validated by a study in healthy volunteers and another study in patients with drug-induced TdP [161, 162]. Their data also suggest that LRD and Tp-Te might measure the same electrophysiological interval and that the ECG abnormalities characterizing patients with a history of TdP are (a) an increased heterogeneity of repolarization at baseline and (b) a sotalol-induced prolongation of the terminal part of the T-wave.

Regulatory Focus and Evaluation of a Drug Effect on QT Interval

Regulatory authorities have been troubled by the facts that for the majority of the drugs withdrawn from the market and discussed earlier, there was no evidence of their QT or arrhythmogenic liability during clinical trials, partly because the cardiac and ECG effects were not evaluated and partly because the evaluation undertaken lacked sensitive and standard methodology. Although the risk of TdP is sufficiently low that it is improbable that it would be detected during clinical trials, the effect of a drug on cardiac repolarization is concentration-related [163, 164] and therefore, a new drug could readily be studied during the pre-approval period for its potential proarrhythmic risk by use of appropriate mechanism-based and concentration-related surrogate markers, namely, APD *in vitro* and the QT interval *in vivo*.

Case study of lidoflazine illustrates just how our appreciation of the significance of drug-induced QT interval prolongation has undergone a major revolution. In a clinical trial of 35 patients comparing the efficacy of lidoflazine with quinidine in atrial fibrillation (AF), lidoflazine was associated with four sudden deaths and the trial was stopped [165]. Lidoflazine was nevertheless approved for marketing in Europe (including the UK) during 1979–1982 but it was denied an approval by the FDA (but it seems not on grounds related to prolongation of QT interval). Other reports of lidoflazine-induced TdP followed and later, Hanley and Hampton reported a significant prolongation of the QT interval in association with lidoflazine in a clinical trial of 24 patients who had received either propranolol, lidoflazine or a combination of both [166]. Five patients developed ventricular tachycardia when receiving either lidoflazine or lidoflazine and propranolol in combination; one of these patients died. The drug was ultimately withdrawn from the market in 1989.

Central to the current regulatory concerns regarding drug-induced QT interval prolongation are the facts that:

- The number of recognized non-cardiac drugs with this liability continues to increase;
- Most of the drugs are prescribed for otherwise relatively benign or low risk conditions;
- For most of these drugs, historically, their potential to prolong the QTc interval and induce TdP was not recognized for many months or years after the drug was approved and in clinical use;
- The population at risk is larger than had hitherto been appreciated.

To this list may be added the concerns that:

- Susceptibility to QT prolongation and TdP is a dynamic process whereby a patient not at risk may be placed at risk due to some intercurrent event such as development of hypokalaemia due to diarrhoea and vomiting or the prescription of an interacting co-medication
- Despite the best endeavors to characterize the risk and provide adequate prescribing information to the prescribing physicians once the effect on duration of QTc interval was identified, clinical experience shows a disappointingly low level of physician compliance with the concurrent use of contraindicated drugs or ECG monitoring of patients as recommended.

In 1997, the European Union regulatory authority, European Medicines Agency, became the first authority to issue a formal regulatory guidance, advising the sponsors of new drugs on appropriate nonclinical and clinical testing of compounds to identify new drugs with QT-liability. This has now been superseded by guidance documents (known as ICH S7B and ICH E14) issued in 2005 by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [167, 168].

Nonclinical Evaluation

ICH S7B [167] is concerned with nonclinical studies and promotes a concept of integrated risk assessment based on the chemical and pharmacological class of the drug together with data from two core tests – *in vitro* IKr assay and *in vivo* studies in a suitable species. It makes a specific reference to hERG channel studies. The integrated risk assessment also takes into account follow up studies specially investigating the electrophysiology of the drug (using APD assay and various proarrhythmia models) as well as data from other studies investigating toxicology, pharmacodynamics, pharmacokinetics, tissue distribution and accumulation and drug interactions.

The IC_{50} value of a drug for hERG block is often compared to its predicted or measured maximal plasma (free) drug concentrations (C_{max}) to compute a predictive value, referred to as the hERG safety margin (IC_{50}/C_{max}). Following a detailed review of the data on hERG or IKr IC_{50} of 53 drugs of wide ranging torsadogenic potency, Redfern et al. suggest that a 30-fold margin between hERG IC_{50} and peak free therapeutic plasma concentrations may be adequate to confidently exclude a clinical effect on cardiac repolarization [169]. This safety margin is also supported by data reviewed earlier by Webster et al. [170]. However, for the sake of greater (regulatory) certainty, Redfern et al. recommend a higher safety margin but correctly emphasize that the acceptable safety margin should depend on the lethality of the disease to be treated, ranging from ten-fold for a lethal disease to higher than 100-fold for (symptomatic treatment of) a benign condition. De Bruin et al. identified a significant association of 1.93 (95 % confidence interval: 1.89–1.98) between the anti-hERG activity of drugs and reporting of serious ventricular arrhythmias and sudden death to the WHO Uppsala Drug Monitoring Centre database. The smaller the margin between IC_{50} and free therapeutic plasma concentrations, the higher was the risk [171]. Although the available data suggest that a 30-fold margin between hERG IC_{50} and peak free therapeutic plasma concentrations may be adequate to establish clinical safety of most drugs, there is at present no consensus on the multiple that should be devoid of an effect in the hERG studies to exclude a clinical risk [172].

It is difficult to quantify the degree of hERG block that corresponds to a clinically relevant prolongation of QT interval. When hERG data and clinical data on dofetilide were correlated, a 10 % hERG blockade by dofetilide was reported to correspond to a QT prolongation of 20 ms (95 % confidence interval: 12–32 ms) [173]. QT-prolonging drugs are seven times as likely to demonstrate hERG safety margin values below 30 compared to drugs that do not prolong QTc. Overall, a hERG safety margin of the order of 45, based on calculated free drug concentrations, provides optimal concordance with clinical QTc prolongation [172]. The reader is referred to an excellent review of this subject by Gintant [172].

Studies investigating a drug effect on hERG current are conducted in heterologous systems which express the hERG gene using Chinese hamster ovary (CHO) or human embryonic kidney (HEK) cells. A number of indirect techniques have been used to study the effect of a drug on hERG channel [174–178]. Indirect assays are less sensitive than those reported using direct measures of hERG current. These indirect methods may be suitable for high throughput rapid screening of thousands of analogues prior to proper testing of potential lead candidate compounds. The characterization of changes in hERG current measured directly in patch-clamp studies remains the "gold standard" for evaluating drug effects. However, the IC_{50} values obtained during hERG assay are highly dependent on experimental conditions (i.e. model, temperature, voltage protocol) [179]. Assessment of data from hERG assay for their clinical relevance is a complex task, requiring a number of factors to be taken into account. These include therapeutic plasma concentration, drug metabolism and active metabolites, severity of target condition and drug effects on other cardiac ion channels that may mitigate or exacerbate the effects of hERG blockade. Since metabolite(s) of a drug can also inhibit hERG channel (e.g. desmethylastemizole), simple assays of inhibition of hERG channel by the parent drug without taking full account of its metabolites may provide erroneously reassuring data. Therefore, *in vitro* studies

should routinely investigate the effect of a drug and its major metabolites not only on hERG but also on hERG trafficking if the nonclinical data are to serve their purpose. On the other hand, despite the generally accepted link between hERG block and delayed ventricular repolarization, the relationship between hERG block and clinical QTc prolongation is poor and excessive reliance on the hERG assay likely results in unwarranted attrition of otherwise promising drug candidates [172]. Inwardly rectifying potassium current (I_{K1}) is hardly ever evaluated in safety pharmacology analyses [80]. A thorough evaluation of a new compound should also include investigation of its effects on all other ion channels involved in the genesis of APD.

APD assays better define the effect of the drug on repolarization and also permit assessment of the effect of the drug on other ion channels. The two hallmarks of class III electrophysiological activity in an APD assay are (a) concentration-dependence and (b) reverse use-dependence. Appearance of EADs in an APD assay should raise significant concerns about the likelihood of a proarrhythmic liability. The relevance of different indicators such as increase in APD_{90}, reverse use dependency and action potential triangulation has been evaluated by comparison with available clinical data on 45 drugs in isolated canine Purkinje fibers [180]. These reference drugs included those with (a) clear risk of TdP (n = 22), (b) rare reports of TdP (n = 13) and (c) without reports of TdP and QT prolongation (n = 10). The results enabled the investigators to derive an algorithm which enabled a clear separation of drugs into the three groups. A recent initiative is aimed at setting up a database (hERGAPDbase) of electrophysiological experimental data documenting potential hERG channel inhibitory actions and the APD-prolongation activities of a wide range of drugs [181]. This database can be accessed at http://www.grt.kyushu-u.ac.jp/hergapdbase/.

One might expect a reasonable correlation between hERG IC_{50} and the concentration that induces prolongation of APD_{90}. However, the experimental conditions, drug concentrations and ion channels involved in the two test systems (*in vitro* hERG and APD assays) are different. Therefore, it is not surprising that often, there is inadequate correlation not only between the findings from these studies but also their correlation with the ability of a drug to prolong the QT interval in man. This is typically the case with drugs that are active at multiple ion channels as demonstrated using brompheniramine as an example [182]. Available data suggest that although there are a number of outcomes possible, hERG IC_{50} is by and large three to ten-fold greater than the concentration causing a 10 % increase in APD_{90} [183] and that the correlation between hERG blockade and APD prolongation can vary from compound to compound.

The authors are not aware of any clinically recognized torsadogen which has been found to be safe in these two assays. Overall, the two *in vitro* assays (hERG and APD) provide a valuable insight into the potential risk of QT interval prolongation in man and when conducted early during drug development, they provide useful information relevant to planning early human studies. The reader is referred to Valentin et al. who have reviewed the value of nonclinical cardiac repolarization assays in supporting the discovery and development of safer medicines [184].

ICH S7B does not specify any particular proarrhythmia model that may be most appropriate to investigate the effect of drugs on cardiac repolarization. However, a number of models of TdP have been developed [185–187]. These models involve the use of tissue slices, isolated heart preparations or whole animals with an appropriate risk factor (bradycardia and/or hypokalaemia). Regulatory authorities have taken into account the data from studies using the following models when integrating risk assessment:

- Perfused canine left ventricular "wedge" preparation investigating the effect of the drug on TDR [188]
- Isolated perfused female rabbit hearts investigating the effect of the drug on triangulation, reverse use-dependence, instability and dispersion of APD. These features, referred to as TRIaD, are associated with a proclivity to induction of TdP [189, 190]
- Anesthetized methoxamine-treated rabbits [191]

- Conscious dogs with chronic AV block with or without diuretic-induced hypokalaemia [88, 192, 193]
- Conscious monkey with chronic AV block [194]

No single model is superior to another and therefore, it is advisable that a drug is investigated in at least two models to confirm or exclude a proarrhythmic risk with greater confidence. An initiative to evaluate the three nonclinical models of QT prolongation (hERG assay, APD assay and *in vivo* studies in conscious telemetered dogs), using six torsadogenic and six non-torsadogenic drugs, concluded that the data from each of these assays demonstrated that compounds that may pose a proarrhythmia risk for patients can be distinguished from those that are considered safe [195].

Clinical Evaluation

ICH E14 [168] is concerned with clinical investigation of a drug effect on QT interval and its focus is a specific 'thorough QT (TQT) study', typically conducted in healthy volunteers, as the primary method for evaluating the potential effect of non-cardiac agents on cardiac repolarization during drug development. This guideline applies to almost all new drugs with systemic bioavailability and may also apply to the established drugs should their post-marketing safety assessment so require. ICH E14 also elaborates on regulatory implications in terms of labeling and risk/benefit and post-marketing risk management strategies.

The core features of a TQT study are the use of a therapeutic and a supratherapeutic dose of the new chemical entity (NCE), the use of a positive control, typically a single 400 mg dose of moxifloxacin, to establish assay sensitivity and placebo. The choice of what constitutes supratherapeutic dose depends on maximal dose tolerated by man and is typically three to fivefold the therapeutic dose. Whether the study is parallel or crossover in design and whether the dosing regimen is single dose or repeated doses depends on the pharmacokinetics of the NCE. It is, however, arguable if 400 mg of moxifloxacin is the most appropriate positive control since its effect is so marked, usually the largest mean placebo-corrected increase from baseline is in the order of 12 ms [172, 196], that it would probably be impossible to miss it in any TQT study (meaning fail to establish assay sensitivity) unless there was a serious problem with its absorption or the study was technically seriously flawed. In a study comparing single doses of moxifloxacin with levofloxacin, the largest time-matched difference in QTcI for 400 mg moxifloxacin compared with placebo was 13.19 ms whereas the corresponding values for levofloxacin 1,000 and 1,500 mg doses were 4.42 and 7.44 ms, respectively [197]. Thus, an oral dose of 1,500 mg of levofloxacin may be a more rigorous positive control to establish assay sensitivity.

When the study is adequately powered, a negative TQT study is one in which the upper bound of the 95 % one-sided confidence interval for the largest time-matched placebo-adjusted mean effect of the drug on the QTc interval excludes 10 ms and the drug is deemed not to have a QT effect of regulatory concern. This definition is chosen to provide reasonable assurance that the mean effect of the study drug on the QT/QTc interval is not greater than around 5 ms. The study is termed 'positive' if the largest time-matched difference exceeds this threshold and it influences the evaluations to be carried out during later stages of drug development, but it does not imply that the drug is necessarily proarrhythmic. When the TQT is deemed to be positive, robust ECG monitoring should be implemented in phase III studies, especially in patients with risk factors and in those who experience any symptoms suggestive of a ventricular tachyarrhythmia.

Widening and flattening of the T wave frequently precede clinical onset of TdP following torsadogenic agents. Therefore, the percentage of subjects developing *de novo* changes in T wave morphology or U waves should also be included in the data package. In the broader context of cardiac safety, the ECGs should be evaluated for effects on other intervals and segments and the data presented.

Recently, concerns have been expressed that a non-inferiority intersection–union test, the test recommended by ICH E14 for the determination of a TQT, might be overly conservative with respect to excluding QT prolongation [198]. However, the criterion, stringent as it is, simply illustrates the intensity of regulatory concerns. In terms of its predictive value, it is reasonable to conclude that

Table 6–3. Likely prognostic significance of mean maximum or peak placebo-corrected QTc increase in interval in man

Mean maximum or peak placebo-corrected	Likely potential torsadogenic risk increase in QTc interval
≤5 ms	None
6–10 ms	Unlikely
11–15 ms	Possible
16–20 ms	Probable
21–25 ms	Almost definite
≥26 ms	Definite

From Shah [15]. Reprinted with permission from British Pharmacological Society, Blackwell Publishing

whereas a positive TQT study has a poor predictive value, a negative study will confidently exclude the potential for a risk. The positive predictive value of the study with regard to clinical relevance may be increased by including subjects who are likely to show an exaggerated QT response (such as those carrying clinically silent mutations of ion channels) (see below). However, there are serious ethical dilemmas associated with this approach.

Based on data on torsadogenic and non-torsadogenic drugs, one of the authors (RS) has computed the likely prognostic significance of the effect of clinical doses on mean maximum or peak placebo-corrected QTc interval in humans as shown in Table 6.3 [15, 199]. Lin and Kung have also summarized data on a number of drugs which suggest that a mean QTc increase of 19.3 ms associated with strong torsadogens was significantly greater than the 8.0 ms for borderline torsadogens. Prolongation greater than 12 ms in the context of monotherapy favored a stronger association with TdP [200]. To put these mean increases in the context of categorical responses, it might be noted, for example, that the mean increase in QTc interval produced by 200 mg sparfloxacin (a known torsadogen) in 813 patients amounted to only 11 ms (+2.9 %), and yet the absolute QTc interval had exceeded 500 ms in 10 (1.23 %) of these patients [201].

Data from a TQT study should be considered not only in terms of the maximum mean effect in the study population as a whole but also in terms of the percentages of individuals with categorical responses that are most indicative of a potentially significant drug effect in an individual. ICH E14 describes a number of such responses but in the opinion of the authors, only two are the most relevant, given the intra-individual variability in QTc interval, namely (a) an increase of 60 ms or more in QTc interval from baseline (ΔQTc), regardless of the resulting on-treatment QTc interval value and (b) an on-treatment QTc interval ≥500 ms, regardless of ΔQTc from baseline.

Since the risk of TdP ultimately depends on the duration of QTc interval and not on an increase from baseline, a new absolute QTc interval ≥500 ms in any subject is a better indicator of the potential risk than is a ΔQTc ≥ 60 ms. The same author (RS) has analyzed data on 199 reports of drug-induced TdP on five drugs known to be torsadogens (cisapride, terfenadine, prenylamine, terodiline and bepridil). The QT/QTc interval values were <500 ms in 21 (10.5 %) patients and ≥500 ms in the remaining 178 (89.5 %) patients. Another analysis of 36 patients with prenylamine-induced ventricular tachycardia in whom QT/QTc intervals were known on therapy before the onset of arrhythmia and after prenylamine was discontinued strongly suggested 500 ms as a powerful predictive categorical response. In a series of 52 patients with TdP, Song L et al. reported a mean QTc of 571 ± 93 ms before and 456 ± 50 ms after treatment [202]. The present author has also observed an inverse correlation between percent increase in QTc interval and baseline QTc interval in 21 patients who had a QTc interval ≥500 ms while receiving sertindole, a potent inhibitor of IKr current. Therefore, the assessment of risk based on a combined evaluation of the above two categorical responses (absolute QTc interval of ≥500 ms or a ΔQTc ≥60 ms) should compensate for the tendency of QTc interval changes to regress to a mean.

Since a drug effect on QT interval is closely related to its concentration, the TQT study is also expected to characterize the concentration-QT effect (PK/PD) relationship of the drug by measuring plasma concentration of the drug (and if appropriate, its metabolite(s)) at each time point of ECG measurement. This is an important feature of a TQT study since PK/PD analysis permits prediction of an effect by extrapolation at extremes of concentration that may occur in worst case scenario and/or in pharmacokinetic outliers. It also allows QT-related risk/benefit assessment at lower concentrations and approval of a lower dose provided that the effect on QT interval is acceptable and there is no loss of efficacy at these lower concentrations. PK/PD analysis provides such valuable information that

in some circumstances, it may be possible to eliminate the need for a TQT study if robust ECG monitoring is also implemented in all the early phase I clinical pharmacology studies that measure plasma concentrations of the drug and/or its metabolites [1,203]. Since phase II dose–response or therapeutic exploratory studies involve relatively larger number of patients and a range of doses, at least one of these studies should also include robust and intensive ECG monitoring in addition to pharmacokinetic blood sampling.

Integrated Evaluation of the Data

Given the implications for the approval and labeling of the NCE and for public safety, regulatory and clinical evaluation of the risk of TdP associated with clinical use of the NCE requires an integrated approach that takes into account:

- Pharmacological and chemical classes of the NCE
- Physicochemical characteristics of the NCE, including stereochemical aspects
- *In vitro* (ion channel and electrophysiology) and *in vivo* nonclinical studies
- High-dose pharmacology studies to steady state, with and without inhibitors of its elimination or inactivation
- Other ancillary pharmacology of the NCE and its metabolites
- Appropriate studies in 'at risk' groups
- Appropriate pharmacodynamic interaction studies
- Evaluations of mean increase in placebo-corrected QTc interval and outliers with categorical responses in clinical studies
- Genotype of the study subjects, especially the outliers, with respect to mutations of drug metabolizing enzymes and cardiac ion channels (especially sodium and potassium)

Risk Factors for Drug-Induced Torsade de Pointes

Patients without risk factors are at very low risk of clinically relevant QT prolongation or TdP. In a vast majority of patients who experience marked drug-induced QT prolongation and/or TdP, there usually are present one or more known risk factors (Table 6.4). Only 38 (11 %) of the 341 cases with cisapride-induced proarrhythmias had no reporter-identified risk factors or contraindications [6]. In another study of 35 cases of fatal cardiotoxicity related to halofantrine (a potent QT-prolonger), 26 (74 %) had at least one predisposing factor for severe cardiotoxicity [204]. De Bruin et al. have reported significantly increased odds ratios (for the risk of cardiac arrest) of 2.1 in patients who received QTc-prolonging drugs, 2.5 in patients receiving doses >1 defined daily dose, 4.0 in patients taking pharmacokinetic interacting drugs concomitantly and 4.8 in patients taking >1 QTc-prolonging drug simultaneously [7]. In a series of 52 patients with TdP, structural heart diseases were found in 67.3 % and electrolyte disorders in 59.6 % patients [202]. In this series, 36.5 % patients had received diuretic therapy and 28.8 % had received antiarrhythmic drugs which might induce prolonged QT interval

Table 6–4. Common risk factors for QT interval prolongation and/or TdP

Dose:	Too high
	Overdose
Gender:	Female
Drug interactions:	Concurrent use of metabolic inhibitors
	Concurrent use of QT-prolonging drugs
	(potassium depleting diuretics)
Genetic susceptibility:	Family history of LQTS
	Pre-existing QT prolongation
Low heart rate:	Sinus bradycardia
	AV block
Cardiac disease:	Congestive heart failure
	Coronary artery disease
	Recent myocardial infarction
	Cardiomyopathy
	Left ventricular hypertrophy
	Atrial fibrillation
Electrolyte imbalance:	Hypokalaemia
	Hypomagnesaemia
	Hypocalcaemia
Endocrine:	Hypothyroidism
	Pheochromocytoma
	Hypoglycaemia
	(hyperaldosteronism)
Non-cardiac diseases:	Autonomic neuropathy
	(moderate to severe hepatic disease)
	Cirrhosis
	HIV infection
	(renal impairment)

Parenthesis indicates factors that may predispose as a result of their secondary effects

[202]. Collective analysis of data from various sources suggests that an obvious risk factor is missing in about 10–20 % of cases. It seems probable that there is a genetic susceptibility in these patients [205, 206]. The potential role of genetic factors is discussed later in this chapter.

Female gender has consistently emerged as a potent risk factor since it was first reported in 1993 that 70 % of the 332 patients who experienced TdP on cardiovascular drugs were females [207]. Across different studies, females account for 60–80 % of all reports of drug-induced QT interval prolongation and/or TdP [6, 171, 204, 208–212]. Almost all the TQT studies, carried out in compliance of ICH E14 guideline, have consistently reported that the QT effect is greater in females than in males. Since the majority of these studies are in healthy volunteers, there are no confounding issues arising from differences in co-morbidity or co-medications. Any gender-related pharmacokinetic differences do not appear to be marked enough to account for this gender difference in QT susceptibility. PK/PD analyses from these studies have also revealed a steeper concentration-response in females. The slope of the relationship between change in the QTc interval from baseline (Δ QTc) and the serum concentration of quinidine was 44 % greater in women than in men (mean 42.2 vs. 29.3 ms/μg/mL) [213]. Similarly, after a single oral dose of quinidine, maximum prolongation of QTc interval was significantly greater in women (33 ± 16 vs. 24 ± 17 ms) although these were no gender differences in the pharmacokinetics of the drug [214]. In a PK/PD study with sotalol, QTc and serum sotalol concentration strongly correlated but the upward shift of the regression line in females indicated a longer QTc at any concentration level [215].

No consistent explanation has been forth coming for this gender effect, probably because the mechanism is too complex. Factors considered likely to account for this gender effect include electrophysiological effects of gender-related hormones [216–219] and density of ion channels [220]. Estrogens evidently facilitate bradycardia-induced prolongation of the QT interval and the emergence of arrhythmia whereas androgens shorten the QT interval and blunt the QT response to drugs. Progesterone has recently been reported to disrupt hERG trafficking [221]. Testosterone is thought to increase IKr and suppress L-type calcium currents. A more recent study in mice has suggested that gender-related differences in the late sodium current may also be an important modulator of gender-related susceptibility to QT prolongation [222]. For a more in-depth discussion of the likely mechanisms that underpin this gender difference, the reader is referred to various detailed reviews [223–225].

Among the other more potent risk factors are hypokalaemia, bradycardia, co-administration of the metabolic inhibitors of the culprit QT-prolong agent and presence of significant cardiac disease, especially congestive heart failure. As stated earlier, when extracellular potassium is very low, hERG channels very rapidly become dysfunctional and are subsequently internalized and degraded within hours [75, 76]. With regard to bradycardia, it is noted that complete atrio-ventricular block has been reported to down-regulate potassium channels, thus reducing the cardiac repolarization reserve. In the series reported by Wysowski et al. [6], inhibitors of the metabolism of cisapride were administered in 37 % of patients whereas significant cardiac disease in one form or another was present in a further 29 % and overdose and electrolyte imbalance accounted for a further 8 %.

Regardless of some *in vitro* data [102], clinical experience shows that co-administration of another QT-prolonging drug to a patient already receiving a QT-prolonging drug or has pre-existing QT prolongation is another important risk factor [7]. A number of non-cardiac diseases are increasingly reported to be associated with pre-existing QT interval prolongation, such as hypoglycaemia [226], cirrhosis [227, 228] and a number of other conditions associated with autonomic failure [229, 230]. It has been suggested that QT-prolonging drugs may have more deleterious effects in those with underlying autonomic dysfunction [231]. Prolonged QTc in cirrhosis returns to normal values in about half of the patients after liver transplantation. A higher prevalence of QTc interval prolongation has also been reported in patients with human immunodeficiency virus (HIV) infection compared to other hospitalized patients (28.6 % vs. 7 %) [232]. It is unfortunately also the case that many drugs used to treat the

above conditions are also QT-prolongers ("double hits"). An association is documented between hypokalaemia and acute psychotic decompensation in a patient with chronic schizophrenia [233]. Some recent clinical studies also indicate that hypokalaemia is a characteristic feature in acute psychotic patients at the time of emergency admission. Since hypokalaemia is one of the major causes of prolonged QT interval and TdP, it was not surprising to find that in 67 drug-free acute psychotic patients, the mean QTc interval was prolonged [234]. This is a matter of concern when using antipsychotic drugs that prolong QT interval. In a study of intravenous haloperidol to control acute psychotic episode, 16 % of the patients had a QTc of more than 500 ms after 8 h [235]. Similarly, recent concerns on QT-liability of some protease inhibitors and high prevalence of QT prolongation in HIV patients must be a matter of concern.

No drug better illustrates this scenario of "multiple hits" than does cisapride. Not only is cisapride a potent QT-prolonger but it was indicated for the relief of symptoms of impaired gastric motility associated with diabetic neuropathy. Diabetic neuropathy is associated with QT interval prolongation [236, 237] as well as with cardiac disease and sudden death. Erythromycin is also frequently used to treat symptoms of gastroparesis but unfortunately, it inhibits the metabolism of cisapride. To further complicate the issue, the approved daily dose of 40–80 mg in the US was significantly higher than the daily dose of 30–40 mg in the UK and in one anaysis, the use of cisapride at daily doses exceeding 40 mg was more frequent in the US than in Europe (28.7 % vs. 14.2 %).

Pharmacogenetic Factors in Drug-Induced QT Interval Prolongation

In about 10–20 % of cases of drug-induced TdP, there is no obviously identifiable risk factor and it seems probable that there is a genetic susceptibility in these patients [205, 206, 238, 239]. Regulatory databases of tachyarrhythmias in association with specific torsadogens include a number of individuals in whom there are no obvious risk factors. These drugs include cisapride [6], terodiline [212] and halofantrine [240].

The dose–response relationship of a drug is determined by its dose-concentration (pharmacokinetic properties) and concentration-response (pharmacodynamic properties) relationships. Concurrently prescribed drugs and mutations of the genes are two important factors that regulate the pharmacokinetics of the drug, typically its elimination, and the responsiveness of its pharmacological targets. Polymorphisms of drug-metabolizing enzymes or pharmacological targets account for much of the observed inter-individual variation in drug response in otherwise healthy individuals. Prolongation of QT interval and TdP are no exception.

Pharmacokinetic Genetic Susceptibility

Although a whole range of drug metabolizing enzymes such as N-acetyltransferase (NAT2), CYP2B6, CYP2C9, CYP2C19 and CYP2D6, display genetic polymorphisms [241], CYP2D6 is by far the most important since it metabolizes a substantial number of QT-prolonging drugs that are administered long-term (e.g. cardiovascular and psychoactive drugs). Therefore, genetic pharmacokinetic susceptibility to the QT-prolonging effect of drugs can best be illustrated by CYP2D6 polymorphism. Depending on the genetically determined metabolic activity of CYP2D6, often expressed in terms of the individuals' metabolic ratios, individuals in a population can be categorized into ultra-rapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM) phenotypes [241]. At a given dose of a CYP2D6 substrate drug, PMs achieve much higher, and UMs much lower, concentrations of the parent drug; the reverse being the case for CYP2D6-generated metabolites.

A number of QT prolonging drugs, especially the neuroleptics, antidepressants and cardiovascular agents, are predominantly metabolized by CYP2D6. These include terikalant, thioridazine, sertindole, risperidone, indoramin and nortriptyline. It would be intuitive to suggest that the risk of TdP following the use of these drugs may therefore be genetically determined in some patients. However, the available evidence suggests that the role of pharmacokinetic genetic

factors in drug-induced toxicity (including effects on cardiac repolarization) may have been overestimated.

QT interval prolongation produced by terikalant, a class III antiarrhythmic drug, has been shown to correlate well with CYP2D6 metabolic ratio [242]. This genetically determined risk resulted in termination of further development of this compound. There is no information on how many other compounds may have been dropped from further development due to their CYP2D6-mediated metabolism. This is a real safety issue that is difficult to manage when a serious toxic effect is concentration related and concentrations cannot be predicted due to genetically determined variability in pharmacokinetics of the drug.

The proarrhythmic effects of prenylamine and terodiline in man are mediated by their (+)-(S)-enantiomer and (+)-(R)-enantiomers respectively and there are stands of tantalizing evidence which suggests that the PM phenotype is associated clinically with impaired metabolism of (+)-(S)-prenylamine or (+)-(R)-terodiline with resultant prolongation of the QT interval and/or induction of proarrhythmias [212]. A number of patients with terodiline-induced proarrhythmias had no identifiable risk factors and their plasma terodiline levels were markedly elevated [243, 244]. Information on the CYP2D6 genotypes of these patients would have been helpful in elucidating the role of genetic susceptibility to terodiline-induced proarrhythmias. Interestingly, CYP2D6 has been shown to metabolize R-enantiomer of tolterodine, a structural analogue of terodiline, used in the treatment of urinary incontinence [245, 246]. CYP3A4-mediated dealkylation provides the main route of elimination of tolterodine in PMs of CYP2D6 [247]. Concentration–QTc modeling results have reported an exposure-related higher QTc effect in PMs than in EMs and increases in QTc interval in PMs treated with tolterodine 2 mg twice daily were comparable to those observed in EMs receiving tolterodine 4 mg twice daily [248].

Since thioridazine is principally metabolized by CYP2D6 and it produces a dose-related effect on ventricular repolarization [249, 250], CYP2D6 genotype had been suggested to be an important determinant of the risk for thioridazine-induced QTc interval prolongation [251]. However, a later study reported that CYP2D6 genotype does not substantially affect the risk of thioridazine induced QTc interval prolongation [252] since its metabolites also prolong the QT interval. Similarly, although haloperidol is substantially cleared by CYP2D6 and there are significant pharmacokinetic differences between EMs and PMs, QT interval prolongation by haloperidol does not seem to be related to CYP2D6 genotype [253]. Sertindole is also associated clinically with marked prolongation of QTc interval and is metabolized by CYP2D6 [254, 255]. It is another excellent example of how CYP2D6-mediated metabolism may not always be relevant in drug-induced QT interval prolongation when the metabolites are active in this respect. Electrophysiological studies have shown that CYP2D6-generated metabolites of sertindole are capable of blocking hERG potassium current at nanomolar concentrations [256]. Procainamide is metabolized by NAT2 and although procainamide is a class I antiarrhythmic drug, its acetylated metabolite, N-acetylprocainamide, is a powerful class III drug known to induce TdP. The role of acetylator genotype in torsadogenesis following clinical use of procainamide has not been investigated.

In contrast, polymorphism of CYP2B6 provides a more persuasive evidence for the role of pharmacokinetic genetic factors in methadone-induced effects on cardiac repolarization. There is 20- to 250-fold inter-individual variation in CYP2B6 expression within the population. The opioid effect of methadone resides predominantly in its (R)-enantiomer [257] and compared to (S)-methadone, it is approximately 3-fold weaker in its potency to block the hERG channel [258, 259]. Poor metabolizers of CYP2B6 have impaired metabolism of (S)-methadone [260] and QTc interval has been reported to be significantly longer in these individuals compared to their extensive metabolizing counterparts [259]. It has been reported that substitution of (R,S)-methadone by (R)-methadone reduces the QTc interval value [261]. A study investigating methadone-related fatalities and genetic variations reported a significant association between high methadone concentrations and the presence of CYP2B6*6 allele that is responsible for the slow metabolizer phenotype [262].

Thioridazine, sertindole, procainamide and methadone illustrate an important point when applying pharmacogenetics to drug development. Pharmacogenetic influences on drug metabolism, and therefore the response to a drug, need to be considered in the context of the activity of metabolites relative to that of the parent drug as well as the chiral aspects of the drug.

Pharmacodynamic Genetic Susceptibility

Compared to the role of genetic polymorphisms in drug-metabolizing enzymes, the evidence for a genetically-mediated pharmacodynamic susceptibility to drug-induced QT prolongation and cardiac arrhythmias in a substantial number of cases is more compelling:

- In families affected by cLQTS, measurement of the QTc interval may not permit an accurate diagnosis of cLQTS. An error rate of 11 % has been reported even with the use of 440 ms as the upper normal value of QTc interval to diagnose those carrying cLQTS mutations [263]. Based on a study of much larger cohort, Hofman et al. have reported a sensitivity of 72 % and a specificity of 86 % even using QTc duration of ≥430 ms among relatives of LQTS patients [264].
- Because of low penetrance (25 %) of the gene, 33 % of the family members of cLQTS probands (who were considered on clinical grounds to be unaffected) were found to be carriers of mutations. These family members are at risk of developing TdP if exposed to drugs that block potassium channels [265].
- First degree female relatives of patients with cLQTS have been reported to have a higher risk of cardiac events than male first- or second-degree relatives and this is independent of ECG findings [266].
- First-degree relatives of patients with acquired long QT syndrome have greater quinidine-induced prolongation of Tp–Te compared to control relatives (63 ± 17 to 83 ± 18 ms, $p = 0.17$ vs. 66 ± 19 to 71 ± 18 ms, $p = 0.648$). The Tp–Te/QT ratio also increased to a greater value after quinidine in acquired LQTS relatives compared to control relatives (mean 0.195 vs. 0.163, respectively) [267].

Individuals with mutations of potassium channel host channels with impaired conductance and have a low repolarization reserve. Since the mutation is often clinically silent due to incomplete penetration of the gene, these individuals have normal ECG phenotype. Available evidence suggests that the presence of hERG mutations results in dysfunctional channels which are usually just as sensitive to a hERG blocker. Some mutations (e.g. Q9E-MiRP1) can increase the sensitivity of IKr to inhibition by a drug. Thus, individuals hosting these mutations are exquisitely sensitive to drug-induced QT prolongation and even low doses of QT-prolonging drugs may trigger severe changes in cardiac repolarization.

Consistent with this evidence, there are anecdotal published reports of patients hosting silent mutations of ion channels who proceeded to develop TdP and other cardiac events in response to drugs at their normal or lower than normal doses such as terfenadine [268, 269], disopyramide [269], cisapride [270–272], halofantrine [273–275], hydroxyzine [276] and clobutinol [277]. The gene/mutations reported in such patients include *KCNH2* (R328C, P347S, A561P, R696C and R1047L), *KCNQ1* (R555C), *SCN5A* (H558R, S1103Y and L1825P), *KCNE1* (D85N) and *KCNE2* (T8A, Q9E and R77W). Interestingly, some patients with hypokalaemia-induced TdP have also been reported to carry mutations of *KCNH2, KCNE2* or *KCNQ1* gene [33, 269, 278, 279]. The frequencies of these alleles vary widely within a given population, and of any particular allele, between populations of different ethnicity [280, 281]. It is not inconceivable, therefore, that there may arise inter-ethnic differences in drug effects on QT interval.

A number of studies have investigated the ion channel genotypes of patients who had developed TdP. Sesti et al. found that 4 of the 98 patients with drug-induced TdP had missense variants in their *KCNE2* gene that encodes for MiRP1 subunit of IKr channel [238]. In another study of 32 patients with confirmed drug-induced TdP, missense mutations were identified in four patients: D85N in *KCNE1* (two cases), T8A in *KCNE2*, and P347S in *KCNH2* [282]. In a study of 29 patients with complete AV block and a QT interval >600 ms, four mutations on genes encoding potassium channels were found in five

patients [283]. These mutations were not found among patients with AV block and a QT interval <600 ms in duration or in healthy volunteers. Dofetilide illustrates well the complexities of determining genetic susceptibility to drug-induced TdP. Among 7 AF patients with dofetilide-induced TdP, *KCNH2* allele R1047L was present in 2 (29 %) patients compared to 5 (5 %) of the 98 patients who did not develop TdP on dofetilide [284]. In an expanded study that included 27 additional TdP patients from other indications (making a total of 34 patients – 16 from congestive heart failure, 13 from AF, 3 from myocardial infarction and 2 from supraventricular tachycardia programs), R1047L mutation was also more common in patients with TdP compared to those without TdP (7.6 % vs. 2.0 %) [285]. *SCN5A* mutation H558R, typically associated with sick sinus syndrome, also occurred more frequently in patients with TdP (37.5 % vs. 14.4 %). However, *KCNH2* mutation K897T was less common among patients with TdP (15.2 % vs. 26.8 %). This difference was not statistically significant but consistent with other reports that K897T predisposes to AF [286] and that it may have a protective effect against TdP in patients with LQTS [287].

Anantharam A et al. have proposed that mutations associated with acquired arrhythmia can be considered as belonging to one of three categories [288]:

- Indirect mutations are those that impair IKr at baseline but do not affect drug sensitivity (e.g. A116V-MiRP1 with quinidine)
- Direct mutations that do not affect IKr pre-drug (normal baseline QT phenotype) but increase sensitivity to drug blockade (e.g. T8A-MiRP1 and sulfamethoxazole)
- Compound mutations are those that both impair channel function at baseline, and also increase sensitivity to IKr blockade (e.g. Q9E-MiRP1 and clarithromycin)

The frequency with which dysfunctional mutations of ion channel account for the cases of drug-induced TdP would obviously depend on the type and frequency of these mutations in the population at large and the pattern of drug usage in that population. It has been estimated that in Finland, 1 individual out of 250 carries a LQTS founder mutation, leading to a marked QT prolongation [289]. In a Finnish study of 16 cases with documented TdP following antiarrhythmic therapy, pre-treatment prolongation of QTc interval was observed in 56 % of the cases but the remaining 44% had normal QTc interval. Three patients (19 %) carried one of the four mutations common in that population, accounting for the majority of cLQTS in Finland [290]. Although the numbers are small, they illustrate the point being made.

The discovery of a mutant channel in a patient with drug-induced repolarization changes does not imply *a priori* that the channel concerned predisposed the patient to the risk; the channel concerned must be shown to have functional consequences and be drug responsive in heterologous expression systems. In a cohort of 92 patients with acquired LQTS, Yang et al. identified missense mutations in five patients. *KCNH2* and *KCNQ1* mutations (one each) reduced K^+ currents *in vitro* but three *SCN5A* variants did not alter the sodium current, suggesting a predisposing role for the two potassium channel mutations but not the three sodium channel mutations in these patients [205]. In some cases, there are no mutations of hERG channel and the patient concerned is found to harbor a *SCN5A*-encoded trafficking deficient gain-of-function sodium channel. In such cases, the baseline QT interval is necessarily normal and the rescue of the mutant sodium channel by an IKr blocker results in surface expression of a channel that augments late sodium current. Thus, cardiac repolarization may be prolonged by dual mechanisms – augmentation of late sodium current producing a phenocopy of LQT3 and inhibition of hERG channel producing a phenocopy of LTQ2. This seems to be the mechanism in some of the cases [271, 272].

The implication of this genetic susceptibility to drug-induced TdP for clinical practice is that patients who survive drug-induced TdP, and the family members of those who did not, should be treated with QT-prolonging drugs with caution after a careful evaluation of risk/benefit and should be screened for ion channel mutations. This also explains why regulatory authorities contraindicate a QT-prolonging drug in an individual with a family history of LQTS or any of its common presentations.

Inter-ethnic Differences in QT-Susceptibility

The issue of ethnicity of the population studied, and extrapolation of the data from one population to another, has been the subjects of much debate, especially now that drug development is a global process. Regulatory authorities are now scrutinizing more than ever the ethnic composition of the population enrolled in pivotal clinical trials or post-marketing studies [291–294]. ICH E5 guideline on 'Ethnic factors in the acceptability of foreign clinical data' [295] recommends the sponsors and the regional regulatory authority in a new region to assess an application for registration for the ability to extrapolate to the new region those parts of the application based on studies from the trial region. To this end, it is recommended that the submission should include (i) adequate characterization of pharmacokinetics, pharmacodynamics, dose–response, efficacy and safety in the population of the trial region and (ii) characterization of pharmacokinetics, pharmacodynamics and dose–response in the new region. ICH E14 speculates that it is not expected that the results of a TQT study would be affected by ethnic factors but acknowledges that the data were limited when it was adopted [168]. There are now some preliminary data which appear to question this assumption [296]. In the context of drug-induced QT prolongation, the key evidence is summarized below, followed by available clinical findings:

- There are significant inter-ethnic differences in the frequency of variant alleles of genes that encode for drug metabolizing enzymes (e.g. CYP2D6, CYP2C19, CYP2C9), resulting in inter-ethnic differences in metabolism of their substrates [297–301]
- There are marked inter-ethnic differences in the frequency of variant alleles of *KCNH2, KCNE2, KCNQ1, KCNE1* and *SCN5A* genes, with some alleles being population-specific [302–304]. For example, *SCN5A* mutation S1103Y is found in about 5–10 % of black people whereas it is almost absent in Caucasian people [303, 305].
- Data indicate that ethnic differences in the clinical expression of LQTS can be attributed to the differences in frequencies of the specific mutations within the two populations [306]
- Evidence available from clinical studies also suggests inter-ethnic differences in response to QT-prolonging drugs. This evidence is summarized below.

Following a single 400 mg oral dose of quinidine, prolongation of QTc interval from baseline was significantly greater in the healthy white subjects compared to their Nigerian counterparts, although the Nigerians had higher intra-erythrocytic quinidine levels [307]. The significance of this interesting observation is limited by the fact that the subjects were studied in different centers – Nigerians in Lagos and the whites in Liverpool, UK– and therefore, probably not by strictly comparable methods. However, in another better-designed study [308], although there was no statistical difference in the pharmacokinetic profiles of quinidine between the Caucasians and the Koreans, the QTc interval values in Caucasians were higher than those in Koreans at the same quinidine concentrations, especially at higher quinidine concentrations and in female subjects. Wheeler et al. have reported from a randomized double-blind study that the peak QTcF-prolonging effect of a single 400 mg dose of moxifloxacin was 17.4 ms at 3.5 h postdose in Hispanics and 15.2 ms at 3.0 h postdose in non-Hispanics [309]. There is no information provided on plasma concentrations of moxifloxacin. Although these QTcF effects are not significantly different and appear typical for moxifloxacin effect in white Caucasians, the effect reported in Hispanics appears greater than that reported previously in this population [310] and this finding does not exclude differences between other more ethnically diverse populations. Florian et al. have reported on the effect of moxifloxacin on QTcF interval by gender and race [311]. Data from 20 TQT studies submitted to the FDA were available for analysis. All TQT studies were conducted in healthy volunteers aged between 18 and 75 years. Moxifloxacin concentration–QTc analysis was performed using baseline- and placebo-adjusted QTcF, previously denoted as ΔΔQTcF. Estimated slopes of moxifloxacin effect ranged from 1.6 to 4.8 ms/μg/mL, thus emphasizing the wide inter-individual variability is response. Data were available from 788 Caucasians, 105 blacks and 72 Asians. Although the time versus ΔΔQTcF profile did not

reveal any significant inter-ethnic difference, the confidence limits for any comparison were too wide. However, an inspection of the reported profiles in the three populations shows that the QT effect of moxifloxacin is greater in Caucasians than in the other two populations.

Together with the above observations on inter-ethnic differences in prevalence of polymorphisms of drug-metabolizing enzymes and mutations of ion channels, these early observations may have significant impact on regulatory acceptance of TQT conducted in foreign populations [281]. Since the QT-response in a Caucasian population appears to be more intense than in non-Caucasian population, a TQT study if undertaken in a Caucasian population need not be repeated in non-Caucasians. However, a TQT study in a non-Caucasian population may underestimate the intensity of QT effect in Caucasians. Further studies, preferably TQT studies, enrolling Caucasians, Asian and African populations are needed to investigate the pharmacokinetic properties and concentration-QT relationships of a few other drugs before firm conclusions can be drawn.

Both the FDA and its Japanese counterpart, the Pharmaceutical and Medical Devices Agency, have indicated that they would accept a TQT study conducted in a foreign population but there might be a need to bridge the drug exposure between the two populations. Genetic analysis of outliers in clinical trials for mutations of ion channels and drug metabolizing enzymes will also greatly increase our understanding of inter-ethnic differences in QT-liability of a drug. In the immediate future, sponsors should consider investigating concentration-QT relationship in domestic and foreign phase I and/or early phase II studies. Comparison of the two relationships should provide a better understanding of the extent to which data can be extrapolated from one ethnic population to another.

Prolonged QT Interval in Risk/Benefit Assessment and Labeling of Drugs

Regulatory authorities now almost routinely include QT-related information in the labeling of drugs and this information is either "descriptive" when there is no likelihood of risk or "restrictive" when there is a perceived risk which can be mitigated by prescribing behavior.

With respect to the risk of drug-induced TdP, there is also an all important issue of the definition of 'clinical risk' and the level of risk that is unacceptable or tolerable. It seems inappropriate to categorize a drug with an incidence of TdP of 1 in 500,000 patients together with another that has an incidence of 1 in 3,000. As with other potentially fatal adverse drug reactions such as myelotoxicity, gastrointestinal hemorrhage, hepatotoxicity or rhabdomyolysis, a level of risk may have to be tolerated. Reporting rates for TdP (to national pharmacovigilance centers) vary widely but the incidence of diagnosed nonfatal TdP in one region of France is estimated at around 10.9 per million per year (95 % confidence interval: 7.8, 14.8) [312]. While an incidence of a potentially fatal event at the rate of 1 in 3,000 is unacceptable for a given modest benefit, an incidence of 1 in 500,000 may be considered acceptable with a whole range of risk/benefits in between. Thus, the perceived risk has to be seen in the context of benefit and available alternatives. The risk of not treating a disease is also an important component in risk assessment. Arsenic trioxide provides a perfect example of how the risk and the benefit need to be clearly juxta-positioned before a drug is deemed unsafe. It is highly effective in patients with relapsed or refractory acute promyelocytic leukemia [313, 314] and it is a mainstay for this indication, despite the fact that it can prolong QT interval markedly in about 40 % and TdP in as many as 25 % of patients [69, 315]. A number of tyrosine kinase inhibitors with QT-liability have also been approved recently for use in oncology on the basis of favourable risk/benefit evaluation. On the other hand, intravenous infusion of AZD1305, a combined ion channel blocker, was dose-dependently effective in converting AF into sinus rhythm (in 38 % at 130 mg/h and 50 % at 180 mg/h) but one patient in each dose group (2.2 and 8.3 %) developed TdP. Consequently, the development of this compound was discontinued because the risk/benefit profile was judged as unfavorable [95].

Provided efficacy is not compromised, it is often possible to mitigate the risk of drug-induced QT interval prolongation by careful evaluation of other factors during drug development and its clinical use [15]. Dose is obviously one important factor as illustrated by pimozide and cisapride. Depending on its pharmacological profile, it may be prudent to develop the metabolite of the culprit drug e.g. fexofenadine as opposed to terfenadine. Astemizole is particularly interesting in this regard. Both astemizole (half-life 20–60 h) and its main metabolite, desmethylastemizole (half-life 18–20 days) are equipotent at hERG channel. Torsadogenesis due to astemizole appears predominantly related to accumulation of its main metabolite, desmethylastemizole [316]. Norastemizole is much safer with a hERG IC_{50} which is approximately 30-fold higher than IC_{50} values of astemizole or desmethylastemizole. Stereoselectivity in activity at potassium channels has also been described for the enantiomers of some drugs. Examples include (+)-(R)-bupivacaine, (+)-(R)-halofantrine, (+)-(R)-terodiline, (+)-(S)-prenylamine and (R)-fluoxetine. As discussed above, the risk/benefit is superior for (R)-methadone compared to (S)-methadone. Substitution of (R,S)-methadone by (R)-methadone reduces the QTc interval duration [261]. Sotazide highlights the risks associated with specific formulations.

Drug-Induced QT Interval Shortening

Compared to its prolongation, our understanding of shortening of QT interval and an appreciation of its significance is relatively recent and also limited. Sponsors have been routinely investigating new drugs for their potential to prolong cardiac repolarization. During the course of these investigations, a number of drugs have been found to actually shorten APD and/or QT interval. Although initially these findings did not attract serious attention, the description of various forms of congenital short QT interval syndromes (SQTS1-SQTS6) has led to a significant reappraisal of this effect. The potentially fatal arrhythmias associated with all these syndromes [317–322] are beginning to re-shape our perspectives on the potential significance of drug-induced shortening of QT interval. To a large measure, this is due to an uncanny parallel that is unraveling between the description of LQTS and the SQTS in terms of associated arrhythmias and how drugs now account for the majority of cases of QT interval prolongation [323].

For the purpose of this chapter, four points merit an emphasis:

- Congenital SQTS is associated with high incidence of syncope, sudden death (possibly due to malignant ventricular tachyarrhythmias), AF or VF and these events can occur at any age including in infants and the young adolescents [324–327].
- If a mutation can result in altered function of the ion channel, it should come as no surprise to find that one mutation may result in loss of function whereas another at the same locus may well result in gain of function. For example, in *KCNH2* gene that encodes for the hERG channel, substitution of asparagine by aspartic acid in position 588 (N588D) leads to loss of function whereas substitution of asparagine by lysine in the same position (N588K) leads to gain of function of this channel [328].
- If drugs can prolong QT interval and mimic congenital LQTS with all the associated consequences, it should come as no surprise if they also shortens this interval, leading potentially to the consequences associated with congenital SQTS.
- Congenital and drug-induced LQTS were thought of as being rare in early 1960s and yet by late 1990s, drug-induced QT prolongation had come to be seen as an epidemic such that every new drug is now required to be characterized for its QT-prolonging property.

Therefore, the possibility that drugs can shorten QT interval and induce proarrhythmias is a real one and deserves careful attention if there are serious concerns on the broader cardiac safety of drugs [329].

Diagnosing Short QT Interval

A large number of studies have sought to define the normal range of QTc interval, including

variability due to gender, race and age. Since the interval can be influenced by many factors, not least the technique of and equipment for recording the ECG, the ECG leads used for measuring the interval and the formula used for correcting the measured QT interval for heart rate, it is not surprising that there is no universally accepted reference range for QTc interval. Furthermore, given the concerns on the risks associated with QT interval prolongation, almost all the studies have focused on defining the upper limit of normal QTc interval and until recently, there had been hardly any discussion concerning its normal lower limit.

The upper limits of normal QTc interval, corrected for heart rate by Bazett's formula (QTcB), recommended in the first regulatory guidance were 450 ms for adult men and 470 ms for adult women [330, 331]. According to Drew et al. a normal QTc interval is <450 ms in men and <460 ms in women [332]. An expert writing group has recently recommended that a QTc interval over the 99th percentile should be considered abnormally prolonged and stated that approximate 99th percentile QTc values for otherwise healthy post-pubertal individuals are 470 ms for males and 480 ms for females [333]. A report from learned cardiac societies on "Key Data Elements and Definitions for Electrophysiological Studies and Procedures" defines the upper limit of QTc interval at 440 ms for adult males and 460 ms for adult females [334]. From a large dataset of ECGs of 46,129 individuals with a very low probability of cardiovascular disease and using the 2nd and 98th percentiles, Mason et al. have determined normal reference range to be 361–457 ms for QTcB interval and 359–445 ms for Fridericia-corrected QTc (QTcF) interval [335]. The debate on what constitutes a QTc interval which is too long, too short or just right is likely to continue, given that in practice there is considerable overlap of QTc intervals between truly healthy individuals and patients affected by SQTS or LQTS [336]. On the basis of available data, the present authors conclude that 360 ms is probably a reasonable value for the lower limit of normal Fridericia-corrected or Bazett-corrected QTc interval. Individuals with QTcF or QTcB intervals of 360 ms or slightly lower are clearly not at risk of proarrhythmias and the issue that comes to the fore is defining the proarrhythmic threshold for QT shortening.

Based on a comprehensive review of 61 reported cases of the SQTS, Gollob et al. have proposed formal diagnostic criteria to facilitate evaluation of cases suspected as SQTS [337]. This cohort had a mean QTc (Bazett correction) value of 306.7 ms with values ranging from 248 to 381 ms in symptomatic cases. Although there was male predominance (75.4 %), there was no discernible gender difference. The mean QTc duration was shorter in symptomatic individuals as compared to their asymptomatic counterparts (296.9 ± 22.1 ms vs. 319.8 ± 26.7 ms, respectively). The criteria proposed rely heavily on family history, past events and genotype and are therefore, unlikely to be suitable for diagnosing drug-induced QT shortening.

With regard to congenital SQTS, the QTc interval in most affected subjects is reportedly <300–310 ms without significant dynamic changes during heart rate variation [324]. A short QT interval is easier to recognize at low heart rates, although with increasing heart rates it tends to be closer to the normal values. Extramiana et al. reported a lower QT rate-dependence in patients with SQTS (exponent of 0.146 ± 0.070) when compared with control subjects (exponent of 0.203 ± 0.039, $p < 0.05$) [338]. Patients with idiopathic VF have lower slopes of QT-RR regression lines and impaired prolongation of QT interval. In four patients, oral administration of disopyramide (300 mg/day) was effective in suppressing VF episodes and increasing the slopes of QT-RR relationships [339].

No doubt, the debate on the proarrhythmic threshold for drug-induced shortening of QT interval will continue in the immediate future [323]. It is our view that a Fridericia-corrected value of <320 ms is probably a reasonable one since it seems to correlate better with other electrophysiologic substrates of proarrhythmia [340]. As with QT prolongation, proarrhythmic shortening of QT interval is also associated with an increase in TDR, a parameter believed to be a better marker of proarrhythmic risk [340, 341]. Since there are other factors that modulate the risk of proarrhythmia, it seems that the expectation of a sharp

cut-off value for proarrhythmic shortening of QT interval may be unrealistic if the data on LQTS are anything to go by.

Epidemiological Evidence Linking Ventricular Fibrillation with Short QT Interval

Drug-induced TdP resulting from QT interval prolongation is often transient and even if sustained, not uniformly fatal. This effect is therefore often observed in an emergency room setting. In contrast, VF is uniformly fatal in most cases, and only rarely are such patients resuscitated successfully to link this malignant arrhythmia with short QT interval [342, 343]. Consequently, although a short QT interval may be an important cause of VF, evidence linking VF with drug-induced shortening of QT interval may be less easy, if at all possible, to gather than has been the case linking TdP with drug-induced lengthening of QT interval.

Approximately half of the deaths in patients with heart failure are sudden deaths most probably due to lethal ventricular tachyarrhythmias such as ventricular tachycardia or VF. In the context of short QT interval, it is interesting that Sugiyama et al. have recently reported the presence of a circulating *KCNH2* channel activator in patients with heart failure and ventricular tachyarrhythmias. This activator was not present in the serum from normal controls and heart failure patients without ventricular arrhythmia [344].

It is not intended to review here in any detail the epidemiological evidence linking malignant ventricular tachyarrhythmias with short QT interval. A number of studies have examined the association between QTc interval and sudden death or "idiopathic" VF. Some of these have reported a probable association [345–347]. In contrast, others have failed to confirm this association, although the conclusions from these studies are limited by either the lack of complete follow up [348] or inadequate study power [349]. The link between SQTS and VF has also been rendered difficult to interpret because of differences in definition of what constitutes a "short QT interval". All the above studies have emphasized that none of the patients had QT interval values as short as those described in the SQTS. In two long-term follow-up studies of patients with SQTS, the QTc interval values were 314 ms (mean value in 53 patients) and 312 ms (median value in 25 patients) [350, 351]. The evidence from these two studies clearly show that although the prevalence of SQTS in population at large may be very low, the risk of VF, cardiac arrest or sudden death in those who have a short QTc interval is much higher than normal.

Drugs as a Cause of QT Interval Shortening

Drawing a parallel from experiences with LQTS, inevitably a question emerges whether drugs are capable of proarrhythmic shortening of QT interval. In this context, it has often been argued that because the prevalence of SQTS in the population at large is very low, drug-induced shortening of QT interval need not be such a concern in the development or during clinical use of drugs. This reasoning defies any logic since drug-induced changes in QT interval are not conditional upon the presence of, or the interaction of the drug with, a genetic substrate. There is no a priori reason, as with LQTS, why there should be any correlation between the prevalence of congenital and drug-induced changes in QT interval. As stated earlier, only 10–20 % of patients with drug- induced LQTS carry a pathogenic mutation.

Nonclinical Evidence Supporting Drugs as a Cause of QT Interval Shortening

Drugs activating ATP-dependent potassium channel have been known for a long time [352]. Among the better known are pinacidil, levcromakalim and nicorandil. There is sufficient evidence that pinacidil and levcromakalim induce shortening of APD and have profibrillatory effects in nonclinical studies [353–357]. Both levcromakalim and nicorandil are known not to have any effect on hERG current.

R-L3, a benzodiazepine, was one of the earliest activators of voltage-gated potassium channel. Its IKs-activating property made it a potential candidate for providing gene-specific therapy for LQT1. Most *KCNQ1* mutant channels, except G306R, responded to R-L3 similarly to wild-type channels [358]. Mallotoxin and NS1643, both of

which are known to be hERG current stimulators, have also been reported to significantly shorten APD and QT interval and elicit VF in isolated hearts [359]. A number of investigational or approved drugs have been reported to accelerate IKr current through an effect on hERG channels [360–364].

In a very extensive program of investigation of 576 compounds, Lu et al. measured hERG current in HEK-293 cells, APD and arrhythmogenic effects in isolated Purkinje fibers and perfused hearts from rabbits [359]. Of these compounds that were screened in the hERG test, 58 % were identified as hERG inhibitors, 39 % had no effect and 3 % were classified as stimulators. Of the hERG inhibitors, 92 were tested in the APD assay and of these, 28.3 % had no effect and 16.3 % shortened APD. Of the 70 compounds without effect on hERG channels, 25.7 % prolonged, while 20 % significantly shortened APD.

A recent industry-wide survey (53 total responses representing 45 different companies) indicated that the number of compounds that induce QT/QTc shortening has increased over the past 5 years with 51 % of responses reporting QT/QTc shortening in nonclinical studies and 22 % reporting a corresponding clinical experience. The reason for the increase is not clear but there was a clear business impact with 13 % (7/56) of these compounds being discontinued in the nonclinical phase due to QT/QTc shortening [365].

Drugs most likely shorten QT interval by impairing inactivation of the hERG channel and, thereby, increasing the current mediated by IKr channel, thus mimicking the effect of certain hERG mutations (e.g. the N588K mutation). Kang et al. have reported that their hERG channel activator (RPR260243) enhanced the delayed rectifier current in guinea pig myocytes but, when administered alone, had little effect on action potential parameters in these cells but it completely reversed the action potential-prolonging effects of dofetilide in this preparation [360]. In contrast, however, Zhou et al. reported that their hERG channel activator (PD-118057) was more potent and shortened APD and QT interval in arterially perfused rabbit ventricular wedge preparation in a concentration-dependent manner [361].

Clinical Evidence of Drugs as a Cause of QT Interval Shortening

Among the drugs already on the market, phenytoin and digoxin are believed to shorten QT interval and both are known to be proarrhythmic. However, the evidence linking either of these drugs to a QT-shortening effect is either absent or only very tentative [366–369]. Interestingly, both phenytoin and digoxin have been shown to inhibit hERG channel current [57, 370] and therefore, it would be helpful to study these two drugs in the setting of a TQT study.

It should be emphasized at the outset that to-date, there is no well-documented example of a clinically marketed drug that shortens QT interval to the extent of being proarrhythmic. Much of the current clinical evidence on QT shortening effect of drugs in man is derived from the setting of pre-existing prolongation of QTc interval. Whether or not, following a normal QT interval at baseline, a proarrhythmic shortening of the QT interval can be induced clinically by drugs acting at IKr or other ion channels remains to be seen.

DeSilvey and Moss [371] were the first to raise and exploit the possibility that clinically used drugs could shorten QT when they reported shortening of QT interval following treatment with primidone in three patients with congenital LQTS. Teh et al. have reported that the mean QTc interval among epilepsy patients was significantly shorter than the QTc interval in the control group [372]. Thirty five epilepsy patients (50 %) and 17 matched controls (24.3 %) had a mean QTc shorter than 400 ms. Patients with cryptogenic epilepsy had a mean QTc interval of 392 ± 29 ms, which was significantly shorter than patients with symptomatic epilepsy (QTc = 410 ± 27 ms).

In the broader context, patients with refractory epilepsy face an elevated risk of sudden death, with rates as high as 1 % per year [373]. This phenomenon, known as sudden unexpected death in epilepsy (SUDEP), is believed to be a seizure-related occurrence, but the exact underlying mechanisms are uncertain. Patients with LQTS are frequently diagnosed and treated as suffering from epilepsy [374]. Similarly, the possibility that some patients with SQTS experiencing

convulsions as a result of a tachyarrhythmia may also be inappropriately diagnosed and treated as having epilepsy should not be dismissed. Based on one well documented case, Aurlien et al. reported four consecutive cases of SUDEP in non-hospitalized patients that were all being treated with lamotrigine monotherapy [375]. All were females with idiopathic epilepsy. In a later study involving DNA analysis in one of these patients, these investigators reported a missense mutation (R523C) in *SCN5A* [376]. This mutation was not identified in 315 unrelated Norwegian subjects referred for genetic testing with respect to LQTS. Unfortunately, the functional properties of this mutant channel were not characterized in any expression systems. Since this 25-years old patient was treated with lamotrigine, they suggested that this drug may have played a part in inducing a terminal cardiac arrhythmia. The mechanism of SUDEP needs to be established or at least, a proarrhythmic cause needs to be excluded but it is interesting that an ICH E14-compliant TQT study has already reported that lamotrigine induced a small reduction in QTcF interval (maximum mean difference from placebo −7.48 ms, 90 % confidence interval: −10.49, −4.46) [377]. Rufinamide is a new anticonvulsant that has also been found in formal cardiac ECG studies to shorten QT interval (see below).

Any contribution from a shortened QT interval to SUDEP is seriously questioned by a recent study which reported on analysis of DNA from post-mortem blood of 68 cases of SUDEP for the three most common LQTS genes (*KCNQ1, KCNH2* and *SCN5A*). This study revealed *KCNH2* variants in 2 cases and *SCN5A* variants in 4 cases, all of which were previously reported in patients with LQTS [378].

Regulatory Perspectives on Drug-Induced QT Shortening

While controlled prolongation of QT interval by a drug may have the merit of being antiarrhythmic (e.g. amiodarone), the merit of a short QT interval is not immediately evident. Together with proarrhythmia associated with congenital SQTS, the apparent lack of benefit from a short QT interval has prompted regulatory authorities to question whether therapeutic drugs that shorten QT interval could prove to be significantly proarrhythmic with otherwise no obvious benefit.

Rufinamide, a triazole-derived anticonvulsant and designated as an orphan drug, illustrates the current pragmatic but cautious regulatory approach to evaluation of drugs that shorten QT interval. Rufinamide is probably the first QT-shortening drug to be approved in the post-ICH E14 period. It is structurally unrelated to currently marketed antiepileptic drugs. It was approved in the European Union in January 2007 and in the USA in November 2008.

Although rufinamide is inactive on the hERG channel, it demonstrated significant, concentration-dependent shortening of QT interval in formal cardiac ECG studies. In a placebo-controlled study, a higher percentage of rufinamide-treated subjects (46 % at 2,400 mg, 46 % at 3,200 mg, and 65 % at 4,800 mg), compared to placebo (5–10 %), had a QT shortening of greater than 20 ms at peak concentrations. Even with doses up to 7,200 mg/day, however, QT interval values below 300 ms were not observed. Moreover, there appeared to be no signal of any drug-induced sudden death or ventricular arrhythmias. Although the review of safety data from clinical trials revealed no deaths with a strong potential link to a shortened QT interval and arrhythmias in patients receiving rufinamide, this possibility could not be excluded with confidence in about five cases whose deaths were thought to be related to seizures. Twenty-three patients on rufinamide and 5 patients on placebo died during the drug development programme but the death rates per 100 patient-years were 0.69 for rufinamide and 2.67 for placebo groups [379].

The FDA-approved label [380] of rufinamide states, "*The degree of QT shortening induced (by rufinamide) is without any known clinical risk*" but goes on warn, "*familial short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in this syndrome are believed to occur primarily when the corrected QT interval falls below 300 ms. Nonclinical data also indicate that QT shortening is associated with ventricular fibrillation*".

The labeling of rufinamide already signals regulatory unease on the significance of drug-induced QT shortening. The FDA label contraindicates rufinamide in patients with familial short QT syndrome and recommends caution when administering rufinamide with other drugs that shorten QT interval. The European labeling [381] advises use of judgment when prescribing rufinamide to patients at risk from further shortening their QTc duration (e.g. congenital short QT syndrome or patients with a family history of such a syndrome). These contraindications and cautions are probably the key to appreciating the emerging regulatory concern regarding the significance of QT shortening. Rufinamide is an orphan drug indicated for Lennox-Gastaut syndrome (with a prevalence of 1 per 10,000 of the population) and the prevalence of familial short QT syndrome is also low (apparently <1 per 100,000 of the population) – the probability of the two conditions co-existing independently in any one patient must be negligible. It will be interesting to closely monitor the post-marketing performance of rufinamide but it is questionable if any useful information will emerge given the rarity of its indication (Lennox-Gastaut syndrome).

ICH E14 Guidance and Drug-Induced QT Interval Shortening

With regard to investigating a drug for its QT-prolonging potential, the TQT study focuses on the point estimate of the drug effect on QTc interval [168]. Analysis of outliers with categorical responses is recommended but is considered to be less sensitive since such studies are not adequatelypoweredforthisanalysis.Pharmacogenetic evaluation, particularly of subjects with categorical responses, is also encouraged.

With regard to investigating a drug for its QT-shortening potential, this is a relatively new and poorly understood potential safety issue and there is hardly any information on the number of drugs that may have this effect, the magnitude of their effects and the clinical significance of the observed effects. In contrast to the known QT-prolonging torsadogenic drugs, there is at present no precedent of a profibrillatory drug with substantial QT shortening effect to provide answers to these important questions. Lack of information is further complicated by an understandable reluctance on part of some sponsors to progress these drugs further into clinical development [365], arising from uncertainties regarding how regulatory authorities might approach such drugs. For example, extensive nonclinical cardiovascular safety pharmacology studies on BAY-79, a highly selective tyrosine kinases inhibitor, revealed inhibition of hERG as well as sodium channels and reverse use-dependent APD shortening. Assessment of the proarrhythmic potential in the TRiAD studies showed effects (APD shortening, triangulation, instability) highly indicative of proarrhythmic potential. QTc shortening associated proarrhythmic potential of BAY-79, together with other considerations, finally resulted in an unfavorable risk–benefit assessment and the development of the drug was discontinued [382].

If cardiac safety of drugs in its broader context is a matter of concern, then the nonclinical observations on the profibrillatory effects of drugs discussed earlier should be a matter of concern which requires further exploration. Raschi et al. were recently able to identify 42 spontaneous reports alleging drug-induced QT shortening in the FDA database [383]. However, the quality of these reports is not adequate enough to establish causality or draw any reasonable conclusions. For rufinamide, one of the total 78 adverse reaction reports associated with its use concerned QT shortening. Therefore, in the immediate short-term future, the paradigm for assessing the regulatory and clinical significance of drug-induced shortening of QT interval may have to rely increasingly on nonclinical evidence. Such drugs should be investigated for their effects on TDR, triangulation of action potential and beat-to-beat variability in repolarization. As for the clinical evidence, the paradigm may have to shift from evaluating the effect of a new drug on central tendency of QT interval to evaluating categorical responses, supplemented by pharmacogenetic testing. This is not to suggest that analysis of central tendency in a TQT study will not uncover significant shortening of QT interval when the effect is sufficiently substantial. Therefore, if the nonclinical data so

Table 6–5. Clinically relevant effect sizes for changes in QTc interval

Parameter	Regulatory thresholds for concern in drug-induced QT interval prolongation (specified in ICH E14)	Potential thresholds for concern in drug-induced QT interval shortening[a]
Change in central tendency	Mean +5 ms	Mean −15 ms
	95 % upper bound:	95 % lower bound:
	+10 ms	−30 ms
	Categorical responses indicative of a clinically significant drug effect	
Absolute QTc interval	≥500 ms	≤320 ms
Change from baseline in an individual	+60 ms	−80 ms

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Values stated are QTc interval values corrected for heart rate by subject-specific correction formula
[a]This is the current view of the author (RS) and the values proposed are estimates only

warrant, a TQT study should be powered and designed to explore this effect as well.

At present, three important issues discussed below warrant addressing when considering whether a drug actually shortens the QTc interval and whether this effect may be a potential harbinger of proarrhythmia. These are (a) the relationship of the effect to baseline QTc interval (b) heart-rate correction formula used to compute QTc interval and (c) the magnitude of a decrease in QTc interval that may be proarrhythmic.

As with diagnosing its congenital counterpart, Bazett formula seems inappropriate for making a diagnosis of acquired form of drug-induced QT interval shortening. In the study by Malik referred to earlier [103], β-blocking drugs typically lengthened QTc interval when corrected by 28 of the 31 formulae and shortened this interval when corrected by the remaining three. However, either effect disappeared when the more rigorous correction formula that provided QTc intervals almost independent of the RR intervals were applied. In patients with liver cirrhosis, nadolol shortened QT interval only with the Bazett formula, remaining unchanged with the other formulas [384]. Importantly, QTc changes were directly related to the baseline value ($p < 0.001$). QTc interval shortened only if prolonged at baseline (from 473.3 ± 5.5 to 458.4 ± 6.5 ms; $p = 0.007$), while it lengthened when normal (from 429.8 ± 3.1 to 439.3 ± 2.9 ms; $p = 0.01$).

Given that the excursion (extent of change from normal point estimate of 430 ms for a normal QTc interval) required for inducing a clinically significant QT shortening (to <320 ms) is larger than that required for QT prolongation (to >500 ms), Table 6.5 provides the author's (RS) estimation of the QT-shortening effect size that may be of clinical relevance [323]. The values pertaining to drug-induced QT shortening in this table are only preliminary estimates to begin the discussion on this important drug-induced effect. These values have been estimated on the assumption that the mean population-based point estimate for a normal QTc interval is 430 ms and the changes now widely acknowledged as reflecting a significant QTc-prolonging effect. For QT interval shortening, the interval has to decrease by a much greater extent to reach a proarrhythmic threshold of 320 ms. Allowing for spontaneous variability, a conservative value of 80 ms decrease from baseline in QTc interval is considered by this author as constituting another appropriate and significant categorical response in an individual. For an evidence of safety robust enough to convince the regulatory authorities and bearing in mind the greater excursion required, a mean decrease in central tendency of 15 with a 95 % lower limit of 30 ms is considered by this author to be approximately equivalent to the corresponding threshold of regulatory concern for QT interval prolongation as identified in ICH E14 guideline.

Shortened QT Interval in Risk/Benefit Assessment of Drugs

There is sufficient nonclinical and clinical epidemiological evidence to suggest that shortening of QT interval may be a potential harbinger of proarrhythmia and therefore, a

drug effect of safety concern. An unexpected by-product of compliance with ICH guidelines on drug-induced QT interval prolongation is identification of an ever-increasing number of drugs that shorten APD in repolarization assays and shorten QT interval.

Given the current uncertainty surrounding the clinical significance of a QT-shortening effect and a clinically relevant effect size, it may well be that drugs that shorten APD may be approvable subject to a niche indication together with a commitment for heightened a post-marketing surveillance and a safety study to exclude a clinical risk. For example, rufinamide is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults with, in the USA, a requirement for further analyses aimed at investigating its potential to interact with other QT-shortening drugs. More importantly however, as with QT interval prolongation, there is a need for development of better nonclinical models and a clinical database on which to base informed decisions on the safety and risk/benefit of drugs that shorten APD or QT interval.

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7
Acquired Form of Brugada Syndrome

Wataru Shimizu

Abstract

Brugada syndrome is characterized by Type 1 (coved type) ST-segment elevation in the right precordial leads (V1–V3) and an episode of ventricular fibrillation (VF) in the absence of structural heart disease. Seven genotypes have been identified responsible for Brugada syndrome in approximately one-thirds of Brugada patients, and decreases in inward sodium or calcium current (fast sodium current [I_{Na}], L-type calcium current [$I_{Ca\text{-}L}$]) or increase in a transient outward potassium current (I_{to}) are considered to produce Brugada phenotype in the seven genotypes. On the other hand, experimental studies have suggested that an intrinsically prominent I_{to}-mediated action potential (AP) notch and a subsequent loss of AP dome in the epicardium, but not in the endocardium of the right ventricular outflow tract, give rise to a transmural voltage gradient, resulting in ST-segment elevation and phase 2 reentry-induced VF. Therefore, any drugs and interventions that increase outward currents (e.g. I_{to}, adenosine tri-phosphate sensitive potassium current [$I_{K\text{-}ATP}$], slow and fast activating components of IK [I_{ks}, I_{Kr}]) or decrease inward currents (e.g. fast I_{Na}, $I_{Ca\text{-}L}$) at the end of phase 1 of the AP can accentuate or unmask ST-segment elevation, similar to that found in Brugada syndrome, thus producing acquired forms of the Brugada syndrome. In this chapter, such drugs and conditions, which provoke transient Brugada phenotype, developing acquired forms of the Brugada syndrome, will be discussed.

Keywords

Brugada syndrome • ST segment • Ventricular fibrillation • Heterogeneity • Epicardium • Drugs • Ischemia

W. Shimizu, MD, PhD
Division of Arrhythmia and Electrophysiology,
Department of Cardiovascular Medicine,
National Cerebral and Cardiovascular Center,
5-7-1 Fujishiro-dai, Suita,
Osaka 565-8565, Japan

Division of Cardiology,
Department of Internal Medicine,
Nippon Medical School,
1-1-5 Sendagi Bunkyo-ku,
Tokyo 113-8603, Japan
e-mail: wshimizu@hsp.ncvc.go.jp, wshimizu@nms.ac.ip

Brugada Syndrome

Brugada and Brugada reported in 1992 eight patients with a history of aborted sudden cardiac death due to ventricular fibrillation (VF) and a characteristic electrocardiographic pattern, consisting of right bundle branch block (RBBB) and ST-segment elevation in the right precordial electrocardiogram (ECG) (V1–V3) as a distinct clinical entity [1–8]. The presence of RBBB was thereafter revealed to

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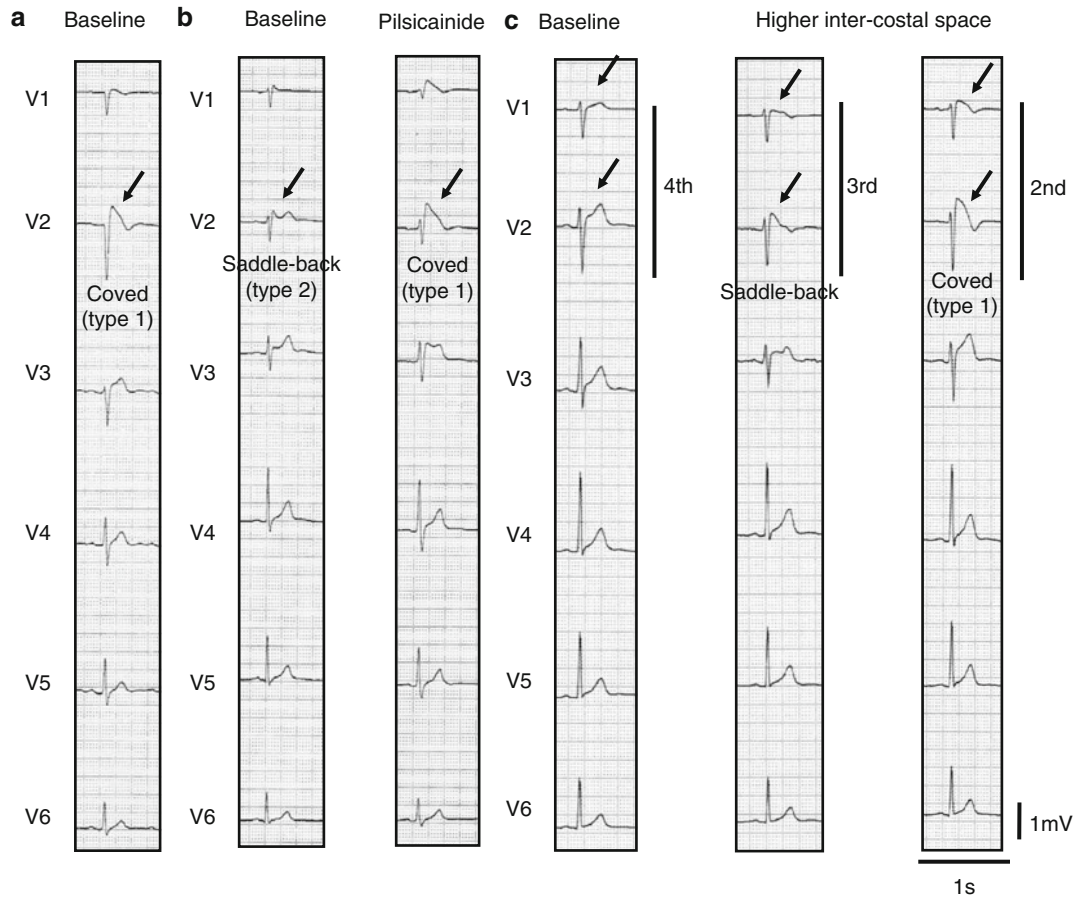

Figure 7–1. Type 1 coved ST-segment elevation spontaneously or unmasked by pilsicainide or higher inter-costal space recordings of V1 and V2 leads. (**a**) Spontaneously Type 1 coved ST-segment elevation (*arrow*). (**b**) Although Type 2 saddle-back ST-segment elevation was seen in V2 lead under baseline condition, pilsicainide, a class IC drug, unmasked Type 1 coved ST-segment elevation in V2 lead (*arrows*). (**c**) Although no ST-segment elevation was observed at standard (fourth inter-costal space) V1 and V2 leads under baseline condition (*arrows*), a Type 1 coved ST-segment elevation was recorded at higher (second inter-costal space) V1 and V2 leads (*arrows*)

be not necessary for the diagnosis of Brugada syndrome, although mild to moderate widening of the QRS duration is often observed [5]. Two specific types of ST-segment elevation, coved and saddleback, are observed in this syndrome. The ST-segment elevation is often accentuated and the coved type ST-segment elevation is more frequently recognized just before and after episodes of VF [9, 10]. The Brugada Consensus Report in 2002 suggested three patterns of ST-segment elevation in the right precordial ECG [5]. Type 1 is characterized by a coved type ST-segment elevation displaying J wave amplitude or ST-segment elevation of ≥0.2 mV followed by a negative T wave (Fig. 7.1a). Type 2 has a saddleback configuration, which has a high take-off ST-segment elevation (≥0.2 mV) followed by a gradually descending ST-segment elevation (remaining ≥0.1 mV above the baseline) and a positive or biphasic T wave (Fig. 7.1b). Type 3 has an ST-segment elevation of < 0.1 mV of saddleback, coved type, or both. The second Consensus Report published in 2005, however, emphasized that Type 1 coved ST-segment elevation is required to diagnose Brugada syndrome [7], because the Type 1 ECG is reported to relate to a higher incidence of VF and sudden cardiac death [6]. Type 2 and Type 3 ST-segment elevation are not diagnostic for

the Brugada syndrome. The recordings of V1 and V2 leads at higher (3rd and 2nd) intercostal spaces increase the sensitivity and the specificity of the ECG diagnosis for detecting the Brugada phenotype (Fig. 7.1c) [7, 11], and their diagnostic and prognostic values have been reported [12].

Molecular Aspects

Molecular Genetic studies so far identified seven genotypes responsible for Brugada syndrome. In 1998, Chen and co-workers identified the first mutation linked to Brugada syndrome in *SCN5A*, the gene encoding the α subunit of the sodium channel (BrS 1) [13]. A mutation in a conserved amino acid of the glycerol-3-phosphate dehydrogenase 1-like (*GPD1-L*) gene was then identified in a large Brugada family (BrS 2) [14]. Thereafter, mutations in *CACNA1C* or *CACNB2*, the gene encoding the α1 or β2b subunit of the L-type calcium channel were identified in patients with Brugada syndrome associated with short QT syndrome (BrS 3, 4) [15]. As a BrS5, a nonsense mutation in *SCN1B*, which encodes the function-modifying sodium channel β1 subunit, was identified in a family with Brugada syndrome associated with cardiac conduction disease [16]. As a BrS6, a missense mutation in *KCNE3*, which encodes the potassium channel β subunit and interacts with Kv4.3 (transient outward current: I_{to}) channel, was identified in a proband with Brugada syndrome [17]. Most recently, a missense mutation in *SCN3B*, which encodes the sodium channel β3 subunit, was identified in an asymptomatic patient with Brugada syndrome [18]. In all seven genotypes, decreases in inward sodium or calcium current (late sodium current [I_{Na}], L-type calcium current [$I_{Ca\text{-}L}$]) or increase in an outward potassium current (I_{to}) produce Brugada phenotype [19, 20]. However, approximately two-thirds of Brugada patients have not yet been genotyped, suggesting the presence of further genetic heterogeneity [19, 20]. Other candidate genes for the Brugada phenotype include the genes encoding delayed rectifier potassium current (I_K), or genes which code for adrenergic receptors, cholinergic receptors, ion-channel-interacting protein, promoters [21], transcriptional factors, neurotransmitters, or transporters.

Cellular Mechanism of Brugada Phenotype

Repolarization Theory

An I_{to}-mediated phase 1 notch of the action potential (AP) has been reported to be greater in the epicardial cells than in the endocardial cells in many species, including humans, by experimental studies [22]. Since the maintenance of the AP dome is determined by the fine balance of currents active at the end of phase 1 of the AP (principally I_{to} and $I_{Ca\text{-}L}$), any agents that cause a net outward shift at the end of phase 1 can increase the magnitude of the AP notch, leading to loss of the AP dome (all-or-none repolarization) in the epicardium, but not in the endocardium, contributing to a significant voltage gradient across the ventricular wall during ventricular activation [22]. The heterogeneous loss of the AP dome in the epicardium was shown to produce premature beats via a mechanism of phase 2 reentry in experimental studies using isolated sheets of canine right ventricle [23]. The Brugada syndrome seems to be a clinical counterpart of the mechanism of all-or- none repolarization in the epicardial cells and phase 2 reentry-induced premature beat between the adjacent epicardial cells.

An experimental model of the Brugada syndrome employing arterially perfused canine right ventricular (RV) wedge preparations provided direct experimental evidence for the cellular mechanism of ST-segment elevation [24–29]. The I_{to}-mediated AP notch and the loss of the AP dome in the epicardial cells, but not in the endocardial cells, of the right ventricle gives rise to a transmural voltage gradient, producing ST-segment elevation in the ECG (Fig. 7.2) [8]. In the setting of coved type ST-segment elevation, heterogeneous loss of the AP dome (coexistence of loss of dome regions and restored dome regions) in the epicardium creates a marked epicardial dispersion of repolarization, giving rise to premature beats due to phase 2 reentry, which sometimes precipitates non-sustained polymorphic ventricular tachycardia (VT) or VF (Fig. 7.2) [8]. Our developed high-resolution optical mapping system, which allows us to record transmembrane APs from 256 sites simultaneously, suggested that a steep repolarization gradient between a loss of dome region and a restored

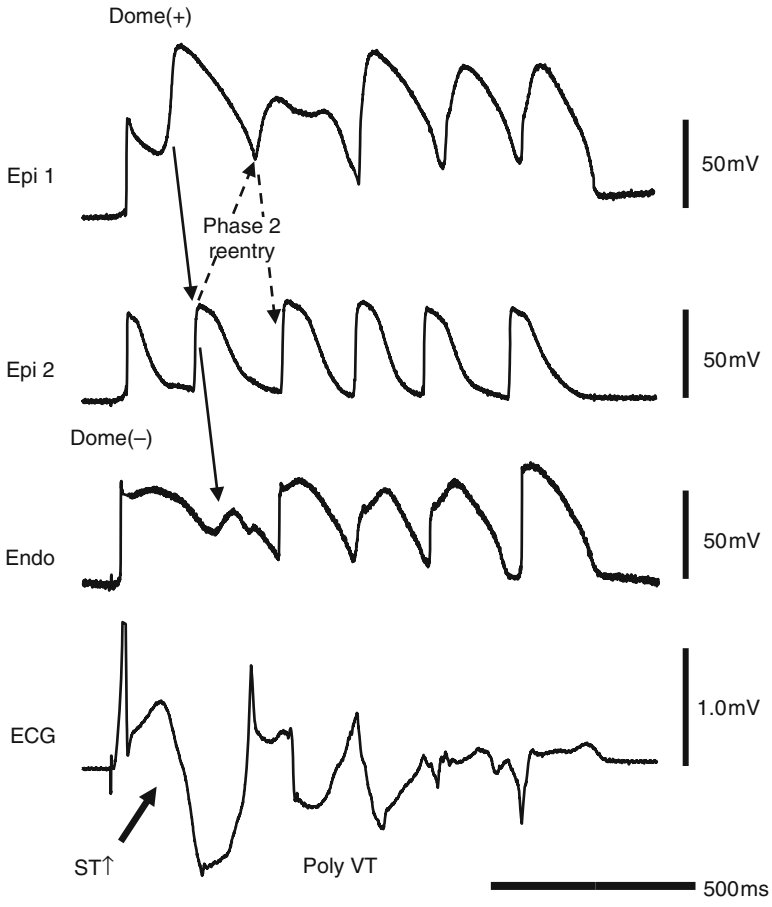

Figure 7–2. Coved ST-segment elevation and phase 2 re-entry-induced nonsustained polymorphic ventricular tachycardia (Poly VT) in a Brugada model employing an arterially perfused canine right ventricular wedge preparation. Transmembrane action potentials simultaneously recorded from two epicardial (*Epi*) sites and one endocardial (*Endo*) site together with a transmural electrocardiogram (*ECG*) (BCL 2,000 ms). Combined administration of terfenadine (5 μM/L) and pilsicainide (5 μM/L) causes heterogeneous loss of the action potential dome in the epicardium (restored dome in epicardial site 1, loss of dome in epicardial site 2), giving rise to coved type Brugada ECG. Electrotonic propagation from the site where the dome is restored (*Epi 1*) to the site where it is lost (*Epi 2*) results in development of phase 2 re-entry-induced premature beat, triggering poly VT

dome region in the epicardium is essential to produce phase 2 reentry-induced premature beats, and that mild to moderate conduction delay is required to degenerate the reentrant pathway into VF [8, 26].

Depolarization Theory

The depolarization theory hypothesizes that the conduction delay in the right ventricular outflow tract (RVOT) may produce the ST-segment elevation, and that the abnormal current created by the delayed depolarization of the RVOT may induce polymorphic VT or VF in the Brugada syndrome [30]. The delayed depolarization of the RVOT compared to that of other RV regions creates a potential difference between them. The membrane potential of the RVOT is more negative than that of the RV during the hatch phase action potential. Therefore, the current flow conducts from the RVOT intercellular space to the extracellular space, travelling towards the right precordial lead ECG (V1–V3) positioned over the RVOT, which is reflected as the ST-segment elevation in leads V1–V3. Moreover, the depolarization theory hypothesizes that polymorphic VT or VF in the Brugada syndrome may be originated from the border zone between early and delayed depolarizations. Several clinical studies have demonstrated conduction delay in patients with Brugada syndrome [31–33].

Acquired Form of Brugada Syndrome

The ST-segment elevation is well known to be dynamic day-to-day even in the same patient with Brugada syndrome, and to be modulated by several drugs (mainly antiarrhythmic drugs) and autonomic agents [34]. Class IC antiarrhythmic

Table 7–1. Acquired form of Brugada syndrome

1. Antiarrhythmic drugs
   (1) Sodium channel blockers
      Class IC drugs (Flecainide [35–39], pilsicainide [40, 41], propafenone [42–45])
      Class IA drugs (ajmaline [36, 39, 46], procainamide [34, 36], disopyramide [34, 35], cibenzoline [47])
   (2) Calcium channel blockers
      Verapamil [48]
   (3) β blockers
      Propranolol [49], etc.
2. Antianginal drugs
   (1) Calcium channel blockers
      Nifedipine, diltiazem, etc.
   (2) Nitrate
      Isosorbide dinitrate, nitroglycerine [48], etc.
   (3) Potassium channel openers
      Nicorandil, etc.
3. Psychotropic drugs
   (1) Tricyclic antidepressants
      Amitriptyline [50–54], nortriptyline [55], desipramine [56, 57], clomipramine [58], dosulepin [59, 60], etc.
   (2) Tetracyclic antidepressants
      Maprotiline [50], etc.
   (3) Phenothiazine
      Perphenazine [50], cyamemazine [54], etc.
   (4) Benzodiazepine
      Clonazepam [57], alprazolam [59], lorazepam [60], etc.
   (5) Selective serotonin reuptake inhibitors
      Fluoxetine [54], paroxetine [61], etc.
   (6) Other antidepressants
      Trazodone [57], risperidone [60], etc.
4. Other drugs
   (1) Histaminic H1 receptor antagonists
      Dimenhydrinate [62–64], etc.
   (2) Anti-inflammatory drug
      Mesalazine [65], etc.
   (3) Psychoactive recreational drug
      Cocaine [66–69], cannabis [70]
   (4) Anti-psychotic drug
      Lithium [71–74], thioridazine [75]
   (5) Local anesthetics
      Bupivacaine [76]
   (6) Short-acting hypnotic agent
      Propofol [77, 78]
5. Hypertestosteronemia [79]
6. Low visceral fat [79]
7. Myocardial ischemia
   (1) Right ventricular infarction/ischemia [80–83]
   (2) Vasospatic angina [84, 85]
8. Myocarditis, pericarditis
   (1) Acute myocarditis [86–88]
   (2) Chronic myocarditis [89]
   (3) Acute pericarditis [90]
9. Temperature
   (1) Hyperthermia (febrile state) [91, 92]
   (2) Hypothermia [93–97]
10. Electrolyte abnormalities
   (1) Hyperkalemia [98–103]
   (2) Hypokalemia [104, 105]
   (3) Hypercalcemia [106, 107]
   (4) Hyponatremia [100, 104, 108]
11. Meal, increased insulin level [109, 110]
12. Polymorphysms in *SCN5A* [21]

drugs, which are used as a diagnostic tool in latent Brugada syndrome, amplify or unmask the ST-segment elevation most effectively as a result of their strong effect of blocking fast INa [35, 36]. Several drugs and conditions other than IC drugs are reported to induce transient ST-segment elevation like that in Brugada syndrome. According to the repolarization theory of molecular and cellular aspects in Brugada syndrome, any interventions that increase outward currents (e.g. I_{to}, adenosine tri-phosphate sensitive potassium current [$I_{K\text{-}ATP}$], slow and fast activating components of IK [I_{Ks}, I_{Kr}]) or decrease inward currents (e.g. $I_{Ca\text{-}L}$, fast I_{Na}) at the end of phase 1 of the AP can accentuate or unmask ST-segment elevation, similar to that found in Brugada syndrome. This is described as an "acquired" form of Brugada syndrome similar to the "acquired" form of long QT syndrome (LQTS) (Table 7.1).

Antiarrhythmic Drugs

Class IC sodium channel blockers (flecainide, propafenone, pilsicainide) produce the most pronounced ST-segment elevation secondary to strong use-dependent blocking of fast I_{Na} due to their slow dissociation from the sodium channels [35–45]. Pilsicainide, a pure class IC drug developed in Japan, is thought to more strongly induce ST-segment elevation than flecainide, which is widely used throughout the world and mildly blocks I_{to}.

Class IA sodium channel blockers (ajmaline, procainamide, disopyramide, cibenzoline, etc.), which exhibit less use-dependent block of fast I_{Na} due to faster dissociation of the drug for the sodium channels, are expected to show a weaker ST-segment elevation than class IC drugs [34–36, 46, 47]. However, net effects of IA drugs on ST-segment augmentation are influenced by their blocking effect of I_{to} to ameliorate their blocking effect of I_{Na}. Ajmaline is reported to

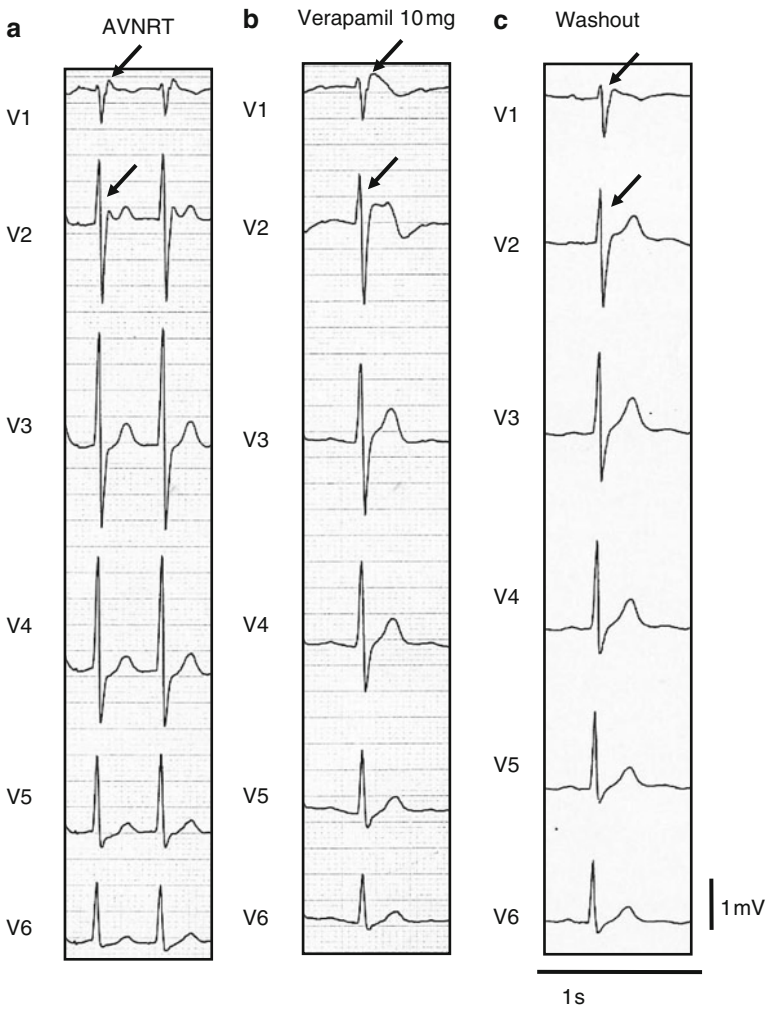

Figure 7–3. Acquired form of Brugada syndrome induced by intravenous verapamil in a patient with atrio-ventricular nodal reentrant tachycardia (*AVNRT*). During AVNRT (**a**, *arrows*) intravenous administration of 10 mg verapamil successfully terminated AVNRT, but unmasked Type 1 coved ST-segment elevation in lead V1 and Type 2 saddle-back ST-segment elevation in lead V2 (**b**, *arrows*). The ST-segment elevation disappeared after washout of verapamil (**c**, *arrows*)

induce or enhance Type 1 ST-segment elevation more frequently than flecainide, a IC drug, probably due to less inhibition of I_{to} by ajmaline [39, 46]. Disopyramide and procainamide show weaker accentuation of the ST-segment elevation due to their smaller effect on fast I_{Na} and mild to moderate action to block I_{to} [34–36]. In contrast, quinidine generally normalizes ST-segment elevation owing to its relatively strong I_{to} blocking effect, and is proposed as a pharmacologic treatment for the Brugada syndrome [48, 49].

Class IB sodium channel blockers (mexiletine, lidocaine, etc.) dissociate from the sodium channel rapidly and therefore blocks fast I_{Na} principally at rapid rates. At moderate and slow heart rates, class IB drugs have little or no effect on fast I_{Na}, thus are unable to cause ST-segment elevation [35].

ICa-L blockers such as verapamil (Fig. 7.3) and β-blockers are expected to accentuate ST-segment elevation and possibly to induce VF as a result of inhibiting $I_{Ca\text{-}L}$ [50, 51]. It is reported that vasovagal syncope is accompanied in some patients with Brugada syndrome [50]. β-blockers are often used as a first line of therapy for vasovagal syncope. Therefore, unmasking of Brugada syndrome must be always taken into account in the use of β-blockers for vasovagal syncope.

Antianginal Drugs

Calcium antagonists (nifedipine, diltiazem, etc.) and nitrates, which have a blocking action of $I_{Ca\text{-}L}$, are often used as a first line of therapy for ischemic heart diseases. An $I_{K\text{-}ATP}$ opener, nicorandil,

is another choice of therapy. These antianginal drugs are expected to provoke ST-segment elevation in patients with the "acquired" form of Brugada syndrome [7, 50].

Psychotropic Drugs

Many psychotropic drugs have been reported to unmask Brugada-like ST-segment elevation. These include tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, clomipramine, dosulepin, etc.), tetracyclic antidepressants (maprotiline, etc.), phenothiazine (perphenazine, cyamemazine, etc.), benzodiazepine (clonazepam, alprazolam, lorazepam, etc.), and other antidepressants (trazodone, risperidone, etc.), most of which block fast I_{Na} usually with overdose (Fig. 7.4) [53–63]. The selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and paroxetine, are reported to produce ST-segment elevation, probably as a result of their effect to depress fast I_{Na} and $I_{Ca\text{-}L}$ [64, 65].

Other Drugs

Dimenhydrinate, a sedating, first-generation histaminic H1 receptor antagonist, commonly used as an antiemetic, is reported to produce Brugada-like ST segment elevation [66–68]. Dimenhydrinate exhibits an anticholinergic action and blocks fast I_{Na}; the latter effect may cause the ST-segment elevation. Mesalazine, an anti-inflammatory drug for inflammatory bowel disease, is reported to unmask type 1 ECG [69]. ST-segment elevation is also reported to be provoked by intoxication of psychoactive recreational drug, such as cocaine [40–73] and cannabis [74] mainly due to its fast I_{Na} blocking effect. Antipsychotic drug, such as lithium [75–78] and thioridazine [79] are reported to unmask Brugada ECG. Local anesthetics, bupivacaine [80], and short-acting hypnotic agent, propofol [81, 82], are also reported to induce Brugada ECG.

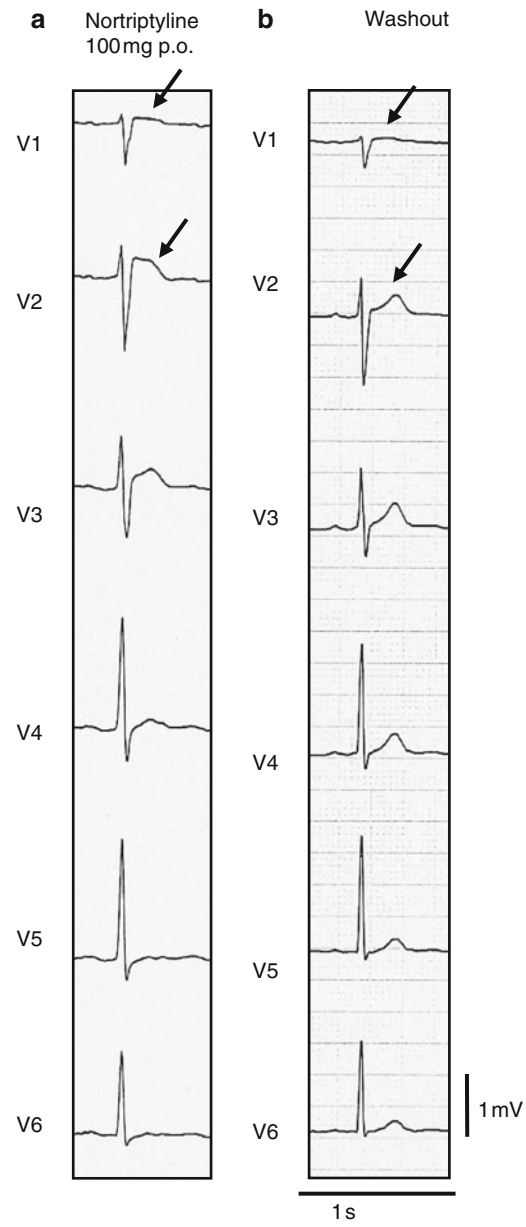

Figure 7–4. Tricyclic antidepressant-induced acquired form of Brugada syndrome. Type 1 coved ST-segment elevation was observed in leads V1 and V2 during oral nortriptyline (100 mg/day), a tricyclic antidepressant (**a**, *arrows*). The ST-segment elevation disappeared after washout of nortriptyline (**b**, *arrows*)

Hypertestosteronemia and Low Visceral Fat

All of the mutations so far identified in patients with Brugada syndrome display an autosomal dominant mode of transmission. Therefore, males and females are expected to inherit the defective gene equally. However, clinical Brugada phenotype is much more prevalent in males than in females, especially in Asian countries [83]. The male predominance in the Brugada

syndrome is at least in part due to intrinsic differences in the ventricular AP between males and females [84]. Recent clinical studies suggested that a male hormone, testosterone, may be attributable to male predominance in patients with Brugada syndrome. Matsuo and co-workers have reported two cases of asymptomatic Brugada syndrome, in whom coved type ST-segment elevation disappeared following orchiectomy as therapy for prostate cancer [85], indicating that testosterone may contribute to the Brugada phenotype in these two cases. Shimizu and co-workers suggested that males with Brugada syndrome were independently and significantly associated with higher testosterone level and lower body-mass index compared with age-matched control males, indicating a critical role of testosterone on the male predominance in Brugada syndrome [86]. These data also suggested that hypertestosteronemia and low visceral fat may be a risk factor to provoke Brugada phenotype.

Myocardial Ischemia, Myocarditis, and Pericarditis

Acute myocardial infarction (AMI) or acute ischemia involving the RVOT mimics ST-segment elevation similar to that in Brugada syndrome, as a result of the depression of $I_{Ca\text{-}L}$ and the activation of $I_{K\text{-}ATP}$ during ischemia [87–90].

Several reports have demonstrated a combination of Brugada syndrome and vasospastic angina or induced vasospasm with acetylcholine (ACh) and/or ergonovine maleate (EM) [84]. Along the same lines as the AMI, vasospasm of the coronary artery supplying the RVOT region is expected to produce Brugada-like ST-segment elevation. Noda et al. systematically evaluated the frequency of induced coronary spasm and the change of ST-segment elevation with intra-right coronary injection of ACh and/or EM in patients with Brugada syndrome [91]. Coronary spasm was induced in 3 (11 %) of 27 Brugada patients, suggesting that coronary spasm was not rare in Brugada syndrome. The ST-segment elevation was augmented by 11 (33 %) of the 33 right coronary injections [ACh: 6/11 (55 %), EM: 5/22 (23 %)] without any induction of coronary spasm (Fig. 7.5). VF was induced by 3 (9 %) of the 33 right coronary injections [ACh: 2/11 (18 %), EM: 1/22 (5 %)]. These results suggested that mild ischemia and vagal influences act with the substrate responsible for Brugada syndrome to elevate the ST-segment and precipitate VF by decreasing $I_{Ca\text{-}L}$ and activating $I_{K\text{-}ATP}$, and that congenital and possibly acquired form of Brugada syndrome may place a patient at higher risk for ischemia-related sudden cardiac death.

Acute and chronic myocarditis and acute pericarditis are reported to induce Brugada ECG [93–97].

Temperature: Hyperthermia (Febrile State) and Hypothermia

A number of reports have demonstrated that febrile state can unmask Brugada-like ST segment elevation and provoke VF [98, 99]. Some functional studies have demonstrated that high temperature (febrile state) reduced I_{Na} in the mutant sodium channel, and was expected to accentuate or unmask Brugada ECG [100].

On the other hand, a prominent J wave associated with ST-segment elevation mimicking Brugada ECG has long been described as an Osborn wave in hypothermic states due to accidental exposures to cold [101–105]. This is probably due to low temperature-induced increase of I_{to}.

Electrolyte Abnormalities

Severe hyperkalemia [106–111], hypokalemia [112, 113], hypercalcemia [114, 115], or hyponatremia [108, 112, 116] are associated with ST-segment elevation in the right precordial leads like that in Brugada syndrome.

Meal and Increased Insulin Level

The increased insulin level after meal or glucose tolerance test is reported to accentuate or unmask Brugada ECG [117]. Ikeda et al. reported that large meal induced Brugada ECG due to vagal stimulation [118]. This effect may contribute to circadian or day-to-day variation in the degree of ST-segment elevation in this syndrome. Although insulin increases outward

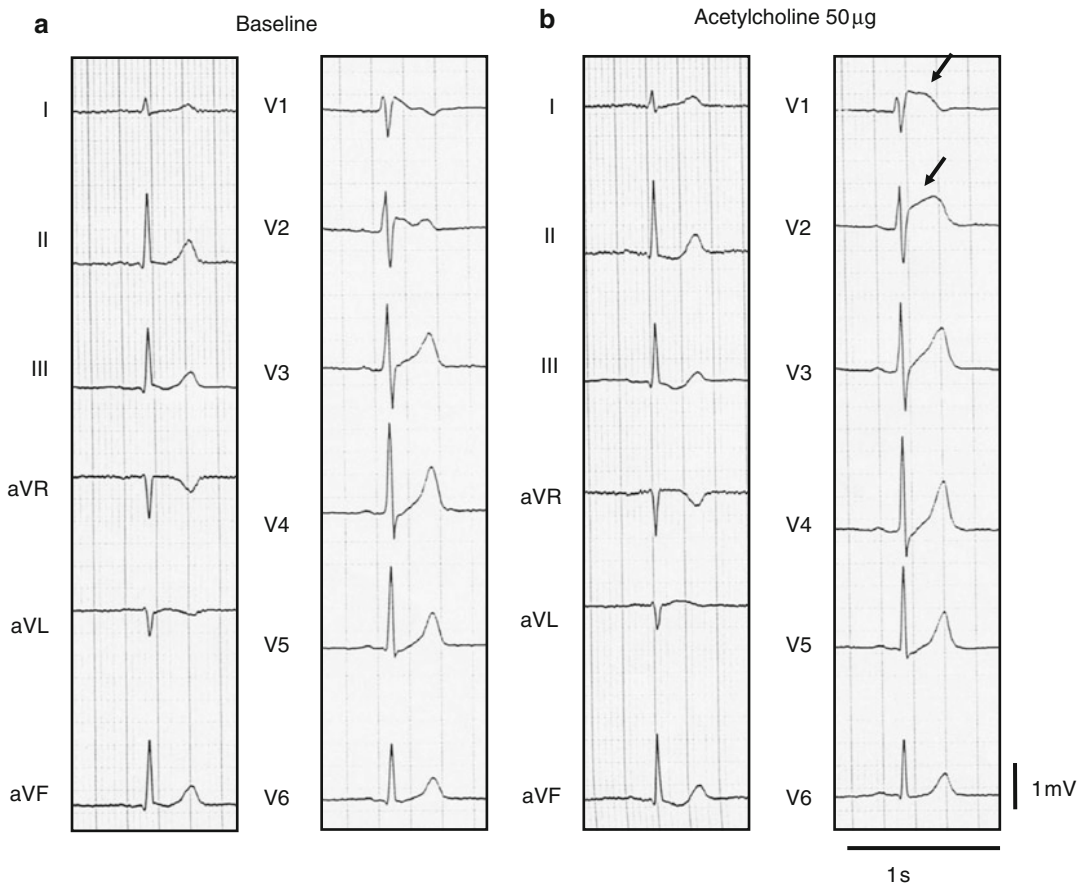

Figure 7–5. Type 1 coved ST-segment elevation induced by intra-right coronary injection of acetylcholine. Twelve precordial leads electrocardiogram (ECG) under baseline conditions (**a**) and intra-right coronary injection of 50 μg acetylcholine (ACh) into the right coronary artery (**b**) in a patient with diagnosed Brugada syndrome. Injection of ACh augmented the ST-segment elevation in leads V1 and V2 in both cases (**b**, *arrows*)

current by activating Na^+/K^+ pump and stimulates $I_{Ca\text{-}L}$, predominance of the former is thought to contribute to augmentation of the ST-segment elevation.

Mechanical Compression of the RVOT

Unmasking of Brugada-like ST segment elevation due to mechanical compression of the RVOT by a mediastinal tumor or haemopericardium was reported [119–123]. This effect is most likely a result of an affect of the impact on multiple ion channel currents leading to an outward shift of net current active during the early phases of the epicardial action potential in the RVOT.

Polymorphisms

A mutation or polymorphisms in genes responsible to congenital form of LQTS (LQT1, *KCNQ1*; LQT2, *KCNH2*; LQT3, *SCN5A*) have been identified in some patients with "acquired" forms of LQTS [124]. This makes us imagine naturally that some patients with "acquired" form of Brugada syndrome may inherit polymorphisms or other mutations in *SCN5A* or other genes. Bezzinna and co-workers identified a haplotype consisting of six individual DNA polymorphisms within the proximal promoter region of the *SCN5A* gene only in Japanese population, which reduced transcription of the cardiac sodium channel mRNA [21]. This suggests

that individuals carrying these six polymorphisms would display mild reduction of I_{Na} and would be candidates of "acquired" form of Brugada syndrome.

Conclusion

Many drugs and interventions have been reported to provoke Brugada ECG described as an "acquired" form of Brugada syndrome. Such drugs and interventions have been also associated with adverse events in Brugada syndrome patients [125].

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Part II
Clinical Rhythmology: Diagnostic Methods and Tools

Win-Kuang Shen, Michael J. Ackerman, Brian D. Powell, Arthur A.M. Wilde, and Ihor Gussak

W.-K. Shen, MD
Division of Cardiovascular Diseases,
Department of Medicine
Mayo Clinic College of Medicine,
Mayo Clinic Arizona, Phoenix, AZ, USA
e-mail: wshen@mayo.edu

M.J. Ackerman, MD, PhD, FACC
Department of Medicine,
Division of Cardiovascular Diseases,
Department of Pediatric and Adolescent Medicine,
Division of Pediatric Cardiology,
Department of Molecular Pharmacology and Experimental Therapeutics,
Mayo Clinic, Rochester, MN, USA
e-mail: ackerman.michael@mayo.edu,
haglund.carla@mayo.edu

B.D. Powell, MD
Division of Cardiovascular Diseases,
Sanger Heart & Vascular Institute,
Charlotte, NC, USA

A.A.M. Wilde, MD, PhD, FESC, FAHA
Department of Cardiology,
Heart Center Academic Medical Center,
University of Amsterdam,
Meibergdreef 9, 1105 AZ,
Amsterdam, The Netherlands

I. Gussak, MD, PhD, FACC
Ono Pharmaceutical USA,
Lawrenceville, NJ, USA

Department of Internal Medicine,
University of Medicine and Dentistry of New Jersey,
Robert Wood Johnson Medical School,
New Brunswick, NJ, USA
e-mail: igussak@hotmail.com

8
Introduction to Part IV: Abnormal Electrical Functions of the Heart and Their Diagnoses in Clinic

Benjamin C. Eloff

Keywords
ECG • Diagnosis • Screening

The electrocardiograph (ECG) is the cornerstone of diagnostics for electrical diseases of the heart. Yet, the devices in use today and their outputs would not be unrecognizable to the contemporaries of Waller and Einthoven more than a century ago. Most chapters in this section focus on the ECG and various derivative measurements, which speak volumes to the clinical utility and enduring power of this diagnostic instrument (Fig. 8.1).

When reflecting on the history of ECG technology and its evolution from electrometers and string galvanometers to modern analog-to-digital conversion and digital signal processing, it is hard not to marvel at how the understanding of the heart's underlying electrophysiology has grown based on such small snapshots of time recorded on smoke drums, paper, and flash memory. Equally remarkable are the daunting challenges that remain for the cardiac electrophysiology community.

B.C. Eloff, PhD
Division of Epidemiology,
Office of Surveillance and Biometrics,
Center for Devices and Radiological Health,
United States Food and Drug Administration,
10903 New Hampshire Ave., WO66, RM 3214,
Silver Spring, MD 20993, USA
e-mail: benjamin.eloff@fda.hhs.gov

The past two decades have produced a number of new diagnostic and therapeutic technologies, involving implantable devices, mapping and ablation catheters, and non-invasive tests. However, much room for improvement remains in the ability to prevent, diagnose, risk stratify, and treat cardiac rhythm disorders. As a result of twentieth-century research, the basics of electrical diagnostics are fairly well understood in the clinical community today. However, as in many scientific fields, substantial debate continues on the application, use, and practical utility of many of the finer points of electrophysiological diagnostics.

Electrophysiology is a unique area of science in that it has enabled very close interaction between clinicians and basic scientists, leading to innovation and experimentation. For example, we understand how substitution of just a single amino acid in an ion channel can produce a substrate for fibrillation [2]. This type of translational insight into electrophysiology has enabled development of a number of specialized diagnostic tests, derived from the measurement of electrical currents on the body surface. Some of these tests have added value to clinical decision-making, while others have yet to demonstrate a broad applicability. Many of the specialized diagnostic tests described in the following section undergo some degree of investigation into their best use for clinical practice.

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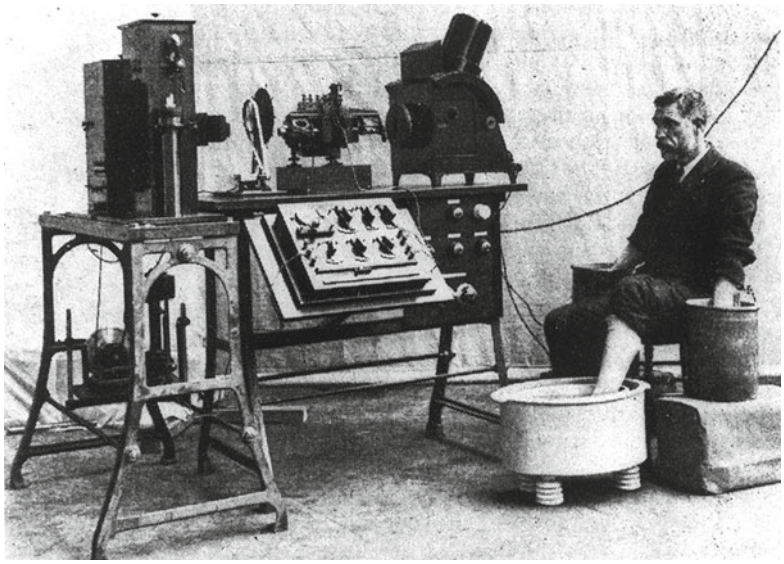

Figure 8–1. Photo of an early string galvanometer electrocardiograph manufactured by Cambridge Scientific Instrument Company, 1911. Modern disposable electrodes replace the jars of salt solution today, but the limb lead positions endure. This predates the Wilson Central Terminal, augmented limb leads, and precordial leads. Signals today are recorded digitally as opposed to the falling glass plate camera (From Barron [1]. Reprinted with permission from BMJ Publishing Group Ltd)

Today, the clinical community is witnessing a further evolution into the era of personalized medicine in which the well-refined tools of the past are combining with advances in information technology, such as real-time computing, genetic testing, mobile computing, and electronic health records. Physicians are being challenged to learn about and discover new scientific advancements and to grasp the interplay among an increasing number of patient characteristics. Even as these physicians are inundated with information flowing from existing ambulatory monitors and event recorders, they will have to incorporate new data streams from high-volume sources like implantable devices and continuous 12-lead ambulatory monitors into their already time consuming clinical practices. The understanding and synthesis of these data into a meaningful clinical diagnosis will require additional research and more of the physician's time than may be available. These factors provide fertile ground for innovation into new diagnostic tools.

The potential for the new data streams to contribute to a fuller understanding of a patient should be achieved while avoiding the pitfalls of applying scientific findings and tests inappropriately in an unselected population where their interpretation could be quite different than in the populations in which the tests were developed. The inherent risks associated with the many therapeutic options available to the clinician make this balanced approach essential to protecting patient safety.

The deeper understanding and integration of the various data streams available to members of the scientific community is supported by vital work currently underway to create and update international consensus standards for data acquisition, format, display, and reporting. This standardization enables clinicians to understand a patient's electrophysiology relatively independent of the hardware that is used, which has clear advantages to the clinical community.

Innovation is an added benefit of standardization. Academic, industry, and governmental partners are now sharing raw patient-level data, while protecting patient confidentiality, in ways that could only be imagined a few years ago. The advent of public-private partnerships to promote pre-competitive scientific collaboration also provides a venue for the open exchange of ideas while promoting innovation. The data being shared in these partnerships is more than just ECG waveforms. It also includes patient characteristics, blood work, genetic testing, and other characteristics. The availability of these data to researchers and innovators in standard formats provides the pre-competitive tools necessary for innovation to tackle future challenges. Sharing of standardized data sets is not

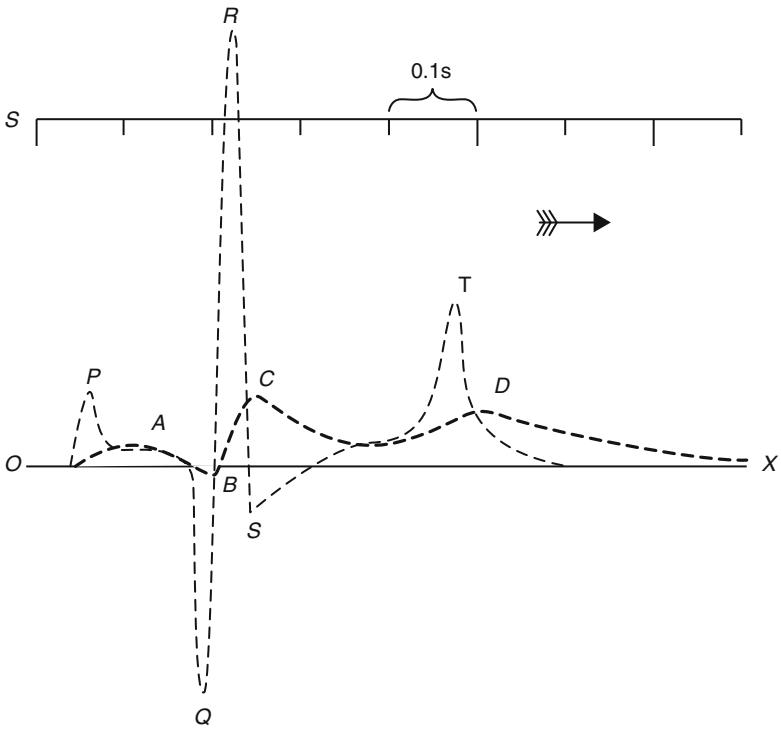

Figure 8–2. Corrected (PQRST) and uncorrected (ABCD) plots taken from early ECG recordings using an Lippmann capillary electrometer. The PQRST curve is similar to what one would record on a modern ECG. This illustrates the underlying physiological basis and enduring power of the ECG (From Einthoven [4])

enough to result in new diagnostic tools alone. In order to widely apply these new technologies, prospective studies in broad and diverse populations for new screening tests will still be needed. Standardization is and will remain a flexible process that enables discovery of new critical diagnostic elements to be incorporated in the future.

The sophisticated diagnostic tools available to cardiac electrophysiologists are extremely useful in identifying rhythm disorders in patients to whom they are applied. However, these tools and cutting-edge therapeutic technologies and regimens are of no use in patients who never get to a cardiologist. The electrophysiologist's challenge is to predict a patient's future arrhythmogenic potential before he or she is ever referred from a primary care physician. In this era of a fully mapped genome and with our knowledge of a vast array of single gene mutations, genetic testing can assist in identifying some patients at risk [3], but these patients are only a small portion of those at risk today.

New developments in molecular diagnostics that give a richer understanding of the complex subcellular and intercellular interactions in the heart may help clinical diagnostics going forward, but current practice is limited to the use of existing tools. Luckily, we stand on the shoulders of giants who have investigated the hazards associated with New York Heart Association heart failure class, ejection fraction, prior myocardial infarction, and other non-electrocardiographic markers. These factors and those identified in new studies will continue to help physicians identify patients at risk for lethal ventricular tachyarrhythmias.

The diagnosis of electrical diseases in the heart remains as fascinating in our time as it was over a century ago. It is still possible to see the work of the field's early pioneers in the innovative diagnostic tools of today. One can only imagine what advances will develop during the next century as technology evolves and we gain a deeper understanding of the basic science of cardiac electrophysiology (Fig. 8.2).

Acknowledgement. The opinions expressed are those of the author, and do not necessarily reflect the position of the FDA.

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9
Diagnostic Electrocardiography

Preben Bjerregaard

Abstract

Based upon three case reports it is shown how important it is for making a correct clinical diagnosis of some cardiac diseases to be able to interpret the ECG correctly. Basic electrocardiography is still one of the most important tools in clinical cardiology.

Keywords

Electrocardiography • Brugada syndrome • Catecholaminergic polymorphic ventricular tachycardia • Tako-Tsubo syndrome • Long QT syndrome

Introduction

As pointed out by Shlomo Stern: "The electrocardiogram is still the cardiologist's best friend" [1].

Since Augustus Desire Waller recorded the first human electrocardiogram in 1887 [2], and its clinical usefulness demonstrated by among other Sir Thomas Lewis and Sir James Mackenzie almost 100 years ago, the electrocardiogram has remained one of the most important diagnostic tools in medicine in a format, which has remained unchanged since Goldberger in 1942 [3] added the unipolar amplified extremity leads.

One of the fascinating aspects of the ECG is diagnostic content, which may be unnoticed for a very long time and then suddenly, when pointed out, become obvious to everyone. Even today new features of the ECG are discovered, which are of prognostic importance or indicate new diseases. Most of them have been related to cardiac repolarization.

In the following, a few clinical examples will be given of ECG abnormalities, which have turned out to be hallmarks of new diseases. The cases presented are real life stories from the authors archive. At a time when new diagnostic tests are developed almost on a daily basis, it is becoming more and more difficult to know, when to use them and how to interpret the test results. It is then reassuring to know, that the ECG still is one of the most valuable diagnostic tools in daily clinical practice, and knowing how to interpret it can be very rewarding.

Later chapters will deal with tools, which have been developed in order to assess the significance of various ECG findings in more detail and thereby become the important next step in the work-up of patients at risk. In some cases genetic screening is the only way to confirm a diagnosis.

P. Bjerregaard, MD, DMSc
Division of Cardiology, VA Medical Center,
Washington University in St. Louis,
915 North Grand, St. Louis,
MO 63106, USA
e-mail: preben.bjerregaard@va.gov

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Table 9–1. Family with Brugada syndrome, prolonged QT and RBBB causes by mutation in the sodium channel gene SCN5A

		1 GREAT-GRANDFATHER Seizure episodes several years **SCD** while driving at age 51 ECG not available		
SIBLINGS/GRANDPARENTS:				
2 70 y.o. female (wife) ***Asymptomatic*** ECG: normal		**3**[X] 72 y.o. male, **GRANDFATHER** ***SCD, myocardial infarction (2006)*** QTc: 573 ms, RBBB Giant negative T-waves V_2–V_6	**4**[X] 70 y.o. male (brother) ***Asymptomatic*** QT_c: 450 ms ICD	
SIBLINGS/PARENTS				
5[X] ***45 y.o. male*** ***Collaps in College*** ***QTc: 466 ms*** Procainamide pos. ICD	**6**[X] ***44 y.o. female*** ***Asymptomatic*** ***QTc: 483 ms*** ICD	**7**[X] ***41 y.o. male*** ***Asymptomatic*** ***QTc: 447 ms*** Brugada type 3 ICD	8 ***40 y.o. female*** ***SCD (2003)*** ***QTc: 480 ms*** Brugada type 1	*9* ***31 y.o. male*** ***Asymptomatic*** ***QTc: 383 ms*** Brugada type 2 ICD
CHILDREN				
10 10 y.o. female Asymptomatic QT_c: 422 ms	**11** 22 y.o. female Asymptomatic QTc: 404 ms		**12** 13 y.o. male Asymptomatic QTc: 406 ms	**13** 8 m.o. male QT_c: 402 ms
14 7 y.o. female ***Asymptomatic*** ***QTc: 420 ms***	**15** 14 y.o. female ***Williams Syndrome*** ***QTc: 407 ms***		**16** 8 y.o. female ***SCD (1993)*** ***Ostial ridge* left coronary artery**	**17** 8 m.o. male ***QTc: 403 ms***
18 4 y.o. male Asymptomatic QT_c: 429 ms ICD	**19** 10 y.o. male Asymptomatic QTc: 398 ms			

X: Mutation carrier (Patients number 2, 12, 13 and 17 were not screened)

Case 1

Patient # 8 (Table 9.1) was sitting at a restaurant, when she suddenly collapsed with cardiac arrest. She was resuscitated, but with severe anoxic encephalopathy and died 2 weeks later. She had no history of cardiac disease or syncope prior to the event. She had a daughter (patient # 16, Table 9.1) who had died suddenly at the age of 8 years old, while sitting at her desk in a classroom at school. The autopsy in our patient showed no organic cardiac disease or other explanation for her death. The first ECG shortly after admission to the hospital (Fig. 9.1a) was interpreted as sinus tachycardia with RBBB and right axis deviation. Even though the QT interval appeared prolonged, it was difficult to assess because of the wide QRS complex and tachycardia. The next day the heart rate was slightly slower, and the QRS had normalized (Fig. 9.1b). Repolarization changes in V_1–V_3 suggesting Brugada Syndrome were now present, and a diagnosis of a long QT interval very likely. The family was very interested in being ECG tested, and later all had genetic screening as well. Because of a delay in getting the result from genetic screening and great anxiety in the family, the decision of implantation of an ICD was done prior to getting the result from the genetic screening. Only patient # 5 (Table 9.1) had additional testing done, which included the usual next steps in a patient suspected of having Brugada Syndrome, namely, a Procainamide challenge test and an EP-study. They were both positive and taken as support for the diagnosis

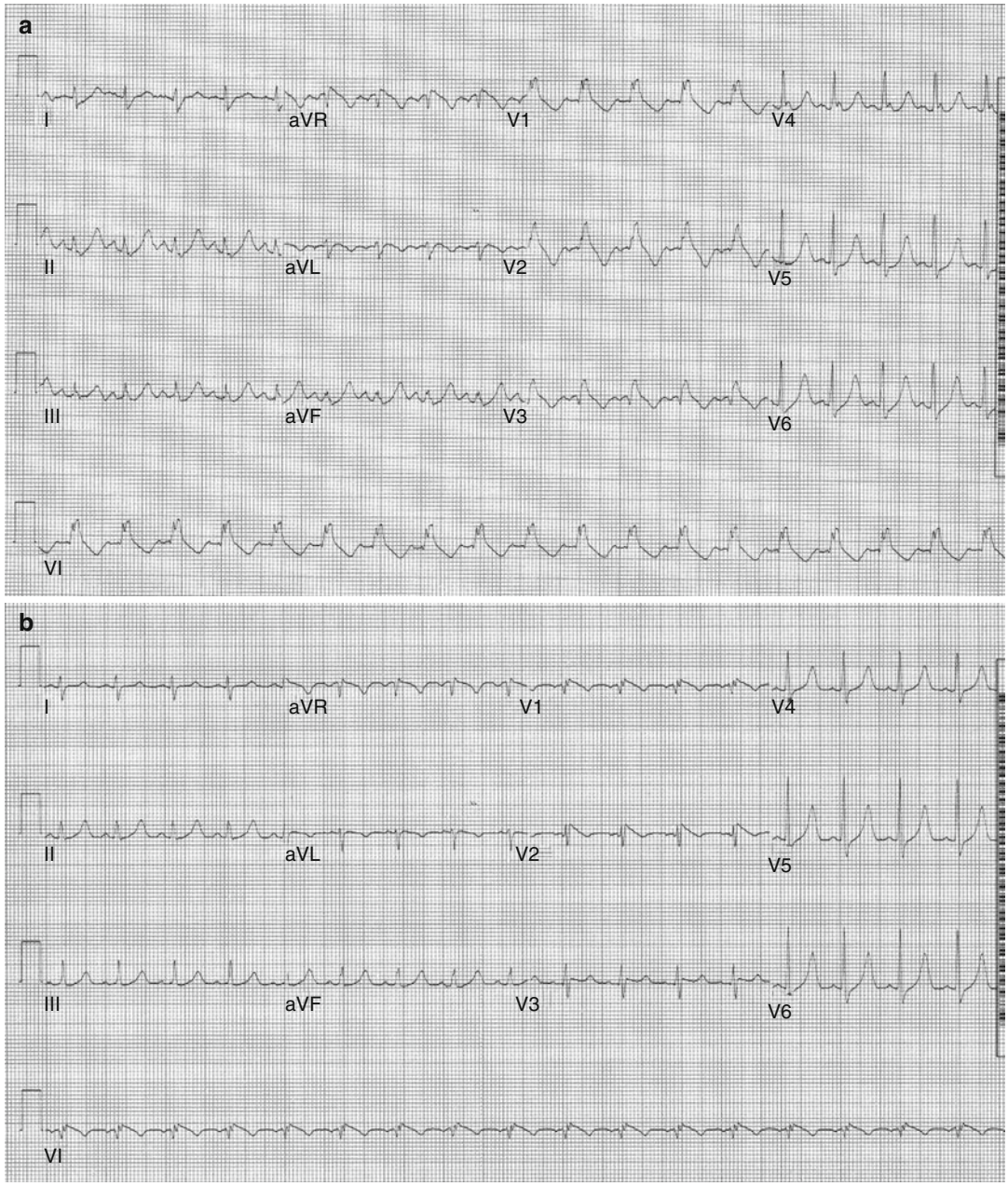

Figure 9–1. (**a**) 12-lead ECG from patient # 8, Table 9.1 showing sinus tachycardia at a heart rate of 115 beats/min, RBBB and right axis deviation. (**b**) 12-lead ECG from patient # 8, Table 9.1 showing sinus tachycardia at a heart rate of 103 beats/min, right axis deviation, QT-interval of 388 ms with QTc = 508 ms, and Brugada type 1 changes in V_1–V_3

of Brugada Syndrome also in other family members with the Brugada sign in the ECG. Lack of funding (health insurance or private funds) prohibited further studies in other family members, and the ICD's implanted were graciously donated by a US ICD manufacturer.

This family illustrates many of the problems we face on a daily basis dealing with primary electrical diseases of the heart, which are inheritable and have a high risk of SCD. Problems exists when the genetic mutation is unknown, and the decision about who should have an ICD is based

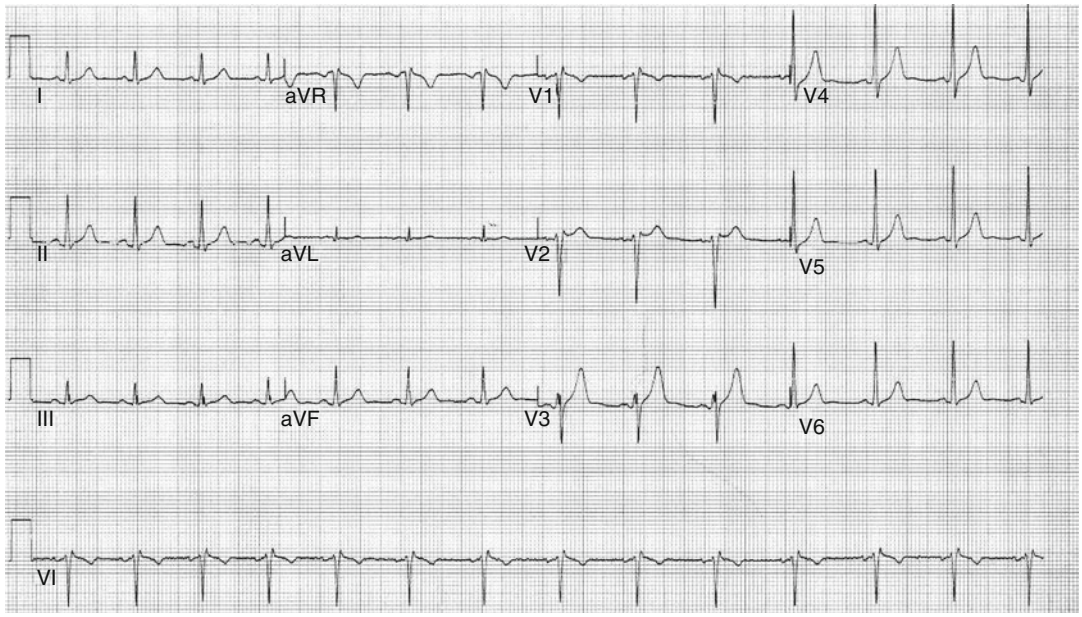

Figure 9–2. 12-lead ECG from patient # 9, Table 9.1 showing sinus rhythm with normal QT interval, but Brugada type 2 changes in lead V_2

purely on clinical presentation and the ECG, and other problems may arise, when it becomes clear, who the carriers of a deadly mutation are.

Patients # 3 and # 16 (Table 9.1) both illustrate, how mistakes can be made in assuming, that all patients, who die suddenly in a family with an inheritable disease with a high risk of SCD, also have the disease or die from it. Patient # 3 (Table 9.1) had a very prolonged QT interval and the genetic mutation, but died from an acute myocardial infarction with cardiac arrest. He was resuscitated at home with severe anoxic encephalopathy as a consequence, but underwent cardiac catheterization prior to his death. He had earlier turned down the offer of an ICD. When the death certificate from patient # 16 (Table 9.1) was found, it showed a congenital ostial fibrous ridge in the left coronary artery as the possible cause of death. Genetic testing on tissue available from the autopsy 13 years earlier showed no evidence of the SCN5A mutation.

Patient # 9 (Table 9.1) illustrates how inconclusive or borderline ECG findings may be over-interpreted, when they occur in a patient from a family with high risk of SCD. This patient received an ICD based upon an ECG with Brugada type 2 changes (Fig. 9.2), at the same time all his siblings received one. He was asymptomatic. When the result of the genetic screening became available, it became clear, however, that he was not a carrier. Since the type 2 Brugada sign can be a normal variant and a negative genetic screening for a known mutation considered very reliable, it is quite likely, this patient received an ICD, he did not need. The ICD was removed without replacement, when it reached ERI.

Patient # 18 (Table 9.1) illustrates a healthy 4 year-old child with a normal ECG on the day of screening (Fig. 9.3). He received an ICD because he was a carrier of the SCN5A mutation. His father (Patient # 5, Table 9.1) had received an ICD, and because the family was still unsure about the circumstances around the SCD of an 8 year old girl in the family (patient # 16, Table 9.1), they wanted the boy protected against SCD. He was, therefore, provided with an external defibrillator, he carried in a backpack for 2 years without any complications, and now has an implantable defibrillator.

Mutations in the SCN5A gene encoding for the voltage-gated cardiac Na^+ channel have been linked to a variety of clinical entities causing sudden cardiac death, including Brugada Sydrome, Long QT syndrome and progressive conduction system disease. While the diseases are distinct, the overall spectrum of related phenotypes is becoming very complex, and phenotype overlapping between these three diseases as in our family [4] has also been described by others [5–7].

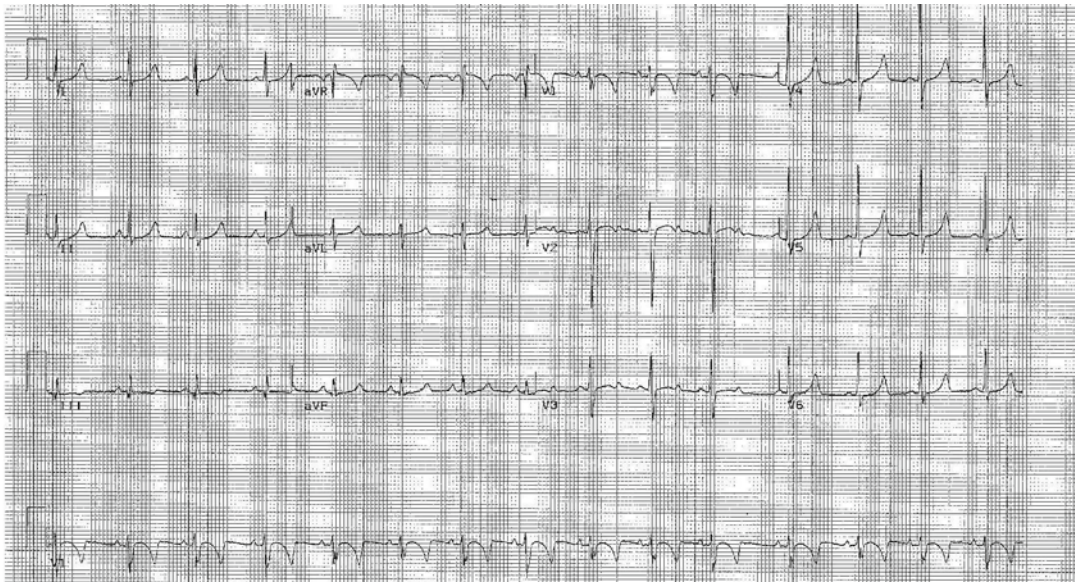

Figure 9–3. 12 lead ECG from patient # 18, Table 9.1 showing normal sinus rhythm at a rate of 88 beats/min, QT-interval of 360 ms with $QT_c = 432$ ms and non-specific T-wave abnormalities in V1–V3

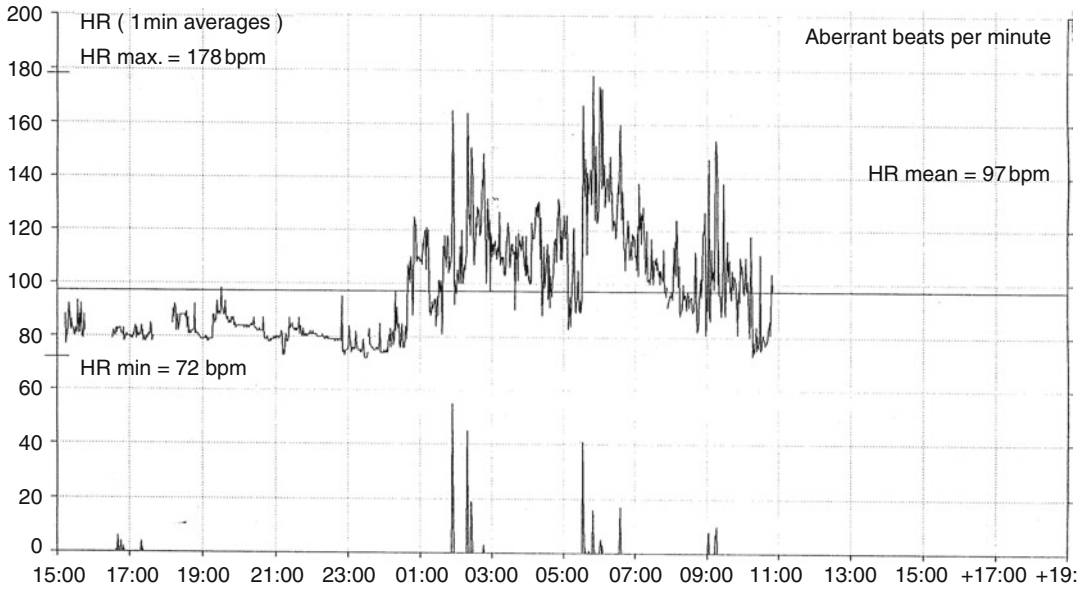

Figure 9–4. 24-h trend of heart rate and number of aberrant beats in patients # 7, Table 9.2

Case 2

The supervisor in my laboratory with more than 20 years of experience in scanning of Holter recordings did hardly believe her eyes, when she was watching the nighttime continuous ECG recording of a 16 year-old girl. After a daytime recording with normal sinus rhythm at a maximum heart rate of 110 beats/min and only few PVC's (few couplets and triplets) the heart rate at 2 AM started to gradually accelerate to rates as high as 180 beats/min, and remained above 100 beats/min the rest of the night (Fig. 9.4). The diary, which was later confirmed

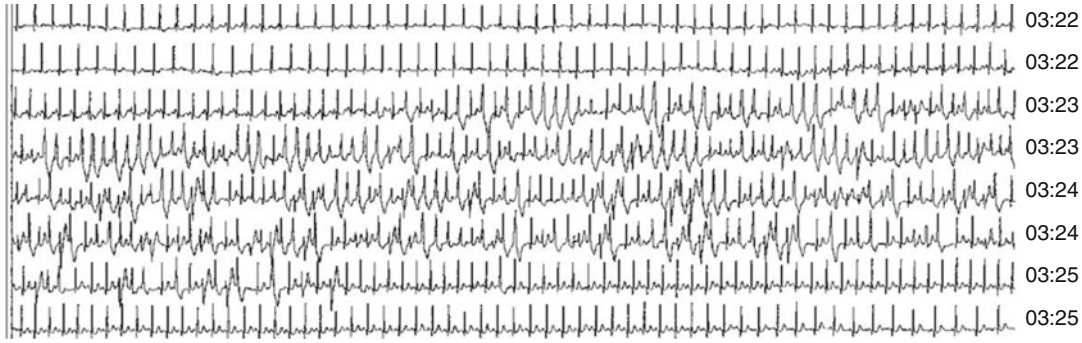

Figure 9–5. 3 min ECG rhythm strip from 24 h Holter recording of patient # 7, Table 9.2 showing an arrhythmic event related to a brief increase in heart rate and immediate cessation of the arrhythmia as the heart rate slows down again

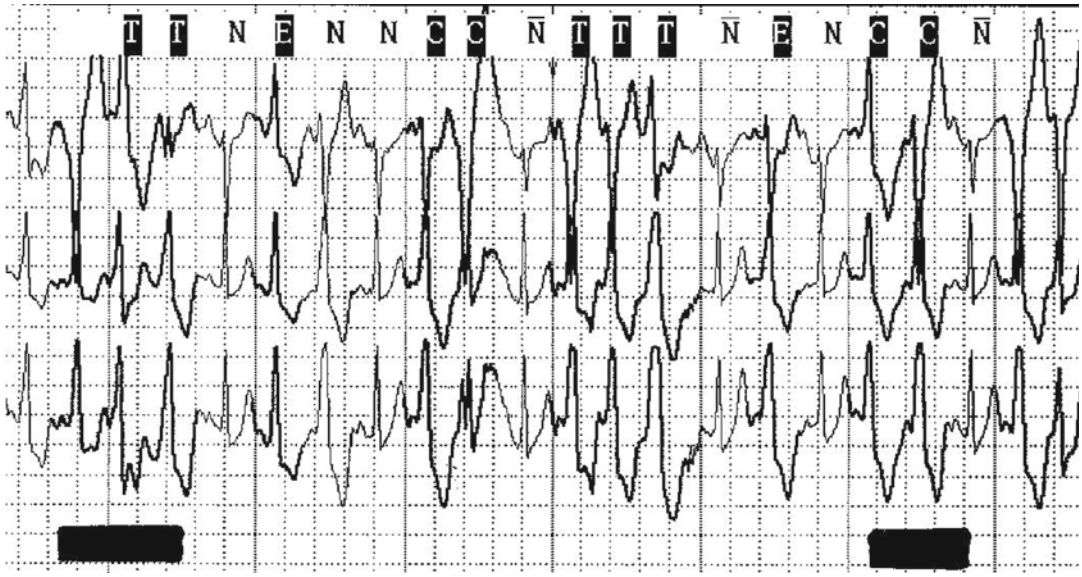

Figure 9–6. Brief ECG rhythm strip from patient # 8, Table 9.2 showing bi-directional PVCs in lead 1, while all the PVCs in leads 2 and 3 are uniform

by both the patient and her mother, indicated that the patient had been sleeping all night. The next morning the patient had several similar episodes, while she was physically active at home. All episodes followed the same pattern. A sudden acceleration in heart rate either as sinus tachycardia, junctional or atrial tachycardia was accompanied by ST depression and PVC's, initially isolated and uniform, but later, as the heart rate got faster, they became multiform with couplets, triplets and salvos. Occasionally atrial-flutter or –fibrillation would occur leading to a complex mixture of atrial and ventricular tachy-arrhythmias (Fig. 9.5). A special feature was bidirectional PVC as couplets (Fig. 9.6). The patients 12-lead ECG, echocardiography and a drug-free EP-study were normal. When a low dose of isoproterenol (0.02 μg/kg/min) was administered, however, the arrhythmias were quickly reproduced.

This clinical picture is very characteristic of *catecholaminergic polymorphic ventricular tachycardia* (*CPVT*) [8]. The mystery regarding the nightly episodes was solved, when the patient informed us about taking 0.125 mg of hyoscyamine sulfate (an anticholinergic drug) at bedtime for an abdominal disorder. A Holter recording off the drug showed no arrhythmias during sleep.

Table 9–2. Family with a clinical picture of catecholaminergic polymorphic ventricular tachycardia

	1 52 y.o. **GREAT-GRANDMOTHER** **SCD** while dancing		
Siblings/grandparent			
	2 62 y.o. **GRANDMOTHER** Recurrent syncope Normal ECG Positive Holter		**3** 19 y.o. male Recurrent syncope **SCD**
Siblings/parents			
4 Newborn Congenital Heart Disease	**5** 24 y.o. **MOTHER** Recurrent syncope **SCD**	**6** 19 y.o. female **SCD** (Drowning?)	**7** 25 y.o. **MOTHER** Recurrent syncope Holter positive
Children			
	8 17 y.o. male Recurrent syncope Holter positive ICD	**9** 17 y.o. female Asymptomatic Holter negative	**10** 3 y.o. male Asymptomatic
	11 16 y.o. male Recurrent Syncope Polydactyly Holter positive ICD		**12** 2 y.o. male Asymptomatic

The index patient (# 7, Table 9.2) presented with a 2-year history of approximately 10 episodes of syncope. They always happened during physical activity or emotional distress, and she would usually lose consciousness completely. She was treated with an ICD and beta-blocker, and has received shocks by the ICD. She has also had additional syncopal episodes due to her usual tachy-arrhythmia, but at a heart rate below the detection rate for VF programmed at 220 beats/min. It is usually not feasible to program the detection rate lower, since it will lead to a higher increase in number of shocks, which are unnecessary, since treatment is directed at preventing SCD and most of the tachycardia episodes terminate spontaneously. Due to the autosomal dominant inheritance of the disease she was strongly encouraged not to become pregnant. As seen from Table 9.2, patients # 10 and # 12 are both her children. Since genetic testing was not performed, it is still not known, whether they have the disease.

Table 9.2 clearly shows the tragic story, which unfolded, when the patients family history was revealed. The mother of the index patient (patient # 2, Table 9.2) had lived with syncopal episodes, since she was a teenager, and Holter monitoring clearly showed, that she had the same diagnosis as her daughter, she felt some improvement during treatment with a betablocker and opted not to get an ICD. Her brother (patient # 3, Table 9.2) started to have syncope at the age of 9 years-old and had to be taken out of school, because some of the other children took advantage of the fact, that he would pass out every time, they scared him. It could happen several times a day and was considered a benign event, because he always woke up soon after. One time he did not wake up after passing out, and died at the age of 19-years-old. Her oldest daughter (patient # 5, Table 9.2) had collapsed in a skating ring, and seriously brain damaged after being resuscitated. She was pregnant at the time and gave birth to patient # 11 (Table 9.2) while on life support, only to die 2 years later. She had a history of recurrent syncope, but no ECG documentation of arrhythmias prior to her death. Her diagnosis of CPVT was, however, established, when both her children were diagnosed with the disease.

Patients # 8 and #11 (Table 9.2) were 8 and 9 years old respectively, when they first had an ECG and Holter monitoring. They had no history of syncope and been rather healthy. Patient # 11 (Table 9.2), who was born while his mother was on life support, was born with syndactyly. A 12-lead ECG was normal in both children. During Holter monitoring patient # 8 (Table 9.2) had only 122 PVC's in a 24-h period, but a diagnosis of CPVT was highly likely due to their relationship to tachycardia and the presence of ventricular bigeminy and eight bi-directional PVC's as couplets in one of the recorded leads (V_1-like). In the two other recorded leads all PVC's had the same morphology (Fig. 9.6). Patient # 11 (Table 9.2) had a total of 208 uniform PVC's during tachycardia with one episode of ventricular trigeminy and quadrigeminy. Despite the lack of symptoms and more complex tachyarrhythmias both were treated with beta-blocker and received an ICD. Despite high doses of beta-blocker they have both had arrhythmic events with ICD shocks and in both of them possibly life-saving. Figure 9.7 shows a VF episode from the ICD of patient # 11 (Table 9.2). It shows how ventricular tachycardia degenerates into ventricular flutter and ventricular fibrillation prior to a 29.8 J shock is delivered and restores a narrow QRS-complex rhythm.

The storage of arrhythmic events in implantable pacemakers and defibrillators offers new opportunities for documentation of the sequence of events behind cardiac arrest. Both in patient # 8 and # 11 (Table 9.2) such events were recorded.

The clinical presentation of our patients is very similar to that reported as CPVT by others [9–13]. It is not known at which point in life the disease becomes clinical manifest, but syncope and SCD is rarely seen before the age of 4 years-old [9]. Based upon recent reports [8, 14], CPVT can be divided into two subgroups: (1) a "juvenile type" that presents with clinical symptoms at around 10 years of age, has no gender difference, and is more likely to have an *RyR2* mutation, and a greater risk of SCD, and (2) an "adult type" that presents with clinical symptoms later than 20 years of age (mean, 40 years of age), appears predominantly in females, and is less likely to have an *RyR2* mutation, and also less likely to be associated with SCD. ECG recording during tachycardia may, therefore, have to be repeated several times in a child before the diagnosis can be excluded. The strong relationship between symptoms and physical or emotional stress was very evident in our family as well as in the family presented by Fisher et al. [13] where "at times of general excitement (e.g., watching soccer), several members of the family often fainted at the same time".

Nam et al. [15] have examined the cellular mechanisms underlying the development of catecholaminergic ventricular tacycardia and shown, that under conditions of defective calcium handling, delayed after depolarization-induced extrasystolic activity can serve as trigger for ventricular tachycardia and ventricular fibrillation.

Genetic screening is pending in our family. If it turns out positive, it will be very helpful in order to make a correct diagnose especially in the young children, who are still asymptomatic. Priori et al. demonstrated in year 2000 [16], that mutations of the autosomal dominant trait in the cardiac ryanodine receptor gene (*RyR2*) is responsible for a high percentage of clinical cases of CPVT. A year later, Lahat et al. demonstrated that a mutation of the autosomal recessive trait in the *CASQ* gene could lead to a similar clinical syndrome [17]. An article by Testes et al. [18] accompanied by an editorial by Gussak [19] cautioned against using the clinical picture alone for the diagnosis of CPVT. Out of 11 patients diagnosed clinically with CPVT and referred for genetic screening, only four hosted novel CPVT1-associated *RyR2* mutations. Three patients had Andersen-Tawil (AT) associated mutations and one LQT5. Three were genotype negative. None of our patients had prolonged QT interval or abnormal U waves as described in AT syndrome, and none of them had periodic paralysis as also seen in this syndrome. It is of some interest, however, that patient # 11 (Table 9.2) had syndactyly, which has been described as a feature of AT syndrome.

This case shows the benefit of obtaining an ECG recording in situations, where a patient normally has his/her symptoms, especially when the ECG at baseline is normal. If tachycardia is not present at any point during a 24 h recording, an exercise stress test is helpful. It also shows the

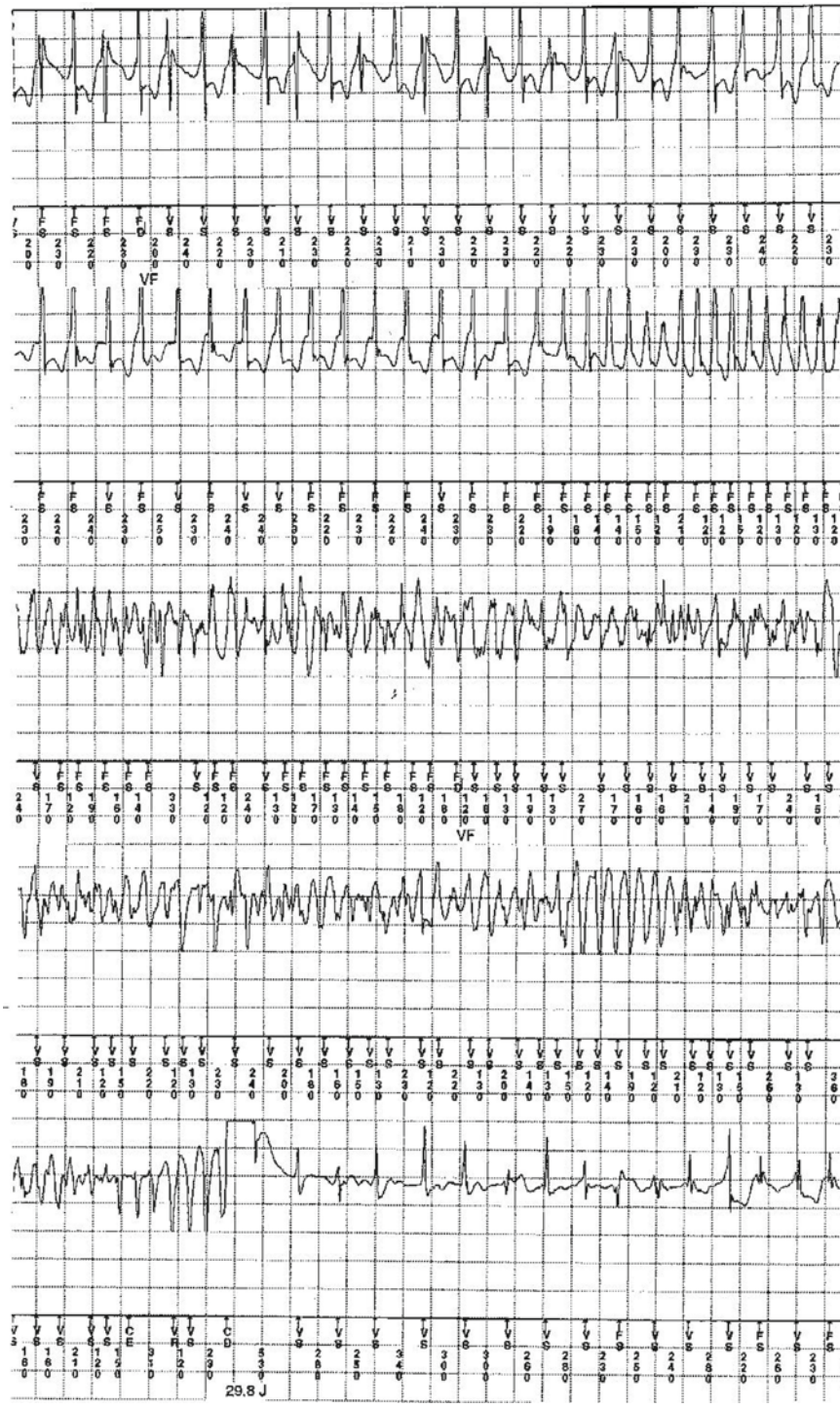

Figure 9–7. An arrhythmic episode with loss of consciousness in patient # 11, Table 9.2 retrieved from the memory of his ICD. It shows a gradual increase in heart rate with a bi-directional ventricular tachycardia leading to ventricular flutter and ventricular fibrillation terminated by a 29.8 J shock, which restores a narrow complex rhythm

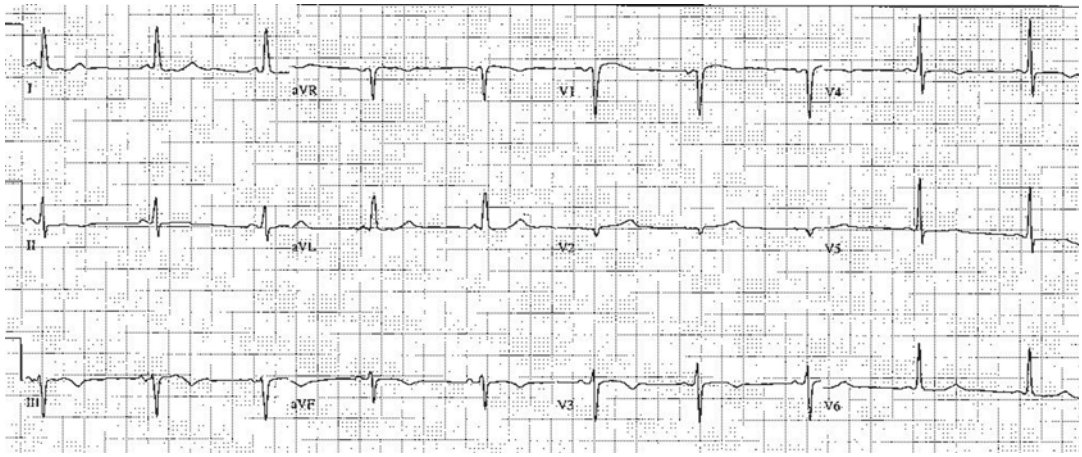

Figure 9–8. 12-lead ECG on admission from 62 year-old female with chest pain. It shows sinus rhythm with minimal T-wave inversion in leads II, aV_F and V_3–V_4. Poor R-wave progression in leads V_1–V_3

importance of meticulously scrutinizing even a few innocent looking PVCs among more than 100,000 beats in a 24 h recording and consider their significance in the context of the clinical picture (patients # 8 and 11, Table 9.2). If CPVT is suspected, bi-directional PVC,s are a strong clue to the diagnosis. It is important, however, to examine consecutive PVCs in several leads, since bi-directional PVCs in some leads may appear uniform in other leads (Fig. 9.6). As also pointed out by Gussak [15] bidirectional PVC's or ventricular tachycardia characterized by 180° alternating QRS axis on a beat-to-beat basis are not patognomonic for CPVT, but seen in patients with AT syndrome and ARVD2 as well.

Case 3

62 year-old African-American female with minor coronary artery disease S/P PTCA and stent placement in the first obtuse marginal branch of the circumflex coronary artery 3 years earlier, presented with intermittent chest pain radiating to her left arm, nausea and dizziness over a 24 h period. Following nitroglycerine and beta-blocker therapy the patient became pain-free. Cardiac enzymes were normal. The ECG on admission showed sinus rhythm with minimal T-wave inversion in leads II, aV_F and V_3–V_4 (Fig. 9.8). R waves were missing in V_1 and V_2 only in some ECG recordings, making it unlikely to be a significant finding. During the following 48 h, while the patient remained asymptomatic and hemodynamically stable, there were dramatic changes in the ECG with marked prolongation of the QT interval and major global T-wave inversion (Fig. 9.9). The patient underwent cardiac catheterization showing no coronary artery stenosis greater than 30 %, but unexpectedly severe left ventricular dysfunction with anterolateral and diaphragmatic hypokinesis and a left ventricular ejection fraction of 30 %. A remarkable finding was a very slow flow in the left anterior descending coronary artery. During the catheterization, when an intracoronary injection of adenosine was given in order to assess the significance of a stenosis of the right coronary artery, the patient had a 5 s episode of self-limiting ventricular fibrillation.

This case represents an electrocardiographic phenomenon, which is lacking an understanding of both the etiology and the cellular electrophysiologic mechanism. Major T wave inversions with significant QT prolongation have been observed in patients following intense emotional distress [20], cerebrovascular accidents [21, 22], severe electrolyte disturbances and myocardial ischemia [23], sometimes accompanied by stunning of the myocardium. In the latter setting is has been part of a new syndrome called *Tako-Tsubo Syndrome*. It was first described in Japan in 1991 [24] and received its name after a round-bottomed narrow-necked Japanese fishing pot

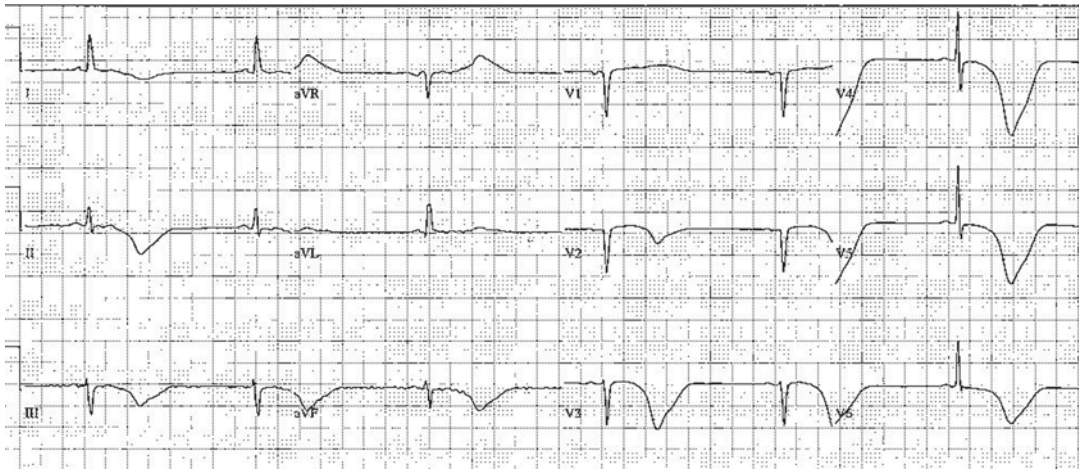

Figure 9–9. 12-lead ECG 2 days following admission for chest pain in 62 year old female. It shows sinus bradycardia at 37 beats/min with QT interval of 728 ms with $QT_c = 571$ ms and major global T-wave inversion. The patient was asymptomatic at the time of the ECG recording

used for trapping octopus. The left ventricle in cases of unexplained stunning of the myocardium, which is being reported at an increased frequency, often takes the shape of such a pot. The syndrome is characterized by transient left apical or mid-ventricular wall motion abnormalities in the absence of acute occlusive coronary artery disease [25, 26]. The disorder occurs most commonly in postmenopausal women, and the episodes are often preceded by an acute increase in psychological or emotional stress. The electrocardiographic changes have varied, but in a recent review of 11 patients ST segment elevation and prolonged QTc was seen in 10 with major global T-wave changes seen in eight [27]. The severe LV dysfunction is usually reversible. The results from a prospective study of 128 patients with Tako-Tsubo Syndrome from a European population were recently published [28]. It showed an in-hospital rate of LV failure of 10 %, but only 1 death. Recovery of LV function was complete in 73 % within 1 month and a good long-term prognosis with a recurrence rate <2 %/year. We have had such patients referred to us for ICD implantation with the indication based upon a low ejection fraction during the acute phase of the disease, and found LV function to be normal, when the patients were examined later. It is, therefore, strongly recommended, that no decision about ICD implantation be made before the ECG has normalized and the patients LV function re-evaluated.

Even though vasospasm and catecholamine cardiotoxicity both have been proposed as possible etiologies to the T-wave changes and stunning of the myocardium described above, none of them have been proven. Ibanez and Benezet-Mazuecos, in an editorial in Mayo Clinic Proceedings [29], have provided strong arguments for the theory, that *Tako-Tsubo* syndrome is an "aborted myocardial infarction" resulting from an acute atherothrombotic event with rapid and complete lysis of the thrombus. Much more work is needed, however, before we know, what is behind the Octopus Trap.

Concluding Remarks

Brugada Syndrome, Long QT Syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia and Tako-Tsubo Syndrome are all examples of diseases, where electrocardiographic findings are crucial for a correct diagnosis and the diagnosis mainly based upon the ECG. Several other diseases could have been included, and many more are the cases, where a correct arrhythmia diagnosis in the setting of a known disease can be crucial for the outcome of a patient.

In a recent editorial in Journal of Electrocardiology, J Willis Hurst [30] raised serious concerns about our current level of teaching electrocardiography in medical schools and of

our residents. Long gone are the days, when a stethoscope, a chest X-ray and an ECG were the only tools available for the diagnosis of heart diseases. Due to the excitement over new and important newer tools such as echocardiography, nuclear cardiology and cardiac catheterization, electrocardiography has been left out.

I hope that the cases that I have presented have shown how fascinating electrocardiography can be, and how an unusual finding may lead to the discovery of a new disease or turn out to be the key to solve the mystery of syncope or SCD in a family over several generations.

As stated by J. Willis Hurst: "Excellent knowledge of electrocardiography is needed now by internists and cardiologists more than any previous time in medical history".

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10
Microvolt T Wave Alternans: Mechanisms and Implications for Prediction of Sudden Cardiac Death

Florian Rader, Lance D. Wilson, Ottorino Costantini, and David S. Rosenbaum†

Abstract

Sudden cardiac death remains the leading cause of death in the U.S.A. Noninvasive measurement of Microvolt T wave alternans (MTWA) during exercise testing has been shown to be a useful tool to identify patients who are unlikely to sudden death events, and, therefore, are possibly less likely to benefit from implantable defibrillators. In addition to its potential value in risk stratification for sudden cardiac death, the fact that MTWA is relatively common in high risk patients raises the questions that alternans may play a role in the mechanisms responsible for triggering ventricular arrhythmias. Extensive research of its underlying molecular and cellular mechanisms not only elucidated the phenomenon of MTWA but also identified the electrophysiological substrate as well as novel therapeutic targets of malignant ventricular arrhythmias. This chapter will review the mechanisms underlying development of MTWA, its measurement, and potential clinical use for screening, identifying and treating patients at risk for sudden cardiac death.

Keywords

Microvolt T wave alternans • Sudden cardiac death • Risk stratification • Repolarization • Calcium cycling • Discordant alternans

Introduction

Sudden cardiac death (SCD) accounts for greater than 50 % of all cardiac deaths every year in the USA alone [1]. While an implantable cardioverter defibrillator (ICD) is effective therapy against the ventricular tachyarrhythmias most often responsible for SCD, it remains difficult to identify the population that derives the most benefit from such devices. Recent studies have focused solely on a reduced left ventricular ejection fraction (LVEF) as a criterion for selecting

F. Rader, MD, MSc
Cedar Sinai Medical Center, LA, USA

L.D. Wilson, MD • O. Costantini, MD (✉)
D.S. Rosenbaum†, MD
The Heart and Vascular Center Case
Western Reserve University/MetroHealth Campus,
Cleveland, OH, USA
e-mail: ocostantini@metrohealth.org

†Deceased

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patients who benefit from implantation of an ICD [2, 3]. However, LVEF, as a measure of contractility, is a dynamic measurement which changes over time, and poorly defines the electrical substrate which leads to SCD [4]. Moreover, the absolute risk reduction derived from ICD therapy in the primary prevention studies based on a low LVEF alone is small (~2.5 %/year), and the rate of appropriate device therapy is ~5–7 % per year. Considering the limitations of health care resources and some of the complications related to device implants, it has become clear that identifying who derives the most benefit from costly ICDs is imperative to increase cost-effectiveness and reduce dollars spent per gained quality-adjusted life year [5]. Based on the current paradigm for risk stratification for SCD, one would have to implant approximately 15–20 ICDs to save one life. Microvolt T wave alternans (MTWA) could improve cost-effectiveness of ICDs and prevent complications of ICDs in patients who don't need them.

Among other risk stratification tests, MTWA has emerged as a simple and cost effective [6] tool to better define the electrical substrate of patients with a known cardiomyopathy, and to identify patients at the highest and lowest risk of ventricular tachyarrhythmias. Moreover, mechanistic understanding of MTWA in heart failure has lead to promising new therapeutic targets in the prevention of SCD.

In this chapter, we will review the mechanisms underlying its development, its measurement, and its potential use as a clinical tool for screening, identifying and potentially treating patients at risk for SCD.

Historical Background

Cardiac alternans was first recognized as pulsus alternans by Traube in 1872, and was associated with poor outcomes [7]. More recently, T wave alternans (TWA), defined as beat-to-beat oscillations in the amplitude of the T wave that occur on an every-other-beat basis, has been recognized as a marker of increased risk for ventricular tachyarrhythmias.

Visible TWA occurs when oscillations in T wave amplitude are large enough to be discerned on the surface ECG. It was first reported in dogs by Hering [8]. Lewis reported the same phenomenon in humans concluding that it increased the risk of adverse events [9]. TWA was subsequently reported in a range of clinical conditions, including HIV cardiomyopathy [10], long QT syndrome [11], coronary vasospasm [12], acute myocardial infarction [13], Prinzmetal's angina [14], antiarrhythmic drug therapy [15], alcoholism [16] and electrolyte imbalance [17]. Even though visible TWA is associated with ventricular arrhythmias, it is quite rare (0.1 % incidence) [18].

In the 1980s the spectral analysis method was developed for the detection and quantification of microvolt (MTWA), which is not visible on the surface ECG (i.e. "microvolt-level" alternans). This work confirmed a close relationship between MTWA and cardiac electrical instability [19, 20]. In 1994, Rosenbaum [21] reported, for the first time in humans, a relationship between MTWA and susceptibility to ventricular arrhythmias by demonstrating a strong correlation between a positive MTWA test and inducible ventricular tachycardia by electrophysiological studies (EPS). In addition, MTWA was equivalent to EPS in predicting arrhythmia-free survival and the risk of developing life-threatening ventricular arrhythmias was increased 13 fold in patients with positive MTWA tests.

Initially, atrial pacing was used to achieve the heart rate elevation necessary to elicit MTWA, but exercise soon became the preferred method for eliciting MTWA [22, 23]. This led to the ability to use MTWA as a simple, inexpensive, and non-invasive test to risk stratify patients at risk for SCD.

Cellular Mechanisms of Repolarization Alternans

Cellular Basis for Electrocardiographic T Wave Alternans

There is compelling evidence that MTWA results from beat-to-beat alternation in the time course of membrane repolarization at the cellular level (Vm-ALT) [24–27]. Alternations in cellular action potential shape and duration were initially observed from single ventricular sites using microelectrodes [28–30] and contact electrodes [31–34]. However, the mechanisms

linking cellular alternans to electrocardiographic TWA was definitively established through detailed measurements of the time course of membrane voltage (Vm) throughout the ventricle at a time when MTWA was elicited on the surface ECG. These studies were performed using high-resolution optical mapping techniques in a guinea pig model of pacing-induced TWA [24–26]. Importantly, TWA in this model exhibits characteristics of MTWA in humans [21]: (1) TWA was induced reproducibly above a critical heart rate threshold, (2) The magnitude of alternans was titratable and persists at a steady state (i.e. does not require abrupt rate change), (3) TWA affected primarily the peak of the T wave rather than the ST segment or QRS complex, (4) TWA was a consistent (actually requisite) precursor to ventricular fibrillation (VF), and (5) The guinea pig possesses action potential and calcium handling properties that are comparable to humans [35].

These finding suggested that disorders that produce MTWA in heart disease arise from abnormalities of intracellular processes. These studies also demonstrated that MTWA on the surface electrocardiogram actually corresponds to substantially greater alternans of repolarization at the myocyte level [24]. This may explain why the detection of very subtle ("microvolt-level") MTWA has physiological and prognostic significance in patients.

Cellular, Subcellular and Molecular Basis for Repolarization Alternans

It was originally hypothesized that alternans of the membrane voltage at the cellular level (Vm-ALT) may be caused by incomplete recovery (from deactivation or inactivation) on alternating beats of one or more ionic currents that govern repolarization [8, 29, 36–38]. The membrane ionic and intracellular processes that control the extent of APD shortening following a premature stimulus or change in heart rate are collectively referred to as APD restitution [31, 39–41]. The "restitution hypothesis" stated that Vm-ALT occurs when the slope of the APD restitution curve is >1, which has been taken as evidence that sarcolemmal, rather than calcium cycling or other cellular mechanisms, determine Vm-ALT [42–46]. However, although a variety of sarcolemmal currents can exhibit alternating-type activity, few have been definitively shown to be mechanistically responsible for producing Vm-ALT [47]. Moreover, although the "restitution hypothesis" for cellular alternans has been primarily demonstrated in modeling studies, it has not been well supported experimentally [27, 48].

There is convincing data for a primary role of sarcoplasmic reticulum (SR) calcium (Ca) cycling in the mechanism of Vm-ALT [7, 32, 49–50]. Inhibiting calcium cycling by blocking the ryanodine receptor (RyR), I_{Ca}, or by depleting SR calcium stores with caffeine, eradicates Vm-ALT [52, 56, 57]. However, because of the inter-dependence of membrane voltage (Vm) and intracellular Ca, which are under tight regulatory control, sorting out the mechanistic relationship between beat-to-beat alternations in Ca cycling vs. cellular ionic currents in the development of cellular Vm-ALT presents a difficult "chicken and egg" problem. Vm-ALT can cause alternans of the Ca transient (Ca-ALT) by several mechanisms [58, 59] and conversely, Ca-ALT can cause Vm-ALT [60, 61]. However, the seminal observations of Chudin et al. [62] that beat-to-beat alternation of Ca transient amplitude is similarly induced under current-clamp (where Vm-ALT occurs) and voltage-clamp (i.e. where Vm-ALT is prevented) conditions proved that Ca-ALT, is not dependent on Vm-ALT, and strongly supported the notion that cellular alternans arises from SR Ca cycling.

Dual voltage-calcium imaging was used to generate an independent line of evidence supporting a primary role of calcium cycling rather than APD restitution in the mechanism of Vm-ALT [27]. The guinea pig model of TWA includes an epicardial gradient of APD restitution, thus providing an opportunity to determine if myocytes with steepest restitution slope are most susceptible to Vm-ALT. To the contrary, when compared to Vm-ALT resistant myocytes, Vm-ALT susceptible myocytes failed to exhibit steep restitution or prolonged APD [27]. Instead, Vm-ALT susceptible myocytes had the slowest time constant for diastolic calcium reuptake, and greatest propensity for rate-dependent cytosolic calcium accumulation, strongly suggesting that calcium cycling, rather than restitution properties, dictates Vm-ALT [27]. Similar finding were observed in isolated ventricular myocytes [48].

According to the aforementioned discussion, it is generally believed that Ca-ALT occurs when heart rate exceeds the capabilities of Ca cycling machinery to maintain Ca homeostasis on a beat-to-beat basis. The subcellular mechanisms of Ca-ALT, and therefore Vm-ALT, have been experimentally explored in intact heart preparations, where it has been demonstrated that Vm-ALT susceptible myocytes express significantly less SERCA2a (a protein responsible for SR Ca reuptake) [63, 64] and RyR (the protein largely responsible for SR calcium release) [63] compared to Vm-ALT resistant myocytes, suggesting a molecular basis for cellular alternans [63]. Experiments performed in normal myocytes subjected to pharmacological inhibition of either RyR or SERCA2a have also demonstrated, at least conceptually, that dysfunction of either of these key Ca cycling proteins can cause Ca-ALT [63, 65, 66]. These findings support the contention that Ca cycling proteins in general, and two general properties of SR calcium handling, calcium release and reuptake, are directly implicated in the mechanism of calcium cycling alternans. We recently demonstrated a direct causal relationship between SERCA2a and susceptibility to Ca and Vm-ALT [67].

In experimental and clinical HF, increased susceptibility to Ca-ALT is also attributable to impaired Ca cycling, and specifically impaired Ca reuptake, underscoring the potential clinical utility of targeting Ca cycling proteins as a novel antiarrhythmic therapy in disease, which is discussed in "MTWA as Therapeutic Target" of this chapter [68, 69].

Although it is now well established that impaired Ca reuptake via SERCA2a is a mechanism for Ca alternans, the subcellular mechanisms responsible for Ca alternans are clearly complex and multifactorial. Recently, it was demonstrated that Ca-ALT occurs under conditions in which there is a steep relationship between SR Ca load and SR Ca release [65]. Although this implies that SR Ca content will also alternate on a beat-to-beat basis, this condition is sufficient, but not required for alternans, as experimentally, Ca-ALT has been observed during constant SR load, due to refractory properties of the RyR [70]. Regardless of the specific underlying mechanisms at play under different experimental or clinical conditions, a consistent observation is that one or more HR-dependent aspects of Ca cycling are responsible for Ca-ALT, providing a pathophysiological basis for the clinical requirement of HR elevation in MTWA testing.

So what are the mechanisms for generating beat-to-beat alternans of membrane repolarization in response to alternans of Ca transients? This is a critical question because Vm-ALT produces T wave alternans and cardiac arrhythmogenesis. Two likely electrogenic sarcolemmal currents that are sensitive to cytosolic Ca, and therefore can alternate Vm during Ca-ALT, are $I_{Ca,L}$ and NCX. During alternans, alternating large/small Ca releases will prolong/shorten APD, respectively, when forward mode NCX is the predominant electrogenic mechanism. This is sometimes referred to as "electro-mechanically concordant" or "positively coupled" Ca to Vm alternans [60, 61]. Conversely, when $I_{Ca,L}$ is the predominant electrogenic current, large/small Ca releases will shorten/lengthen APD, respectively, by Ca-dependent inactivation of $I_{Ca,L}$. This will produce "electro-mechanically discordant" or "negatively coupled" alternans [60, 61]. Positive Ca to Vm coupling during alternans is almost uniformly observed under normal conditions; however, dissociated or negative Ca to Vm coupling has been observed in disease models, specifically in ischemia, suggesting when it occurs, it is pathophysiological [66, 71].

Mechanism Linking Repolarization Alternans to the Genesis of Arrhythmias

Mechanism of Discordant Alternans Between Cells

The development of spatially discordant alternans (i.e. Vm-ALT occurring with opposite phase between neighboring cells), is key to the link between cellular alternans and cardiac arrhythmogenesis. When Vm-ALT is initiated, it occurs with identical phase (APD either prolongs or shortens simultaneously) in all cells of a particular region of ventricular myocardium (i.e. concordant alternans, Fig. 10.1, panel b, left). However, as illustrated in Fig. 10.1 (panel b, right) after a premature impulse (*)

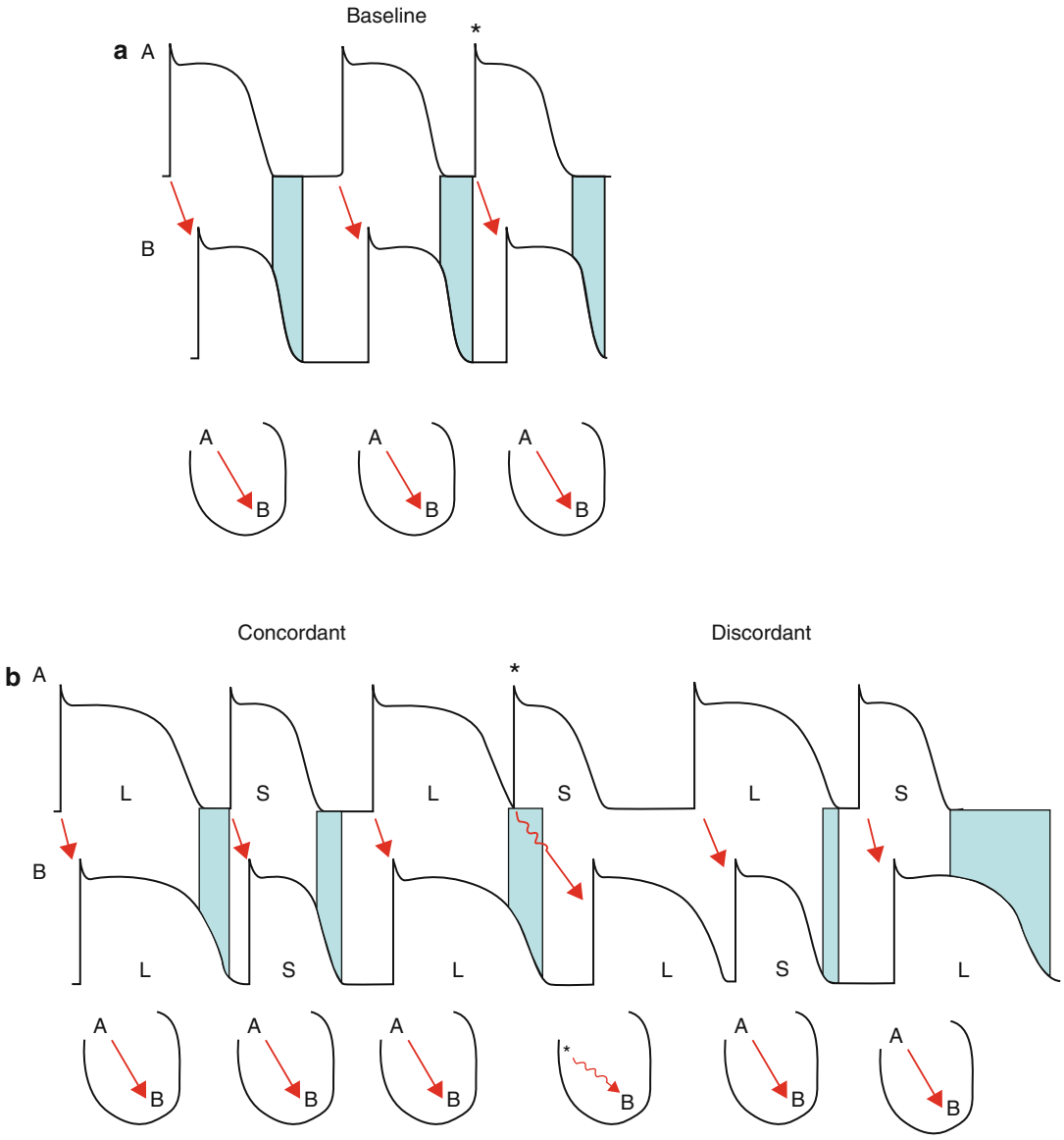

Figure 10–1. Mechanisms of discordant alternans and ventricular fibrillation (*VF*) induced by discordant alternans. Action potential propagation between two ventricular sites, *A* and *B* is shown. Upper panels show action potentials at each site, bottom schematic shows line of propagation between sites. Blue bar represents dispersion of repolarization (*DOR*) between these sites. **Panel a**, Baseline. At slower heart rates where no alternans is present, a premature beat (*) will propagate between site *A* to site *B* with normal conduction velocity, when DOR (shown by *blue bar*) is normal, as the premature beat propagates into fully repolarized myocardium. **Panel b**. During faster heart rates, concordant alternans occurs (*left*). Now, a properly timed premature beat (*) will propagate slowly into partially repolarized myocardium (i.e. in the wake of DOR, *blue bar*). The conduction slowing prolongs the diastolic interval between the next beat in the downstream myocardium (at site *B*). Due to APD restitution, downstream action potentials will prolong, causing a switch in phase of APD relative to the upstream (site *A*) action potentials. This produces discordant alternans (*right*). L indicates a long APD, while S indicates a short APD. **Panel c**. During discordant alternans, marked spatial DOR (*large blue bars*) occurs. Now, when an impulse (*) propagates (from site *A*) into still depolarized myocardium (i.e. in the wake of enhanced DOR after the long beat, blue bar in site *B*), conduction block, initiating reentrant excitation can occur (*VF*). A detailed explanation of these mechanisms is presented in the text

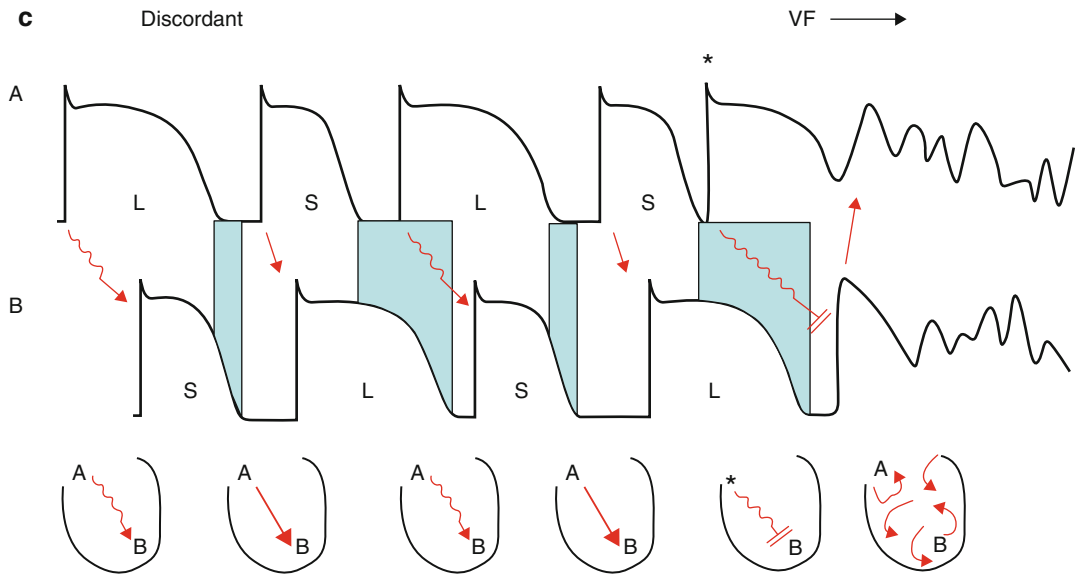

Figure 10–1. (continued)

or change in pacing rate above a critical heart rate threshold, Vm-ALT switches phase in some cells (site B) but not others (site A), such that some cells undergo a prolongation of APD while other populations of cells undergo APD shortening on the same beat (i.e. Discordant alternans) [24, 25]. Although it is unclear why neighboring cells under apparently identical conditions would respond differently with respect to their alternans phase, two fundamental mechanisms for discordant alternans have been proposed: (1) Discordance arises based on intrinsic differences in calcium cycling and/or repolarization properties between cells [24]. However, experimental evidence for this phenomenon is limited [72] and (2) Computer simulations of homogenous tissue predict that conduction velocity restitution alone, or interacting with spatial heterogeneities of repolarization, can potentially explain discordant alternans [42, 73, 74].

The fact that a properly timed premature stimulus applied during cellular alternans changes the magnitude or phase of APD alternans, implicates restitution as a possible mechanism in discordant alternans. In addition, as kinetics of APD restitution are heterogeneous between myocytes located in different regions of ventricle, one would postulate that a properly timed premature stimulus may change the phase of APD alternans in some regions but not others; which is, by definition a requirement for discordant alternans [29, 36]. A mechanism of discordant alternans based on conduction/repolarization dynamics has been proposed [60]. As demonstrated in Fig. 10.1 (panel a), at slower heart rates where no alternans is present, a premature beat (*) will propagate between ventricular sites (site A to site B) with normal conduction velocity, when dispersion of repolarization (blue bar) is normal and the premature beat propagates into fully repolarized myocardium. However, as shown in Fig. 10.1, panel b, during concordant alternans, a properly timed premature beat (or abrupt increase in heart rate) will propagate slowly into partially repolarized myocardium (i.e. in the wake of enhanced dispersion of repolarization, blue bar). The conduction slowing prolongs the diastolic interval between the next beats in the downstream myocardium (at site B). Due to APD restitution, downstream action potentials will prolong, causing a switch in phase of APD relative to the upstream (site A) action potentials. This produces discordant alternans.

Recent computer modeling studies have suggested an alternative mechanism for discordant alternans [45]. According to these simulations,

although discordant alternans can arise, as suggested above, if sufficient heterogeneities of APD restitution are present in myocardium, discordant alternans is also produced even in the absence of spatial heterogeneity of APD restitution, provided that significant restitution of conduction velocity was present [45]. Conduction velocity restitution arises because conduction slows progressively as the coupling interval of a premature stimulus is progressively shortening. In computer simulations, if a tightly coupled premature stimulus causes marked conduction slowing (for example, Fig. 10.1, panel b, premature beat *), a spatial heterogeneity of diastolic intervals is introduced such that each cell is operating on a different point of its APD restitution curve. Under these circumstances, discordant alternans can arise because the premature stimulus changes the phase of some cells but not others, depending on where on the APD restitution curve the premature impulse arrives.

However, it remains unclear how to extrapolate modeling findings to the intact heart, which, unlike computer models, is not homogeneous and is comprised of considerable electrophysiological and structural complexities. Moreover, in contrast to these simulations, experimental studies suggest that in normal myocardium, conduction velocity restitution is minimal relative to APD restitution, because premature stimulus-induced conduction slowing leads to block or fails to capture myocardium before substantial conduction velocity slowing occurs [24, 74]. In experimental studies, the pattern of discordant alternans is also independent of pacing site, further supporting the role of APD gradients rather than conduction restitution in the mechanism of discordant alternans. Clearly, as illustrated in Fig. 10.1, mechanisms of discordant alternans involving conduction velocity restitution and APD heterogeneities are not mutually exclusive. It is possible that heterogeneity of APD restitution between myocytes play a critical role in discordant alternans, but under circumstances when conduction velocity is slowed (e.g. by myocardial disease or drugs), conduction velocity restitution may play an additive role. For example, flecainide can evoke local activation sequence alternans [75] or ST segment alternans [76] that precedes VF. In addition, as heterogeneities of cellular calcium cycling in myocytes can explain spatial differences in susceptibility to Vm-ALT, these same heterogeneities could also explain development of discordant alternans. Moreover, it is quite likely that spatial heterogeneities of repolarization and calcium cycling are inter-related [53]. The recent observation of subcellular discordant Ca-ALT, in which subcellular heterogeneities in Ca cycling properties result in Ca-ALT occurring in opposite phase within an individual myocytes supports the concept that myocyte properties could determine the spatial organization of alternans responsible for discordant alternans. However, how subcellular alternans translates into spatial heterogeneities in cellular alternans at the tissue level remains poorly understood [77].

An additional mechanism contributing to susceptibility to discordant alternans has been related to intracellular uncoupling [25]. Cardiac myocytes are connected via gap junctions that allow the flow of ionic current between cells. In general, electrotonic coupling between cells acts to homogenize repolarization. In contrast, cell-to-cell uncoupling tends to unmask intrinsic differences in cellular electrophysiological properties [78]. Cell-to-cell uncoupling will have an important effect on spatial heterogeneity of repolarization [79] and any tendency for neighboring myocytes to alternate with opposite phase because of differences in APD restitution will be opposed by electrotonic coupling between these regions. In a guinea pig model of alternans, introduction of a structural barrier to electrotonically uncouple neighboring cells greatly facilitated the development of discordant alternans [25]. In parallel, disease or drug-induced uncoupling between cells may promote discordant alternans.

Discordant Alternans Is a Mechanism of Arrhythmogenesis

Mechanisms linking cellular alternans to reentrant arrhythmogenesis have been described [24]. The transformation from concordant alternans to discordant alternans (Fig. 10.1, panel b) has significant consequences on the spatial organization of repolarization across the ventricle.

As shown in Fig. 10.1 (panel b, right), during discordant alternans, marked spatial dispersion of repolarization emerges (blue bars). Discordant alternans also produces a substrate by which conduction block and reentrant excitation can be easily initiated by a premature stimulus (Fig. 10.1, panel c). When an impulse (*) propagates (from site A) into still depolarized myocardium (i.e. in the wake of enhanced dispersion of repolarization after the long beat, blue bar in site B), conduction block, initiating reentrant excitation can occur (Fig. 10.1, Panel c, VF). Consequently, discordant alternans is key to the mechanism linking MTWA to cardiac arrhythmogenesis, and in fact in experimental models of alternans discordant alternans precedes VF. The same paradigm was used to explain the initiation of a variety of arrhythmias including polymorphic and monomorphic VT, as the resultant arrhythmias were determined by structural discontinuities in the tissue, but in each case discordant alternans was required to initiate reentry [25]. Therefore, discordant alternans amplifies physiological heterogeneities of repolarization present at baseline into pathophysiological heterogeneities of sufficient magnitude to produce conduction block and reentrant excitation [24–26]. Recently, using intracardiac electrograms or monophasic action potential measurements, increased susceptibility to intracardiac alternans and importantly discordant alternans has been observed in patients with cardiomyopathy, which not only correlates with surface MTWA measurements, but have been linked to arrhythmia susceptibility [69, 81]. These observations not only provide clinical confirmation of discordant alternans as a potential mechanism of arrhythmias in patients, as has been demonstrated experimentally, but also suggest that intracardiac alternans detected using implantable devices [82] may be a potential strategy to warn patients from and prevent SCD.

Measurement of MTWA in Patients

The measurement of MTWA is based on the principle that the magnitude of MTWA increases with increasing heart rate. In a given subject, MTWA develops at a specific heart rate and is usually reproducible and sustained above that heart rate threshold [22]. In patients with cardiac electrical instability, MTWA develops at slower heart rates than normal subjects. Thus the heart rate at which MTWA appears is an important determinant of whether a test is positive or negative [80, 83].

The test involves an ECG recording made during rest, exercise, and recovery. MTWA is a low frequency, low amplitude signal; therefore, noise reduction is paramount. Multicontact, three-dimensional, noise-reducing electrodes attenuate myopotentials, and mild skin abrasion ensures reduced impedance at the skin-electrode interface. The exercise portion of the test should produce a gradual and controlled heart rate elevation, particularly in the range of 100–110 bpm [83]. This is important because MTWA that develops above 110 bpm is not considered clinically significant. Since the MTWA test is heart rate dependent rather than workload dependent, it can be a sub-maximal stress test, and manual control of the treadmill to achieve the required heart rate may be the best "exercise protocol". The modified Bruce or Naughton exercise protocols may also be used depending on the subject's functional capacity and a bicycle exercise protocol has been described [22]. In general, a subject should exercise with a goal to achieve a heart rate of at least 120 bpm. Detailed descriptions of MTWA measurement and the techniques used for noise reduction have been published [84].

Interpretation of MTWA Tests

Sustained alternans is defined as MTWA that is >1.9 μV, lasts longer than a minute and persists above a patient specific heart rate threshold. Comprehensive rules and criteria for interpretation have been published [85]. If sustained MTWA is present and the onset heart rate (OHR) is ≤110 bpm, the test is positive. If sustained alternans is absent, or if it develops above the 110 bpm threshold, and the test is clearly negative at a heart rate ≥105 bpm, the test is negative. Finally, if the patient can't reach a heart rate of 105 bpm, or if there is a "gap" in the ability to interpret the test during the critical heart rate

period (100–110 bpm) the test is considered indeterminate. An example of the latter scenario would be a test where MTWA develops at a heart rate >110 bpm, but frequent PVCs or noise obscure the test such that one can be sure the test were negative only up to a heart rate of 90 bpm.

TheAlternansBeforeCardioverter-Defibrillator (ABCD) trial enhanced these criteria to improve reproducible interpretation of MTWA test [85]. These enhancements include interpreting a test as positive if MTWA is present during a predominant portion of the test; interpreting the test as negative no matter how dense the ventricular ectopy if there is greater than one minute of artifact free time at heart rates >105 bpm: and interpreting the test as indeterminate if there is no MTWA at heart rates >110 bpm, but noise or PVCs obscure interpretation in the critical heart rate range of 100–110 bpm.

Most studies have grouped indeterminate tests, which occur in 20–30 % of cases [86], with positive tests into an "abnormal" group, as indeterminate tests are at least as predictive of poor cardiovascular outcomes as positive ones [87–90]. In a meta-analysis on the utility of MTWA [91], 8 of 19 studies included indeterminate results in the outcome analysis; Sensitivity testing did not reveal any difference in the overall utility of MTWA whether the indeterminate tests were included as abnormal or excluded from the analysis. Finally, MTWA is currently a qualitative test. However, there is some data suggesting that the magnitude of the alternans voltage [92], and the onset heart rate [93] of MTWA may have additive value in predicting adverse cardiovascular events.

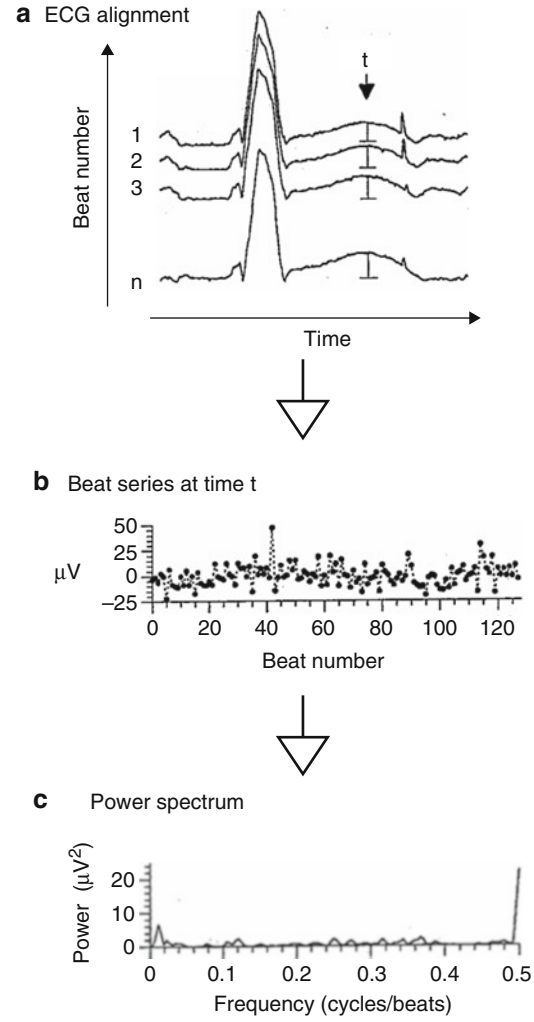

Figure 10–2. Algorithm used to measure microvolt-level electrical alternans from the surface ECG. (**a**) Sequentially recorded ECG complexes are aligned about their QRS complexes using cross correlation. Beat-to-beat fluctuations of ECG amplitude are measured separately for each point of the ECG. In this example, a point of the ECG located at a time, t, is evaluated for electrical alternans. (**b**) Beat-to-beat fluctuations in the amplitude of the point t are represented as a beat series. (**c**) The power spectrum is calculated from the fast Fourier transform of the beat series shown in panel **b** (From Poelzing and Rosenbaum [79]. Reprinted with permission from The American Physiological Society)

Signal Processing for Detection of MTWA

The spectral analysis or frequency domain method [20] for measuring MTWA is based on the concept that MTWA occurs at a specific frequency of 0.5 cycles/beat (every other beat). Using spectral analysis, changes in the T wave that occur at the alternans frequency can be easily detected and separated from changes that occur at other frequencies which are regarded as noise.

The algorithm for the spectral analysis method of measuring MTWA has been described in detail [79] and is illustrated in Fig. 10.2. First, a 128 beat sequence of QRS complexes is selected for analysis and the QRS complexes are aligned such that each point on the T wave corresponds to the same point on all the subsequent T waves (Fig. 10.2,

Panel a). A point is then selected on the T wave (t), and the voltage is measured for that point on each T wave. The voltage for that selected point in each beat forms a beat series (Fig. 10.2, Panel b). A power spectrum for all the frequencies of alteration for that point is then created using the Fast Fourier Transform. The same process is repeated for all the points on the T wave and the spectra are averaged.

MTWA, which is usually not evident on examination of the beat series, becomes evident on spectral analysis as a peak in voltage fluctuation occurring at the 0.5 cycles/beat frequency (Fig. 10.2, panel c). Voltage fluctuations at other frequencies are due to other sources such as respiration, movement, myopotentials or baseline drift of the ECG signal. The noise level is measured from frequencies adjacent to the MTWA frequency (0.45–0.49 cycles/beat), the designated noise band. The alternans power (measured in μV^2) is the difference between the power at the alternans frequency (0.5 cycles/beat) and the power at the noise frequency band. The alternans voltage or Valt (measured in μV) is the square root of the alternans power. An alternans voltage of >1.9 μV is considered abnormal.

An important feature of the spectral analysis method is that an estimate of the statistical significance of the MTWA measurement can be obtained, and is defined as the ratio of the alternans power to the standard deviation of the noise level in the noise band (the K score). A K score of >3 is considered significant.

Alternative methods of measuring MTWA have been suggested such as the modified moving average method [94, 95] and complex demodulation method [96]. These methods do not fully account for fluctuations outside of the alternans frequency (especially random noise) and their application to patients has not been standardized.

Clinical Utility of MTWA

Prediction of SCD

The utility of MTWA testing in predicting the risk of SCD was established in several observational studies and in different populations. Although case studies and small series describe its use in patients with long QT syndrome, arrhythmogenic right ventricular dysplasia [97], hypertrophic cardiomyopathy [98], and Brugada syndrome, these do not constitute, for now, an established area of clinical utility.

The vast majority of the data has been collected in patients with reduced left ventricular ejection fraction (LVEF), either due to coronary disease or to a non-ischemic dilated cardiomyopathy. An abnormal MTWA test is predictive of an increased risk of ventricular arrhythmias or total mortality in both patient groups [87–89, 99–101]. However, the positive predictive value (PPV) of the test is only 15–20 % at 1–2 years of follow-up. This is similar to other single risk stratifiers including LVEF and electrophysiological studies (EPS). On the other hand, the greatest strength of MTWA testing lies in its high negative predictive value (NPV), which is above 95 % in almost all studies [89, 91, 99, 102]. The ABCD trial confirmed these findings within the first year of follow-up. However, at year two, the negative predictive value decreased, suggesting a need for repeat MTWA testing as the arrhythmic substrate may change over time [86]. The reliable NPV was demonstrated in ischemic, as well as non-ischemic cardiomyopathies, a group for whom other risk stratifiers, including EPS, performed poorly. Bloomfield et al. [99] followed 549 patients with LVEF $\leq$ 40 % with both ischemic or non ischemic cardiomyopathy for an average of 20 months, and reported that patients with an abnormal MTWA test were more than five times more likely to die or have a sustained ventricular arrhythmia than patients with a negative test. A normal MTWA test had a NPV of 97.5 % for the primary endpoint of total mortality or sustained ventricular tachyarrhythmia (Fig. 10.3). Gehi et al. [91] summarized results of 19 studies and 2608 subjects in a meta-analysis. The overall NPV and PPV was 97.2 and 19.3 % respectively. The average follow-up was 21 months and indeterminate results were excluded from the analysis. Subgroup analysis from this meta-analysis showed that there was no significant difference in the NPV of different clinical subgroups. However, the PPV varied significantly depending on the patients' clinical situation. For instance, the PPV was lowest in the primary prevention of SCD for post MI patients regardless of LVEF (6 %) and highest in

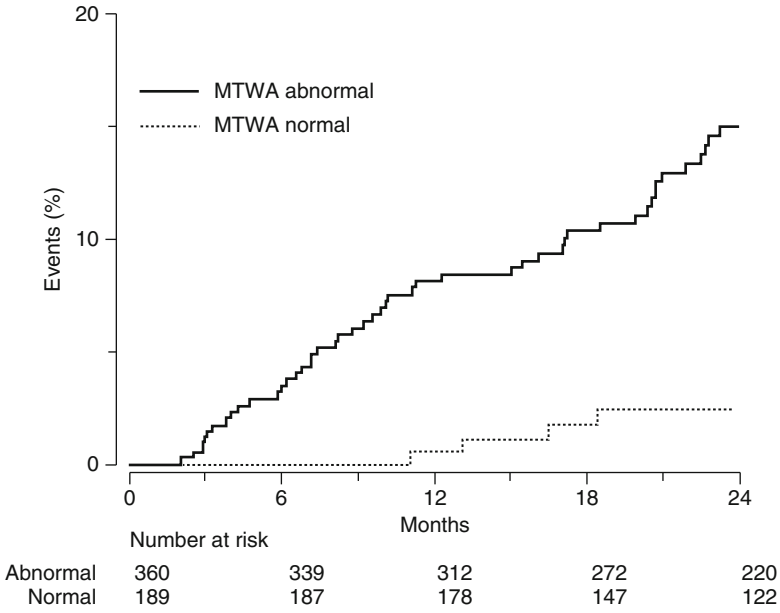

Figure 10–3. Kaplan-Meier mortality curves for patients with normal versus abnormal microvolt T-wave alternans (*MTWA*) test results. In 2 years of follow-up, only four events occurred in the 189 patients with a normal MTWA test; 47 events occurred in the group with an abnormal MTWA test. Abnormal MTWA tests comprise positive tests (n = 162, 2-year event rate 12.3 %) and indeterminate tests (n = 198, 2-year event rate 17.5 %) (From Kitamura et al. [93]. Reprinted with permission from Elsevier Limited)

patients with a history of a prior ventricular tachyarrhythmic event (51 %). This is not surprising, as one would expect the patients who already have experienced a tachyarrhythmic event to have the arrhythmogenic substrate that causes an abnormal MTWA. Interestingly, the PPV of patients with depressed LVEF (i.e. the CHF population that clinicians are most interested in risk stratifying for SCD) was fairly high (25.5 %), with no significant difference between ischemic and non-ischemic cardiomyopathy.

It is important to mention that not all studies confirmed MTWA to be a useful risk prediction tool. Gold et al. [103] did find a difference in mortality between patients with negative and non-negative test results. However, there was a clear separation between survival curves at 24 months, which was also the time point when ICD implantation started to offer a survival benefit in the main study. This suggests that a positive MTWA test is associated with increased mortality when SCD events become clinically prevalent. Chow et al. [104] were unable to demonstrate predictive value of MTWA testing in non-negative patients with ischemic cardiomyopathy. However, most events were ICD therapies and a recent meta-analysis showed that MTWA may have a higher predictive accuracy for non-ICD events (i.e. mortality) [105]. Ikeda et al. demonstrated a potential use of MTWA testing in post myocardial infarction patients with LVEF ≥ 40 %, a group of patients that does not meet criteria for ICD eligibility, but may be at high risk for SCD [106]. In contrast, Tapanainen et al. showed that MTWA testing performed within two weeks after myocardial infarction was not predictive of cardiovascular events, but the NPV (99 %) was preserved. The poor predictive performance of MTWA testing in this study could be explained by a high number of indeterminate tests, because of exercise limitations shortly after infarction [107].

Improvement of ICD Cost-Effectiveness

A compelling body of evidence suggests that patients who have a normal MTWA test have reasonably low risk of SCD so as to minimize benefit of ICD in such patients. Figure 10.4 shows the effects of risk stratification by LVEF alone compared to additional electrophysiologic study and MTWA testing. When more stringent risk stratification beyond LVEF are applied, the proportion of patients without benefit from their ICD shows a marked decline, while the proportion of patients, who are unprotected from SCD increases only minimally. Since MTWA testing is a non-invasive and simple method of risk stratification in patients with low

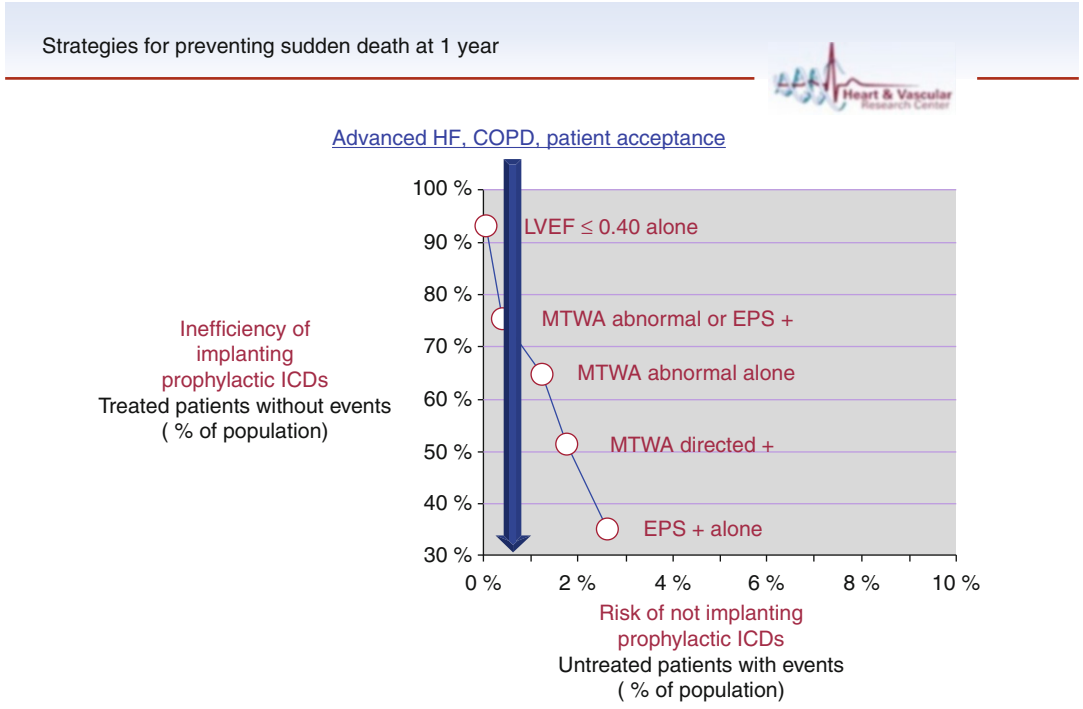

Figure 10–4. Conceptual figure showing that with addition of risk stratification tools such as LVEF, electrophysiologic study or MTWA, the number of unnecessary ICD implants decreases, while the number of unprotected patients, who would benefit from ICDs increases only marginally. With addition of co-morbidities (i.e. COPD, older age) the competing risk of dying from a non-arrhythmic event increases and therefore the number of unprotected patients without ICD is small

LVEF, it could improve cost-effectiveness of primary prevention from SCD and may protect patients from unnecessary, untoward complications from ICDs.

Sanders et al. [5] demonstrated, in a cost-effectiveness analysis of eight randomized trials of ICD placement for prevention of SCD, that ICD therapy was more cost-effective in earlier trials, in which risk stratification with an electrophysiologic study was required (i.e. MADIT-I, MUSTT) when compared to later studies (MADIT-II, ScD-HeFT), in which a low LVEF was the only risk factor. The cost effectiveness of a non-invasive MTWA-guided strategy was studied by Chan et al. [6] who studied MADIT II like patients with ischemic cardiomyopathy and LVEF ≤ 0.30. In addition to finding that MTWA is a significant independent predictor for all cause (HR of 2.24, $p < 0.002$) mortality, the authors concluded that risk stratification with MTWA testing, in addition to a low LVEF, significantly improved the cost-effectiveness of ICD implantation. In a subsequent analysis [108], the same group showed that patients with positive MTWA are one of the subgroups of patients who derive a benefit from ICD prophylaxis, while those with a negative test did not.

Comparison with Other Risk Stratification Tools

When compared to other non-invasive risk stratification tests used to predict SCD, MTWA has been shown to be superior [88, 103, 109], including signal averaged electrocardiogram (SAECG) [103, 110], baroreflex sensitivity (BRS), QT dispersion, QRS duration [111], non-sustained ventricular tachycardia on a 24-h Holter monitor, and heart rate variability. In fact, Hohnloser et al. found MTWA to be the only independent predictor of ventricular tachycardia or ventricular fibrillation in 95 patients undergoing ICD implantation for secondary prophylaxis of SCD [103]. This held true for established risk stratifiers such as LVEF and

EPS. Using MTWA as an initial screening tool and combining it in some patients with other non-invasive tests, or with EPS may improve the predictive value of MTWA alone [107, 110]. Rashba et al. [112] demonstrated, in 144 patients with ischemic cardiomyopathy referred for EPS, that MTWA was the only non-invasive independent predictor of death, ventricular tachyarrhythmic event, or appropriate ICD shocks. Interestingly, a negative EPS increased the already high NPV of MTWA further.

Limitations of the MTWA Test

Because MTWA testing requires elevating heart rate ≥105 bpm, the test is "indeterminate" in patients who cannot achieve this target heart rate, whether due to intrinsic heart disease, medication or decreased functional capacity from any cause. Interestingly, it has been suggested that heart rate elevation for MTWA testing may be accomplished using pharmacotherapy, such as dobutamine [113]. In addition, MTWA test is also "indeterminate" when frequent ectopy obscures the beat-to-beat variations in the T wave. As discussed above, patients with decreased functional capacity and frequent ventricular ectopy have inherently a higher mortality and it therefore makes sense for these MTWA tests to be considered abnormal.

In contrast, in patients with permanent atrial fibrillation, because of the heart rate irregularity, and in patients dependant on ventricular pacing, because of the profound changes in repolarization, MTWA test cannot be performed.

Effect of Medications on MTWA Testing

Despite varying effects of medications on MTWA, the test retains a significant predictive value for ventricular tachyarrhythmias [114–116]. In a study of patients with dilated cardiomyopathy given class I, III and IV antiarrhythmic medications, MTWA was shown to have a better predictive value than left ventricular ejection fraction for the occurrence of ventricular tachyarrhythmias [117].

Whether to do a MTWA test on or off beta-blockers has been a matter of controversy. Since these agents have been shown to reduce the magnitude of MTWA [114, 118–120], patients on beta-blockers may be less likely to have a positive test. Some investigators have suggested that this correlates with the ability of beta-blockers to reduce cardiovascular mortality [118–120]. Other experts feel that to assess risk more accurately, and to decrease the heart-rate indeterminate tests, the beta-blocker should be withheld prior to the test. However, MTWA has successfully predicted cardiovascular events in patients taking beta blockers [101, 109], and our current thinking is that patients should be tested on the medical therapy that they are chronically taking, in order to assess their risk of SCD accurately. The effects of class I antiarrhythmic drugs such as procainamide [121], and class III drugs, such as sotalol and amiodarone [119, 122, 123] have been studied in small numbers of patients. All drugs seem to reduce the magnitude of MTWA, but the significance of this is unclear.

Novel Application of MTWA

Intracardiac MTWA Measurements

Recently, built-in MTWA measurement algorithms of ICDs have been developed. Averaged T-wave amplitude alternations and nonalternans variability from intracardiac electrograms can be measured and were greater before ventricular tachycardia or ventricular fibrillation occurred when compared to electrograms at baseline, rapid pacing or before supraventricular tachycardia [82]. These results not only confirm previous observations [81], but also suggest that intracardiac MTWA detection could trigger an alert for patients (i.e. an alarm sound) from impending ventricular arrhythmias, and could initiate pacing therapies to prevent these.

Alternans as Therapeutic Target

As discussed in this chapter, Ca handling proteins, i.e. Ry-receptor and SERCA2a are instrumental in the genesis of cardiac alternans and likely underlie MTWA. In the failing heart decreased SERCA2a expression contributes to

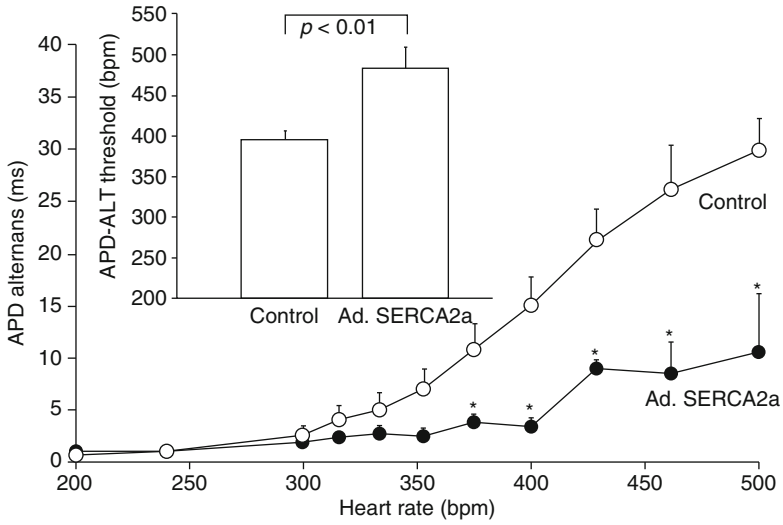

Figure 10–5. The relation between pacing heart rate and magnitude of APD-ALT in Langendorff-perfused whole guinea hearts with and without SERCA2a overexpression shows that the alternans threshold (i.e. the pacing rate at which APD-ALT occurs) is significantly higher (i.e. decreased susceptibility to TWA) after SERCA2a gene transfer (*$p \leq 0.01$). These data suggest that overexpression of SERCA2s creates resistance against electrical instability (From Cutler et al. [67]. Reprinted with permission from Wolters Kluwer Health)

poor mechanical function and vulnerability to ventricular arrhythmias. Overexpression of SERCA2a therefore may improve mechanical function, decrease cardiac alternans and stabilize the electrophysiologic substrate of SCD. We demonstrated recently, that adenoviral SERCA2a transfection in the intact heart increased sarcoplasmatic reticulum Ca reuptake and markedly attenuated Ca and Vm-ALT [67]. Importantly, MTWA threshold was altered (Fig. 10.5) and susceptibility to arrhythmias was significantly reduced. SERCA2a as a molecular target to prevent alternans-related arrhythmias has been studied clinically in the Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID), a phase 2 trial [124]. Thirty-nine patients with NYHA class III and IV symptoms and LVEF ≤ 35 % with ICDs and on stable medical therapy were randomized to one of 3 dose ranges of intracoronary-delivered adeno-associated viral vector loaded with SERCA2a gene vs. placebo. An array analysis of clinical heart failure components showed improvements in symptoms, functional class/performance and LV function, but did not show an improvement of biomarker measurements at the exploratory pre-specified alpha level of 0.2. Although this phase 2 trial provided encouraging preliminary data, a larger randomized trial with clinical outcomes such as death and worsening of heart failure/rehospitalizations is warranted.

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11
Heart Rate Variability: Measurements and Risk Stratification

Yi Gang

Abstract

Heart rate variability (HRV) describes the temporal variation in the intervals between consecutive heart beats in sinus rhythm. HRV assesses cardiac autonomic tone at the level of the sinus node and has been used as a measure of cardiac autonomic modulation.

Depressed HRV has become an established risk stratifier for arrhythmic events and mortality in post myocardial infarction (MI) population. In patients with chronic heart failure HRV assessment is of important prognostic value; reduced HRV identifies patients at significantly increased risk of cardiac mortality. The association of low HRV with susceptibility to life-threatening tachyarrhythmias has been confirmed by most published studies. Reduced HRV alone has only moderate sensitivity and specificity while HRV in combination with other cardiac autonomic tests can identify cardiac patients at particularly high risk of mortality, and improve the predictive power.

Conventional HRV studies use time- and frequency-domain analysis techniques. Increasing evidence suggests that nonlinear method may have significant prognostic power for stratifying patients at high risk of sudden cardiac death. Capturing electrocardiographic data from implantable cardiac devices has facilitated HRV research. Newer techniques testing cardiac autonomic status by evaluating dynamic heart rate behaviour are more promising for risk stratification.

It is clear that HRV assessment is a useful research tool for documenting alterations in autonomic modulation in relation to arrhythmic events and providing prognostic information in patients with various cardiac disorders. The specificity and predictive accuracy of altered HRV in predicting imminent or future fatal arrhythmic events are still low for clinical risk assessment. More research works are needed to identify the optimal and practical approach of HRV assessment for its clinical usefulness.

Keywords

Heart rate variability • Autonomic modulation • Autonomic function • Time-domain analysis • Frequency-domain analysis • Nonlinear method • Risk stratification • Sudden death

Y. Gang, MD, PhD
Division of Clinical Sciences,
Cardiovascular Sciences Research Centre,
St. George's, University of London,
Cranmer Terrace, London, SW17 0RE, UK
e-mail: y.gang@sgul.ac.uk

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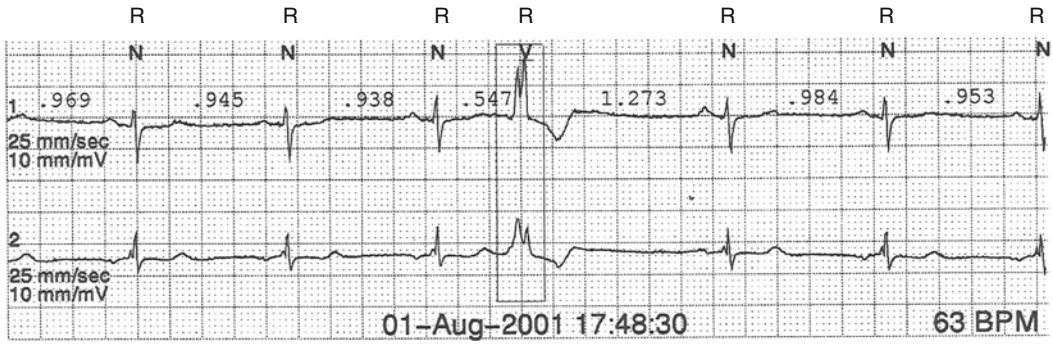

Figure 11–1. A strip of a 24-h Holter ECG recording obtained from a patient with a history of myocardial infarction, showing the N–N/R–R intervals. The individual N–N intervals were automatically measured (in second) and labelled, that are the basis for analysis of heart rate variability (HRV). The ECG strip also shows a single ventricular ectopic beat, which should not be included into the HRV calculation

Introduction

Heart rate variability (HRV) describes the temporal variation in the intervals between consecutive heart beats in sinus rhythm. It is the intervals between consecutive beats that are being analysed rather than the heart rate per se (Fig. 11.1). HRV assesses cardiac autonomic tone at the level of the sinus node and has been used as a measure of cardiac autonomic modulation. The components of HRV provide measurement of the degree of autonomic modulations rather than the level of autonomic tone [1]. Not much attention was paid to early HRV investigations until late 1980s. Kleiger et al. reported in 1987 that reduced HRV predicted increased mortality after acute myocardial infarction (MI) [2]. This report had a significant impact on clinical research of HRV. Since then HRV has been widely explored for the purpose of risk stratification [3–7]. This chapter will focus on the application of HRV to risk stratification in adult patients with cardiac disorders, in particular on the relation of HRV to sudden cardiac death (SCD).

Methodology and Indices of HRV Measurement

Despite the efforts of the Task Force of the North American Society of Pacing and Electrophysiology and the European Society of Cardiology to unify and standardise the methodology for HRV measurements, there has been no consensus so far for the best method and/or index of HRV for clinical use in different settings. Conventional methods for quantifying HRV have been categorised as time-domain, frequency-(spectral) domain, geometric and nonlinear analysis [8], which emerged later but has drawn more attention in recent years. Heart rate turbulence (HRT) [9] and heart rate deceleration capacity (HRDC) [10] can also be considered under the wide umbrella of HRV.

Conventionally, HRV analysis has been performed on the 24-h Holter monitoring ECGs or short-term (usually 5–20 min) ECG recordings at rest or during manoeuvre. Taking advantage of the storage function of implantable cardiac defibrillator (ICD) it has recently become possible to evaluate HRV on heart rate recordings retrieved from ICD memory, particularly HRV patterns can be evaluated on specific time windows before the onset of ventricular tachyarrhythmias and under control conditions [11]. Furthermore, Long-term continuous HRV can be analysed from an implanted cardiac resynchronization device [12]. Recommended by the Committee [8] in 1996, two type of recordings should be used whenever possible: (a) short-term recordings of 5 min made under physiological stable conditions processed by frequency-domain methods and/or (b) nominal 24-h recordings processed by time-domain methods. Though time-domain HRV analysis was attempted on 10-s ECGs [13], long-term ECG recordings analysed by the time-domain methods should contain at least 18 h of analysable ECG data that include the whole night to obtain reliable results [8]. It is essential to perform

visual check and manual corrections of individual RR intervals and QRS complex classifications for statistical time-domain or frequency-domain methods [8].

Time-Domain Analysis

In time-domain analysis, the intervals between consecutive normal-to-normal beats are measured over a purposely pre-defined time period of ECG recordings. A set of statistic indices can be calculated from the intervals directly or indirectly:

Statistical Methods [8]

1. *SDNN* is the standard deviation of all normal-to-normal (NN) intervals. It is the simplest variable to calculate and most commonly used HRV index. Though it can be obtained from ECG recordings of 5 min to 24 h, its measurement depends on the length of recording period. Thus it is inappropriate to compare SDNN measures derived from recordings of different length [8]. SDNN reflects all the cyclic components responsible for variability in the period of recording and estimates overall HRV.
2. *SDANN* is the standard deviation of the 5-min average NN intervals. It is less affected by editing error or arrhythmias compared with SDNN, thus providing a 'smoothed out' version of SDNN and an estimate of long-term fluctuation of heart rate.

   Similarly, *SDAAM* was developed as the standard deviation of the 5-min median atrial-to-atrial depolarisation intervals derived from implanted cardiac electronic devices [12].
3. *SDNN index* is the mean of the 5-min standard deviation of NN intervals calculated over 24 h. SDNN index reflects the average of variability in NN intervals that occur within 5-min period.
4. *NN50* and *pNN50*. NN50 is the absolute count of differences between successive NN intervals >50 ms, while pNN50 is the proportion of differences >50 ms in the total number of NN intervals. Both NN50 and pNN50 are measures of short-term variation, estimating high-frequency variation in heart rate.
5. *RMSSD* is the root mean square of successive differences between adjacent NN intervals. RMSSD is a measure of short-term variation and estimates high-frequency variation in heart rate. It has been demonstrated to have better statistical properties compared to *pNN50*.

Geometric Methods

This method calculates the sample density distribution of NN interval durations or sample density distribution of differences between adjacent NN intervals, such as HRV triangular index (HRVi) [3], TINN, and Lorenz plot of NN intervals. HRVi is the integral of the density distribution (the number of all NN interval) divided by the maximum of the density distribution. It has been well accepted as a powerful risk stratifier in post MI. HRVi is dependent on the length of the bin, more influenced by the lower than the higher frequencies. Its major advantage lies in their relative insensitivity to the analytical quality of the series of NN intervals [8, 14, 15]; while major disadvantage is the need for a reasonable number of NN intervals to construct the geometric pattern, at least 20-min recording is required, preferable 24 h. HRVi expresses overall HRV measured over 24 h and strongly correlated with SDNN, if they are derived from long-term recordings of adequate quality.

Of various time-domain HRV variables, SDNN, SDANN, RMSSD and HRVi were recommended by the Task Force Committee in 1996 [8].

Frequency-Domain Analysis

Of various spectral methods, most commonly used methods to transform signals into the frequency-domain are based on fast Fourier transform (FFT) and autoregressive analysis to calculate power spectral density (PSD; ms^2/Hz), which provides basic information of how power (variance) distributes as a function of frequency. Simplicity of algorithm and high processing speed are the main advantage of FFT while autoregressive analysis is superior for its

smoother spectral components, easy post processing of the spectrum, and accurate estimation of PSD. Its disadvantage is the need of verification of the suitability of the chosen model and its complexity. Both of these mathematic methods yield similar results [8].

Spectral Components

From short-term recordings, three spectral components can be distinguished in the calculated spectrum, which included high frequency (HF), low frequency (LF) and very low frequency (VLF) components. From spectral analysis performed on long-term recordings, an additional spectral component, ultra low frequency (ULF), may be distinguished. In addition, total power and LF/HF ratio are commonly calculated from the spectral results of both short-term and long-term recordings. The spectrum can be divided into three or four bands, usually in the following frequency ranges: ULF ≤0.003 Hz, VLF 0.003–0.04 Hz (≤0.04 Hz if calculated from short-term recording), LF 0.04–0.15 Hz, HF 0.15–0.4 Hz.

For an accurate spectral analysis of HRV, mechanisms modulating the heart rate should not change during the ECG recording time, however, it cannot be considered stationary during the 24-h period for the physiological mechanism of heart rate modulations responsible for LF and HF power components. Thus it is recommended to use short-term recordings free of ectopy, missing data and noise for frequency-domain analysis. It should always be strictly distinguished whether the spectral analysis is performed on short-term or long-term ECGs, and normalised units should always be quoted with absolute values of the LF and HF power in order to describe completely the distribution of power in spectral components [8].

HRV represents the most promising quantitative markers of autonomic activity. Although the physiologic basis of HRV components cannot be simplified as it has been frequently described, it is commonly accepted that HF component reflects the efferent vagal activity; LF component is affected by both sympathetic and parasympathetic activities, while the LF/HF ratio is often used as a proxy for the sympatho-vagal balance. The physiologic basis for ULF and VLF is rather less clear than HF and LF components. Analysis of transient physiological phenomena by specific methods remains a challenging research topic.

Reference Values

There have been so far no well accepted 'normal values' of HRV measures available for use in various clinical settings. As no recent report is found concerning the reference values of all HRV indices in large normal populations, Table 11.1 lists the reference values of standard time-domain and frequency-domain measures of HRV reported in 1995 by Bigger et al. [16].

Nonlinear Methods

The nonlinear methods differ from traditional HRV analysis because they are not designed to assess the magnitude of variability but rather quality, scaling, complexity and correlation properties of the signal. Several algorithms have been developed to describe nonlinear characteristics

Table 11.1 Reference values of traditional measures of heart rate variability in healthy subjects aged 40–69 years [16]

Variable	Unit	Normal value (mean ± SD)	Variable	Unit	Normal value (mean ± SD)
Time domain analysis of nominal 24 h			Spectral analysis of stationary supine 5-min recording		
SDNN	ms	141 ± 39	Total power	ms^2	3,466 ± 1,018
SDANN	ms	127 ± 35	LF	ms^2	1,170 ± 416
RMSSD	ms	27 ± 12	HF	ms^2	975 ± 203
HRV triangular index		37 ± 15	LF	nu	54 ± 4
			HF	nu	29 ± 3
			LF/HF ratio		1.5–2.0

HF high frequency power, *HRV* heart rate variability, *LF* low frequency power, *nu* normalised unit, *RMSSD* the root-mean-square of successive differences between adjacent normal to normal intervals, *SD* standard deviation, *SDANN* the standard deviation of the 5-min average normal to normal intervals, *SDNN* the standard deviation of all normal to normal intervals

of HRV signals [17–22]. Commonly processed indices of nonlinear methods include the exponent β (beta) of 1/f slope for long-term analysis, the scaling exponent α (alpha) for short-term recordings, which provide measures of presence or absence of fractal correlation properties of RR intervals at different time scales and reflect the complexity of heart rate behaviour. Power-law slope [23, 24], approximate entropy (ApEn) [20], detrended fluctuation analysis [18], and poincare plots [20, 25] are of other nonlinear measures of HRV often being used in clinical studies. There has been great progress in the nonlinear method over last decade and a variety of nonlinear variables reflecting different aspect of HRV have been investigated in patient populations [19, 20, 22, 24, 26, 27]. An increasing number of studies have been reported regarding its value in risk stratification [24, 28], particularly in identifying patients at risk of SCD [22, 29]. However, the computing programs for nonlinear analysis are currently not available on commercial systems. Indices of exponent α (alpha) or β (beta) do not have correspondence to conventional time- or frequency-domain parameters from ambulatory Holter recordings. The optimum nonlinear measures remain to be determined. The standard measures and consented reference values are also lacking.

Other Techniques for Analysing Behaviour of Heart Rate

Of a variety of analytical techniques used for evaluating behaviour of heart rate, HRT and HRDC are developed in recent years and are most promising in risk stratification. HRT describes the phenomenon of short-term fluctuations in sinus cycle length after a single ventricular premature complex (VPC). It characterises the fluctuations by two numerical parameters, i.e. turbulence onset (TO) and turbulence slope (TS) [9]. TO describes an early acceleration phase of the heart rate after ventricular ectopic beats; TS characterises a late deceleration phase. HRDC is proposed as deceleration-related heart rate variability quantifying the characterisations of cardiac vagal modulations [10]. Other reported techniques include wavelet transform-based approaches [30, 31], prevalent low-frequency oscillation [32], and other more complicated model [33].

None of the HRV analysis methods has been established for clinical application. More practical approach is needed so that the benefit of HRV assessment in risk stratification can be translated into clinical practice.

Stability and Reproducibility of HRV Measurements

Early studies suggested great stability of HRV measures derived from 24-h ambulatory monitoring in normal subjects [34, 35], and in cardiac patients over short period of time [36, 37]. In general population, reductions in HRV was found in men whereas increases in HRV in women over 5-year follow-up period as observed in participants of the Whitehall II Cohort Study [38]. In normal older subjects, HRV measures remained stable over 12 months if their activity level was not changed [39]. Persistently high HRV in the elderly may represent a predictor of longevity [40].

Later studies noted the evolution of HRV after acute MI. Ortak et al. found that HRV increased significantly over 12-month period. Their study included 100 consecutive patients; HRV was prospectively evaluated at about 10 days and 12 months after MI [41]. Consistent findings were reported by Jokinen et al. that conventional measurements of HRV improved significantly between 5 and 7 days and 12 months after MI [42]. Previous studies were conducted over varied time period; subjects were investigated at different settings. Data regarding the stability and reproducibility of HRV measures, particularly of new HRV measures, remain limited.

Effect of Intervention and Other Factors on HRV

Numerous clinical studies have demonstrated the beneficial effect of beta-blockers on HRV [43–50]. The Beta-blocker Heart Attack Trial (BHAT) revealed that 6-week propranolol

therapy improved HF power and blunted the morning increase in the LF/HF ratio in 88 patients with acute MI but no change in placebo groups (n = 96) [43]. Many studies found that beta-blocker therapy induced a significant increase in HRV measures related to parasympathetic activity in patients with chronic heart failure (CHF) [45, 46, 48]. In the substudy of the European Myocardial Infarct Amiodarone Trial (EMIAT) depressed HRV was demonstrated to identify post MI patients who might benefit from prophylactic treatment with amiodarone [51]. Some antiarrhythmic drugs may reduce HRV [52–54]. Higher dose of statin was found to be associated with significantly higher HRV measures in vascular surgery patients [55]. The effects of hormone replacement therapy on cardiac autonomic modulation in postmenopausal women have been inconsistent [56, 57].

The benefit of thrombolytic therapy has been well established in management of acute MI. Earlier and better improvement of HRV was observed in post MI patients who had thrombolytic treatment compared with those who did not or failed such therapy [58, 59]. The improvement was independent of infarction site [60]. The Occluded Artery Trial-Electrophysiological Mechanisms (OAT-EP) trial demonstrated that opening a persistently occluded infarct-related artery by either coronary artery intervention or medical therapy significantly increased HRV (SDNN, rMSSD); HRV was measured at baseline and 1 year after the therapies from 10-min Holter ECG recordings in 300 patients [61]. In patients after coronary artery bypass grafting surgery an association between HRV measurements and myocardial ischemic episodes was found [62].

Long-term smoking significantly reduced HRV values [63]; cessation of smoking increased HRV considerably [64]. Exercise training augmented total HRV [39] or modified HRV toward vagal dominance [65]. The level of physical activities significantly affect some of the HRV measures while long-term HRV was demonstrated to be relatively stable at various physical activity level in healthy adults [66]. Stress management significantly increased HRV in patients with stable coronary artery disease compared with patients under usual care [67]. An association was found between decreased HRV with increased CRP in middle aged men even after adjustment for conventional CAD risk factors [68].

Many but not all interventions associated with increased HRV are also associated with better survival rates [69, 70]. Data on the effect of HRV modification on clinical outcomes remain limited.

HRV in Risk Stratification of Cardiac Patients

HRV in Patients After Myocardial Infarction

Despite incomplete understanding of the physiological significance of HRV parameters, this methodology is of substantial utility to identify patients with an increased cardiac mortality, particularly in the survivors of an acute MI. The association between reduced HRV and increased mortality in post MI has been intensively investigated over more than two decades [2, 3, 6, 7, 71]. Its value for risk stratification in post MI population has been established [8].

The study by Kleigher et al. stresses the significant implication of reduced HRV in post-MI risk stratification [2]. Copie et al. demonstrated that HRV index <17 units had a 40 % sensitivity, 86 % specificity and 20 % positive predictive accuracy for predicting cardiac death in 579 survivors of acute MI followed up for ≥2 years [5]. Power law regression parameters were found to be powerful predictors of death of any cause or arrhythmic death in 715 patients with recent MI [23]. Both traditional and nonlinear HRV were independently associated mortality after MI [72] even in the fibrinolytic era [73]. A multi-parametric HRV analysis better predicted increased arrhythmia risk than the standard measurement of global HRV in acute MI survivors [28]. La Rovere et al. [74, 75] demonstrated more conclusively that both HRV and baroreflex sensitivity predicted cardiac and arrhythmic death among 1,284 post MI patients in the trial of Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI). Nonlinear HRV measures (the short-term scaling exponent alpha1 and power-law slope beta)

were found to predict the risk of acute coronary event independent of other clinical and autonomic variables [76]. More recent studies using other HRV techniques also confirmed the value of HRV in risk stratification of post MI patients [10, 22, 32, 77].

HRV analysis may play a critical role in further risk stratification of high-risk population. Camm et al. [6] evaluated the predictive power of HRV in patients (n = 3,717) with acute MI and low LVEF (15–35 %) from the randomized, placebo-controlled, double-blind study (ALIVE) of azimilide 100 mg. The study has convincingly demonstrated that low HRV (≤20 units) independently predicts significantly increased total mortality in patients after MI with depressed LV function. Similarly, Huikuri et al. found that HRV was a particularly stronger predictor among a variety of noninvasive ECG markers for ventricular arrhythmias during 2-year follow up in 312 post-MI patients with LVEF ≤40 % [7].

HRV in Coronary Artery Disease

In 1995, Huang et al. [78] reported that all time-domain and frequency-domain measures of HRV were reduced in patients with acute coronary syndromes compared to normal controls ($P < 0.001$). The study consisted of 52 patients with unstable angina, 52 patients with acute MI, and 41 normal subjects. There was no significant difference in HRV measures between patients with unstable angina and acute MI. In patients with unstable angina who stabilized after admission, HRV increased over the second 24 h of Holter monitoring. In contrast, HRV was further depressed in patients who had episodes of chest pain or transient ST-segment depression during the second 24 h [78]. The association of lower HRV with angina or MI was confirmed by late reports [21, 79].

Depressed HRV was associated with CAD events and CAD mortality in patients with angina [78, 80], in postmenopausal women [81], and in general population [79]. Tsuji et al. investigated the association of reduced HRV with risk for new cardiac events (angina, MI, CAD death, or CHF) in a community-based population (n = 2,501 eligible) from the Framingham Heart Study with follow-up of a mean of 3.5 years. After adjustment for other relevant risk factors, all time- and frequency-domain measures except the LF/HF ratio were significantly associated with risk for a cardiac event ($P = 0.0016$–0.0496). One standard deviation decrement in SDNN was associated with a hazard ratio of 1.47 for new cardiac events [79]. A multicentre prospective study (n = 543) showed that conventional HRV measures predicted short- and medium-term mortality independently in patients with unstable angina and preserved LV function (LVEF ≥40 %) [82]. Reduced HRV was identified as one of the dominant risk predictors for CAD mortality in the Women's Health Initiative (WHI) study [81].

The data are limited concerning the association of HRV measurements with severity of the disease and the evolution of HRV with development of coronary event. More evidences from large prospective studies are required to ascertain the clinical implications of HRV measurements and its predictive value for new coronary events in CAD.

HRV in Patients with Chronic Heart Failure

Over the last decade, numerous studies have showed that chronic heart failure (CHF) is associated with autonomic dysfunction, which may be quantified by measuring HRV. UK-HEART prospectively examined the value of HRV as an independent predictor of death in 433 outpatients with CHF (age 62 ± 9.6 years old; NYHA functional class I to III; mean LVEF 0.41 ± 0.17) over a mean follow-up of 482 ± 161 days. The annual mortality rate for the study population in SDNN subgroups was 5.5 % for >100 ms, 12.7 % for 50–100 ms, and 51.4 % for <50 ms of SDNN. Compared with other conventional clinical measurements reduced SDNN value better identified patients at increased risk of death and predicted death of progressive CHF [83]. Late studies confirmed that patients with reduced SDNN were at significantly increased risk of all-cause mortality in CHF [84, 85]. In CHF patients with the most severe functional impairment, however, HRV measures may not provide independent prognostic information [86].

La Rovere et al. convincingly demonstrated that reduced short-term LF power during controlled breathing predicted SCD in patients with CHF independent of other clinical variables [87]. Their finding was supported by a later report from Guzzetti et al. Spectral analysis of long-term HRV provided information related to the mode of death in CHF patients with sinus rhythm [88].

The prognostic value of long-term continuous HRV measurements from cardiac resynchronisation devices was demonstrated in 288 patients with CHF. Continuous HRV was measured as SDAAM sensed by the device. SDAAM <50 ms averaged over 4 weeks was associated with increased mortality risk (hazard ratio 3.20, P = 0.02). In patients who required hospitalization or died SDAAM were persistently lower over the entire follow-up period [12]. These findings suggest the potential value of evaluating continuous long-term SDAAM for clinical management in patients with CHF. A later study also illustrated that continuously measured HRV parameters appeared to provide important prognostic information on mortality in patients with CHF using ECG data derived from cardiac resynchronisation and defibrillation devices [89]. Cardiac resynchronization therapy significantly modified HRV (SDANN, SDAAM); lack of HRV improvement after the therapy identified patients at higher risk for major cardiovascular events in patients with symptomatic heart failure [12, 90].

HRV, Ventricular Tacharrhythmias and Sudden Death

There are experimental and epidemiological evidences of an association between depressed HRV and SCD [22, 29, 87, 88, 91, 92] even though the pathophysiological link of this association has not been completely understood. Table 11.2 presents a summary of selected studies assessing the predictive value of HRV for SCD.

In early 1990s, Algra et al. evaluated HRV in 193 patients who died suddenly over 2-year period, potentially due to cardiovascular causes, from a multicentre cohort of 6,693 patients who had a 24-h Holter recording. Their findings strongly support that patients with reduced HRV have a significantly increased risk for sudden death [91]. Compared with their randomly selected controls from the cohort, their sudden death cases had significantly reduced LV function and much more of them had a history of MI. This study investigated a large group of sudden death cases but is limited by its retrospective nature and HRV assessment in a heterogeneous cohort.

A later investigation in 575 survivors of acute MI demonstrated clearly that depressed HRV (P < 0.001) and ventricular tachycardia runs (P < 0.05) at the time of hospital discharge predicted arrhythmic death (n = 29) over 2-year follow-up [92]. Reduced α_1 (<0.75) was identified as an independent predictor of arrhythmic death (n = 75) with adjusted relative risk of 1.4 (95 % CI 1.1–1.7, P < 0.05) in a substudy of DIAMOND trial consisted of 446 survivors of acute MI with a LVEF ≤35 % [22]. Similarly, reduced α_1 (<1.0) predicted SCD (n = 29) with adjusted relative risk of 4.3 (95 % CI 2.0–9.2, P < 0.001) independent of other predictors in 325 subjects aged ≥65 years of general population [29]. Recently, another spectral index of HRV was shown to predict SCD (n = 17) in 590 patients with a recent MI [95].

In CHF, depressed HRV was demonstrated to predict the risk of SCD [87, 88]. In idiopathic dilated cardiomyopathy, however, HRV (SDNN) failed to predict sustained ventricular tachycardia (VT), VF or SCD (n = 38) during a follow-up of 52 ± 21 months in a prospective observational study (n = 263) [94]. HRV also failed to predict SCD (n = 18) in another prospective study including 106 CHF patients [96]. The study patients were of high-risk (LVEF <40 %) category; approximately 52 % patients had ischaemic heart disease.

The temporal relation of HRV alteration to the onset of fatal arrhythmias is of critical implication for prevention of arrhythmic events and for clinical management in good timing. Early studies observed such temporal relation based on data from 24-h Holter recordings [26, 93, 97, 98]. HRV was significantly reduced before onset of spontaneous episodes of VT; the ratio between LF and HF increased substantially before the episodes (P = 0.05) [97]. Nonlinear methods also

Table 11.2 Heart rate variability and sudden cardiac death: summary of selected studies

First author of the study	Study population (N =)	Study design	HRV method	Main parameter investigated	Main findings of the study
Bigger [4]	Recent MI (N = 715)	Observational; 4-year follow-up	Holter recording; FD analysis	ULF, VLF, LF, HF	VLF strongly associated with SCD
Algra [91]	Hospital patients (N = 193 sudden death; 230 control)	Observational; 2-year follow-up	24-h Holter recording; TD analysis	Short-term RR variation <25 ms	Adjusted relative risk for sudden death 2.6 (95 % CI 1.4–5.1)
Hartikainen [92]	Recent MI (N = 575)	Observational; 2-year follow-up, 29 SCD cases	24-h Holter recording; Geometric method	HRV triangular index	Depressed HRV independently predicted arrhythmic death
Perkiomaki [25]	PMI, CA (n = 30) PMI, VT (n = 30)	Case control	Holter recording; TD analysis, Poincare plot analysis	SDNN, and Poincare plot	Low HRV is related to susceptibility to VF not to stable monomorphic VT
Shusterman [93]	CA, VF, VT (N = 53)	Observational	Holter recording; TD & FD analysis	HF, LF, LF/HF, SDNN, RMSSD	LF, LF/HF ratio decreased significantly before the onset of VT
Huikuri [22]	Recent MI and impaired LVF (N = 446)	Observational; follow-up of 685 ± 386 days	Holter recording; TD & FD analysis, fractal analysis	Exponents α_1 & α^2 and exponent β'	Reduced α_1 predicted arrhythmic death better than others
Pruvot [11]	PMI with ICD (N = 58)	Observational	ICD recording; FD analysis	TF, VLF, HF, LF	Reduction in HRV before VTA onset
Makikallio [29]	Age ≥65 years (N = 325)	Observational; 10-year follow-up	24-h Holter; conventional and fractal scaling measures	Short-term fractal scaling exponent	Reduced α_1 as independent predictor of SCD
La Rovere [87]	CHF (N = 444)	Observational; 3-year follow-up	8-min ECG recording; TD & FD analysis	LF	Reduced LF as independent predictor of SCD
Guzzetti [88]	CHF (N = 330)	Observational; 3-year follow-up	24-h Holter; TD & FD analysis	VLF, LF	Reduced night-time LF linked to SCD independently
Grimm [94]	Idiopathic DCM (N = 263)	Observational; follow-up of 52 ± 21 months	24-h Holter recording; TD analysis	SDNN	HRV was not predictive of major arrhythmic events
Kiviniemi [95]	Recent MI (N = 590)	Follow-up of 39 ± 14 months 17 SCD cases	24-h Holter recording Spectral analysis	V (index)	V (index) was most powerful predictor of SCD; adjusted RR 4.2, 95 % CI 1.2–15.2
Tamaki [96]	Stable CHF (N = 106)	Prospective, comparative Follow-up of 65 ± 31 months 18 SCD cases	24-h Holter recording TD & FD analysis	MIBG & HRV, SAECG etc.	HRV was not associated with SCD

CA cardiac arrest, *CHF* chronic heart failure, *CI* confidence interval, *DCM* dilated cardiomyopathy, *FD* frequency domain, *HF* high frequency power, *HRV* heart rate variability, *ICD* implantable cardioverter defibrillator; *LF* low frequency power, *LVF* left ventricular function, *MI* myocardial infarction, *MIBG* cardiac iodine-123 metaiodobenzylguanidine imaging, *nu* normalised unit, *PMI* post myocardial infarction, *RMSSD* the root-mean-square of successive differences between adjacent normal to normal intervals, *SAECG* signal-averaged electrocardiogram, *SCD* sudden cardiac death, *SD* standard deviation, *SDANN* the standard deviation of the 5-min average normal to normal intervals, *SDNN* the standard deviation of all normal to normal intervals, *TD* time domain; *TF* total power, *ULF* ultra low frequency power, *VLF* very low frequency power, *VF* ventricular fibrillation, *VT* ventricular tachycardia, *VTA* ventricular tachyarrhythmias

revealed alterations in RR-interval dynamics before spontaneous onset of ventricular tachyarrhythmias [26]. HRV before electrophysiologic study was significantly lower in subjects with inducible VT (n = 12) compared to those without clinical or electrocardiographic evidence of VT (n = 20). This HRV analysis was performed on very short recordings consisted of only 11-beat strip of ECGs [99]. It may be more practical to use such short ECGs in clinical scenarios, however, the method needs to be validated.

A case control study showed that reduced HRV (SDNN and nonlinear method) was associated with susceptibility to VF in post MI patients [25]. Perkiomaki et al. reported that only α_1 was

an independent predictor of ICD shock or death with hazard ratio 1.20 (95 % CI 1.03–1.39) for every 0.10 decrease in α_1 (P = 0.020) [100]. This analysis was based on 10-min high resolution ECG from 55 patients with impaired LV function and an ICD for various indications. Reduced HRV was not associated with stable monomorphic VT. Recently, Battipaglia et al. reported that HRV (very-low-frequency index only) measure was significantly associated with appropriate ICD shocks in DCM patients who had LVEF <40 % [101]. These findings need to be verified in larger ICD population. Which HRV measure would be optimal for this purpose requires further investigations.

Many studies have focused on the behaviour of heart rate before onset of ventricular tachyarrhythmias by investigating the RR intervals preceding an arrhythmic event recorded and retrieved from ICDs [11, 102, 103]. A significant reduction in HRV was found before onset of ventricular arrhythmias compared with control conditions, that may suggest a state of sympathetic excitation proceeding ventricular arrhythmic events [11]. Although others failed to detect significant differences in short-term HRV immediately before the arrhythmic events using the ECG data stored in ICD, they observed that the heart rate and frequency of ectopic beats were significantly increased before onset of VT or VF [103]. These findings may indicate a shift of autonomic balance towards sympathetic predominance and reduced vagal tone before onset of ventricular arrhythmic events that reflects a transient electrical instability favouring the onset of ventricular tachyarrhythmias in patients with cardiac disorders.

HRV and Other Cardiac Disorders

Researchers also tested if HRV analysis may be used for assessing the risk of AF onset. Hogue et al. demonstrated that alteration in HRV and heart rate were independently associated with AF in post CABG patients based on the averaged values for the three 20-min intervals preceding the onset of AF. HRV assessment may provide useful information for investigating mechanisms of post-operative AF and for predicting AF risk [20]. The Cardiac Arrhythmias and RIsk Stratification after Myocardial Infarction (CARISMA) substudy demonstrated that abnormal HRV was associated with increased risk of new-onset AF independent of conventional clinical risk variables in patients with acute MI and LVEF ≤40 % (n = 271) [104]. The role of HRV in diagnosis and therapeutic-decision making in AF have not yet been established. More studies are needed to confirm these findings.

In patients with cardiac hypertrophy reduced HRV were found to be independently associated with the extent of cardiac hypertrophy regardless the aetiology [105]. Preserved HRV identified patients with non-ischaemic DCM (N = 274) at lower risk of mortality as suggested by the results from the trial of Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) [106]. Some of the HRV measures were markedly reduced in patients with chronic obstructive pulmonary disease [107, 108] and correlated with disease severity [107].

Other HRV-Related Autonomic Markers in Risk Stratification

HRDC can be quantified from 24-h ambulatory ECG recordings. It was developed in order to separate the effect of sympathetic from vagal activities on HRV. Diminished deceleration-related modulation of heart rate is believed to reflect impaired cardiac vagal modulation [10]. Bauer et al. tested HRDC in 3 cohorts consisted of >2,000 post MI patients. They confirmed that impaired HRDC was a powerful predictor of mortality after MI and is more accurate than the conventional measures of HRV. Stratification by dichotomised HRDC was especially powerful in patients with preserved LV function [10].

The concept of HRT is first reported in the Lancet by Schmidt et al. in 1999 [9]. HRT describes the phenomenon of short-term fluctuations in sinus cycle length after a single ventricular premature complex [9]. The role of HRT in risk stratification of patients survived acute MI has been well established. Attenuated HRT is associated with increased risk of subsequent mortality in post MI patients [109].

A recent study evaluated HRV and HRT at early and late stage after an acute MI in two

well-characterised cohorts, Cardiac Arrhythmia and Risk Stratification after Myocardial Infarction (CARISMA, N = 312) and Risk Estimation After Infarction, Noninvasive Evaluation (REFINE, N = 322). Both HRV and HRT increased over recovery period; attenuated recovery of HRV and HRT was associated with significantly increased risk of ECG-documented sustained VT/VF in both cohorts [110]. The findings indicate autonomic remodelling after MI that is of significant clinical implication. Reduced HRV (the short-term scaling exponent alpha) and HRT also predicted HF hospitalisation in post-MI patients (N = 569) after adjusted for other risk factors [111].

A more recent study showed that combined measures of HRT and HRDC predicted poor clinical outcome in diabetic patients who survived an acute MI. Of 481 patients (age ≤80 years) presented in sinus rhythm 83 (17.3 %) died during 5-year followed up, including 24 SCD and 21 non-SCD. Both abnormal HRT and HRDC was the strongest predictor of mortality (hazard ratio 4.9, 95 % CI 2.4–9.9) followed by age ≥65 years and LVEF ≤30 % in multivariate analysis [112]. These findings further highlight the significance of cardiac autonomic markers in risk prediction and the need of more practical approach for assessing autonomic modulation [113].

Summary and Further Works

HRV has become an established risk stratifier for arrhythmic events and mortality in post MI population but reduced HRV alone has only moderate sensitivity and specificity. A multiparametric approach combining HRV parameters from all domains may provide better prediction of arrhythmic risk compared with the standard measures of global HRV in post MI patients. Combination of HRV with other major risk factors, in particular novel cardiac autonomic risk markers such as HRT and HRDC, can identify cardiac patients at particularly high risk of mortality, and significantly improve the predictive power.

The association of reduced HRV with susceptibility to life-threatening tachyarrhythmias has been confirmed by most published studies. Increasing evidence suggests that nonlinear heart rate dynamics may have significant prognostic power for stratifying patients at high risk of SCD. In patients with CHF a majority of clinical studies support HRV is of important prognostic value and depressed HRV identifies patients at significantly increased risk of cardiac mortality.

The area of HRV behaviour before the onset of life-threatening ventricular tachyarrhythmias offers exciting possibilities for further research to explore the predictive power for the timing of fatal ventricular tachyarrhythmia onset and the mechanism to initiate the events. The rapid development in technology has made it possible to capture electrocardiographic data from implantable cardiac devices within or out of hospital, which will facilitate HRV research, and further development of computing algorithm. The specificity and predictive accuracy of altered HRV in predicting imminent or future fatal arrhythmic events are still low for clinical risk assessment in cardiac patients. More evidence for the predictive value of HRV measurements in ventricular tachyarrhythmias and SCD is required by carefully designed clinical studies/trials to evaluate its clinical applicability. It is also important to conduct well-designed intervention trials in patients with abnormal autonomic function to reveal the potential clinical role of HRV using either conventional or novel methods.

Although there is growing awareness that nonlinear analysis of HRV may improve the predictive accuracy of Holter monitoring ECG in post MI patients, more clinical studies in large population are needed to confirm the findings. It is promising to explore other novel techniques characterising the behaviour of heart rate from long-term ECG recordings and the application in other cardiac populations. It is clear that HRV assessment by conventional and nonlinear method is a useful research tool for documenting alterations in autonomic modulation in relation to arrhythmic events and providing prognostic information in patients with cardiac disorders. However, the clinical application of HRV assessment using any technique has not been established for monitoring cardiac autonomic status in individual patients. More research is warrant to identify more practical approach and optimal algorithm of HRV assessment for future application of HRV in clinical practice.

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12
Orthostatic Challenge Tests: Active Standing and Head-Up Tilt

Louise R.A. Olde Nordkamp, Nynke van Dijk, and Wouter Wieling

Abstract

Syncope is a frequently occurring symptom and can originate from various causes. When syncope is related to the upright position or when there is a suspicion of a reflex mechanism, tests assessing the orthostatic cardiovascular adjustments are advised. The orthostatic response is classified into three stages: the initial response (first 30 s), which differs among active or passive changes in posture, the early phase of circulatory stabilization (1–2 min upright), and prolonged orthostatic stress (at least 5 min upright). Three tests of the orthostatic circulatory response are available, testing these different stages of the circulatory response. (1) The active lying-to-standing test using continuous blood pressure monitoring is used to study the quick cardiovascular responses directly after active standing and can detect initial orthostatic hypotension. (2) The active lying-to-standing test using the conventional cuff and stethoscope can be used to assess the orthostatic adjustments in the first 3–5 min after standing. It is used to detect classic orthostatic hypotension. (3) The head-up tilt test evaluates prolonged orthostatic stress and can be applied to detect reflex syncope, delayed orthostatic hypotension or postural tachycardia syndrome. Moreover, all tests may prevent recurrences by identification of symptoms and thus helping patients to recognize the premonitory symptoms for their syncope allowing them to take preventive measures and decrease their anxiety for episodes. Education of physical counterpressure manoeuvres during these tests can additionally increase patients' sense of control over their symptoms.

Keywords

Head-up tilt test • Active lying-to-standing test • Continuous blood pressure monitoring • Syncope • Orthostatic hypotension • Autonomic dysfunction • Postural tachycardia syndrome

L.R.A.O. Nordkamp, MD
Department of Cardiology,
Heart Failure Research Center,
Academic Medical Center, University of Amsterdam,
Amsterdam 1105 AZ, the Netherlands
e-mail: l.r.oldenordkamp@amc.uva.nl

N. van Dijk, MD, PhD
Department of General Practice, Family Medicine,
Academic Medical Center, University of Amsterdam,
Amsterdam 1105 AZ, the Netherlands
e-mail: n.vandijk@amc.uva.nl

W. Wieling, MD, PhD (✉)
Department of Internal Medicine,
Academic Medical Center,
University of Amsterdam,
Room F3-241, Meibergdreef 9, Amsterdam
1105 AZ, the Netherlands
e-mail: w.wieling@amc.uva.nl

I. Gussak, C. Antzelevitch (eds.), *Electrical Diseases of the Heart*,
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Introduction

Syncope is a sudden transient loss of consciousness (TLOC) due to global cerebral hypoperfusion characterized by short duration and spontaneous complete recovery [1]. Syncope is common, with a lifetime cumulative prevalence of around 35 % in subjects up to 65 years of age in the general population [2–4], accounting for approximately 1 % of emergency room visits [5].

Syncope can originate from variable causes (Fig. 12.1), including reflex (neurally-mediated) syncope, cardiac syncope [6] and syncope due to orthostatic hypotension (OH). Risk stratification of patients with syncope is mandatory as cardiac causes due to structural heart diseases and primary electrical diseases are major risk factors for sudden cardiac death and overall mortality [7, 8].

The initial assessment of a patient with syncope consists of a careful history, physical examination, including conventional orthostatic blood pressure measurements with cuff and stethoscope and an electrocardiogram. This simple approach is very effective in differentiating between causes of syncope. A certain or very likely cause of syncope can already be identified in more than 60 % of patients [9–11]. History taking should focus on verification of loss of consciousness, clinical features of the medical history that suggest a diagnosis, presence of heart disease and presence of other life-threatening causes.

After a careful history, additional examinations, including tests assessing the orthostatic cardiovascular adjustments are advised when syncope is related to the upright position or when there is a suspicion of a reflex mechanism [6]. Three tests of the orthostatic circulatory response are available. The choice of which additional test should be done depends on the time interval between arising from the supine position and complaints of light-headedness or fainting. (1) The active lying-to-standing test using continuous blood pressure (BP)

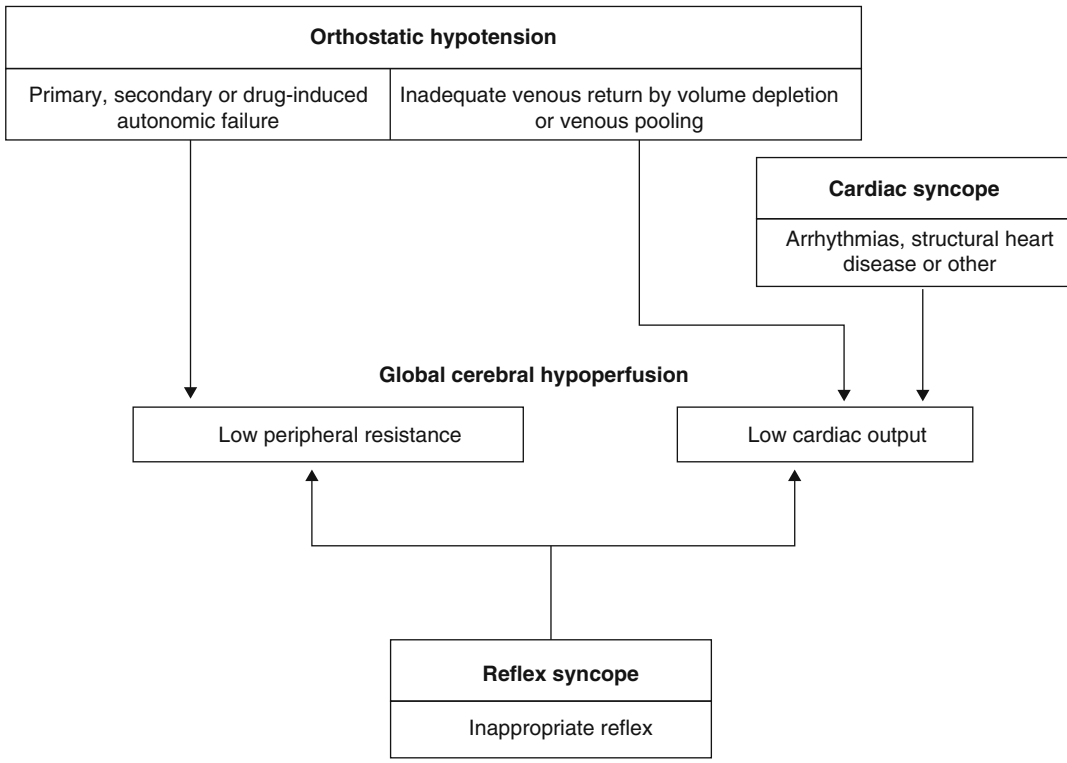

Figure 12–1. Causes of syncope

monitoring is used to study the quick cardiovascular responses directly after active standing (first 30 s) and can detect initial orthostatic hypotension [12]. (2) The active lying-to-standing test using the conventional cuff and stethoscope can be used to assess the orthostatic adjustments in the 3–5 first minutes after standing. It is used to detect classic orthostatic hypotension. (3) The head-up tilt test (HUT) evaluates prolonged orthostatic stress and can be applied to detect reflex syncope or delayed OH. This chapter will outline the physiological mechanisms for cardiovascular adjustments to orthostatic stress provide a detailed description of the three available tests to evaluate the cardiovascular orthostatic response.

Regulatory Mechanisms for Orthostatic Stress

Changing from supine to upright position produces a shift of circulating volume from the thorax to the distensible venous capacitance system below the diaphragm, resulting in a decrease in venous return and cardiac output (CO) and thereby in blood pressure. Decreases in arterial pressure remove the tonic inhibition of the vasomotor centres in the brainstem by the arterial baro- and cardiopulmonary mechanoreceptors, with a resultant decrease in vagal outflow and increase in sympathetic outflow, causing a stabilization of arterial BP by increases in heart rate, cardiac contractility and vasomotor tone [13]. Not only neurogenic autonomic mechanisms, but also mechanical factors are involved in the adjustment of the body to the upright posture. During standing, contraction of lower body skeletal muscles prevents excessive pooling and augments venous return to the heart [14]. Respiration decreases intrathoracic pressure and increases intra-abdominal pressure, thereby promoting venous return as well [15, 16].

In healthy subjects, circulatory stabilization is usually reached within 1 min after the start of orthostatic stress. In the ensuing minutes, blood pressure and heart rate *normally* change only minimally. This normal orthostatic circulatory response to the upright position consists of three phases: (1) the initial response (the first 30 s) which differ depending on the active (standing up) or passive (head-up tilt) change to the upright position, (2) the early phase of stabilization (1–2 min upright) and (3) the prolonged orthostatic period (>5 min upright), all with direct clinical relevance [17].

The circulatory adjustment to postural change in the initial phase and the early phase of stabilization is governed exclusively by the neural system. The initial circulatory response to active standing consists of a transient initial drop in BP with a nadir after about 10 s after the onset of standing up. followed by a rapid recovery and sometimes overshoot of BP (Fig. 12.2). This shortlasting drop in BP is caused by a mismatch between a transient increase in cardiac output due to contraction of leg and abdominal responses on standing and marked vasodilatation in the leg muscles due to their active use [18]. The instantaneous increase in heart rate observed upon active standing results from the inhibition of cardiac vagal tone (muscle heart reflex) and a baroreflex mediated heart rate-increase. The initial fall in blood pressure is adjusted by rapid increases in vasoconstrictor tone. If these initial vasomotor adjustments fail, a patient complains about light-headedness or fainting about 10 s after actively standing up. This condition is known as initial orthostatic hypotension [12]. The initial drop in BP is usually not seen during passive posture changes in which both BP and HR gradually increases until stabilization is reached.

In the early phase of stabilization an increase in diastolic pressure, due to the increased peripheral vascular resistance, with little or no change in systolic pressure at heart level is visible. The heart rate increase amounts on average to about 10 bpm, but varies widely. Both this marked vasoconstriction and moderate tachycardia are associated with the increased sympathetic tone. When there is a severe intravascular volume depletion over-riding the capacity for reflex vasoconstrictor adjustments or with failure of vasoconstrictor adjustments themselves in patients with autonomic failure, classic OH arises. Orthostatic hypotension may be facilitated by conditions such as moderate dehydration, hot environments and athletic competition.

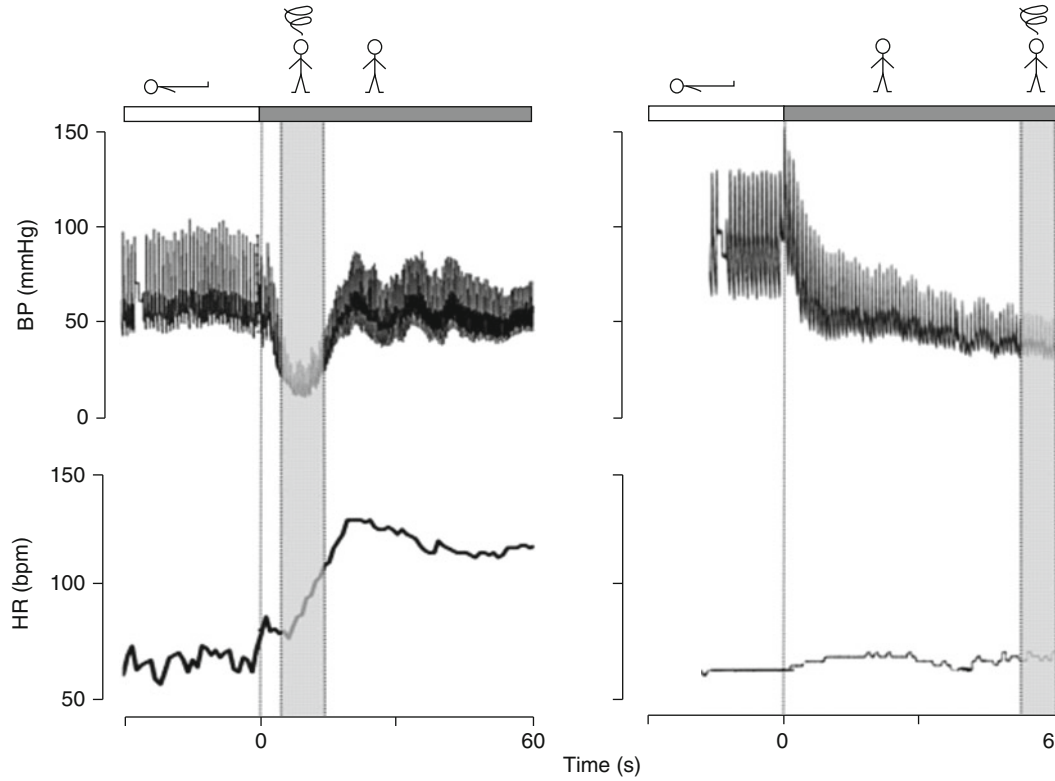

Figure 12–2. Difference in initial and classic orthostatic hypotension. Changes in finger arterial pressure and heart rate during active standing in a patient with initial orthostatic hypotension in an otherwise healthy young man (*left panel*) and classical orthostatic hypotension in a patient with pure autonomic failure (*right panel*). *BP* blood pressure, *HR* heart rate, *bpm* beats per minute (Revised after Moya et al. [6])

After 5 min of upright posture compared to the supine position the mean systolic pressure is raised by 0–10 %, the diastolic pressure by about 10 % and heart rate by 15–30 % [17]. Reflex syncope during prolonged orthostatic stress occurs if progressive pooling of venous blood and extravasation of plasma volume cannot be compensated for by vasoconstrictor responses. The final pathway leading to a rapid fall in blood pressure is caused by a loss of vasoconstrictor tone due to sympathetic withdrawal and cardiac vagal overactivity, resulting in a drop in HR. The trigger that induces this sudden cardiovascular decompensation to (pre-) syncope is still unknown [19].

Active Lying-to-Standing Test Using Continuous BP Monitoring

During the active lying-to-standing test there is an important difference in measuring BP changes using the continuous beat-to-beat BP monitoring and the commonly used cuff. Only with continuous BP measuring it is possible to assess the rapid initial changes in arterial BP (first 30 s), which is mandatory when evaluating initial orthostatic hypotension.

Methods

Continuous beat-to-beat BP monitoring can be done non-invasively using finger arterial pressure monitoring [20]. Finger BP can be obtained in almost all subjects; even in vasospastic or severe atherosclerotic disease [21]. Since conditions of peripheral vasoconstriction limit the use of finger BP monitoring, subjective cold is best avoided and ambient temperature should be above 22 °C. Fingers cuffs are best applied to the middle and annular fingers; thumbs need to be avoided. The position of the hand is advised to be at heart level [21].

Table 12–1. Definitions of orthostatic hypotension, neurally mediated syncope and postural tachycardia syndrome [22]

Initial OH	Transient BP decrease (>40 mmHg systolic BP and/or >20 mmHg diastolic BP) within 15 s of standing
Classical OH	Sustained reduction of systolic BP of ≥20 mmHg or diastolic BP of ≥10 mmHg within 3 min of standing or HUT to at least 60° on a tilt table
Delayed (progressive) OH	Symptomatic classical OH that occurs beyond 3 min of standing
Reflex syncope triggered by standing (vasovagal syncope)	Initial normal adaptation reflex followed by an active reflex including reflex bradycardia
Postural tachycardia syndrome	Symptomatic and sustained heart rate increment of ≥30 bpm within 10 min of standing or HUT in the absence of OH

OH orthostatic hypotension, *BP* blood pressure, *HUT* head-up tilt testing, *bpm* beats per minute

Interpretation of Responses

Complaints of IOH are common. Initial OH is thought to be due to a mismatch between CO and vascular tone and is defined as a transient BP decrease (>40 mmHg systolic BP and/or 20 mmHg diastolic BP) within 15 s of standing (Table 12.1) [22]. The sensitivity and specificity of continuous BP measuring are unknown. Reproducibility of finger BP depends on cuff reapplication; if measurements are continued without reapplication finger BPs are highly reproducible [21].

Active Lying-to-Standing Test Using the Manual Cuff

The commonly used cuff for manual intermittent determination of the BP in supine position and during active standing for 3 min is adequate for routine clinical testing. It will simply and reliably give an impression of the orthostatic adjustment of the arterial BP to orthostatic stress.

Methods

The frequently used protocol is the short, bedside orthostatic test: the patient's BP is measured after 5–10 min of rest in supine position; the patient arises and the measurements are then repeated about 1–2 times per min while the patient stands motionless for 3–5 min with the cuffed arm supported at heart level. On standing, the patient is asked to report dizziness, faintness or light-headedness, with the examiner recording its transience and/or persistence. The procedure is aborted for safety reasons if blood pressure drops precipitously or presyncope ensues [23].

Interpretation of Responses

Classical OH is defined as a sustained reduction of systolic BP of at least 20 mmHg or diastolic BP of 10 mmHg within 3 min of standing (Table 12.1) [22]. It is a measurement result (physical sign), symptoms of dizziness or fainting do not need to be present. Depending on the clinical setting OH will be detected in 50–100 % of patients with autonomic disturbances within 3 min in the upright posture [24, 25]. Because the fall of BP is dependent on the baseline BP, a reduction in systolic BP of 30 mmHg may be a more appropriate criterion for OH in patients with supine hypertension [22].

There is marked variation in the reproducibility of hemodynamic responses to orthostasis. In one study, only 68 % of the elderly subjects with postural symptoms and documented OH had reproducible orthostatic blood pressure responses [26]. Also the postural responses demonstrate endogenous circadian rhythm [27, 28] and seasonal [29] variability. OH is underestimated in the evening and in the winter. A specific form of OH, postprandial hypotension, is almost immediately apparent after a meal with a nadir within 30–60 min postprandially, and can be found after any meal during the day [30].

Head-Up Tilt Test

During HUT a patient is passively changed from the supine to the upright position using a tilt-table. In some individuals, the combined effect of prolonged orthostatic stress and standing motionless induces a large fall in cardiac output and triggers a vasovagal reflex with hypotension due to a decrease in vasoconstrictor tone and bradycardia and a subsequent syncope.

HUT has become the technique of choice for eliciting susceptibility to reflex syncope in patients who present with syncope of unknown cause. HUT can also reveal classical or delayed orthostatic hypotension and the postural tachycardia syndrome [22]. HUT is not useful to assess initial orthostatic hypotension, as this condition requires an active change of posture.

Methods

Different HUT protocols with variations in duration, tilt angle, type of support and pharmacological provocation are used. The different HUT protocols used substantially influence outcome [31, 32]. Most HUT protocols contain two phases, a basic phase and a drug provocation phase.

Before the test, patients, in particular those over 60 years old, should fasten for no more than 2–4 h in order to avoid the confounding effects of relative dehydration and hypotension [33]. Where practicable, drugs affecting the cardiovascular and autonomic nervous systems and those likely to affect intravascular volume should be discontinued for at least five halve lives before the test [33], unless they are implicated as an attributable cause of syncope, in which case testing should be done while on medication. The test should be performed in a quiet, dimly lit room at a comfortable temperature to minimize stimuli affecting autonomic nervous function. Beat-to-beat BP and heart rate measurements are continuously measured. According the European Society of Cardiology guidelines [6] the procedure should be preceded by a supine pre-test phase of at least 5 min, when no venous cannulation is used, and of at least 20 min when cannulation is undertaken. A rapid and smooth tilt toward upright posture with an angle between 60° and 70° should be achieved, amounting to 87–94 % of the full upright orthostatic stress stimulus. While in head-up tilt position, the patient should be instructed to avoid movement of the lower limb musculature in order to maximize venous pooling. The duration of the drug free, passive tilt test is recommended to be between 20 and 45 min [6]. There are little hard data available on the relative merits of different drug free passive test periods, but a significant increase of false negative results was demonstrated with shorter tilt periods by Fitzpatrick et al. [31]. In this study the mean time to syncope was 24 min.

If the passive phase is negative, the use of either intravenous isoproterenol or sublingual nitroglycerine for drug provocation is recommended [6]. By increasing sympatho-excitation and/or augmenting venous pooling, these agents enhance the effect of tilt-induced orthostatic stress and facilitate induction of vasovagal syncope. Isoproterenol should be infused in upright position at a rate from 1 up to 3 μg/min in order to increase average heart rate by 20–25 % over baseline. To overcome this cumbersome method of administration with the need for continuous infusion and titration to the heart rate, nitroglycerine can be used. Nitroglycerine should be administered sublingually with a fixed dose of 300–400 μg without returning the patient into supine position. The drug challenge phase should be between 15 and 20 min. Both protocols have a similar rate of positive responses (61–70 %) [32, 34]. The use of isoproterenol is safe in patients without ischemic heart disease or sick sinus syndrome. No complications have been reported with the use of nitroglycerine. Minor side effects during the drug phase are common and are associated with the drug used: isoproterenol can provoke palpitations and nitroglycerine can cause a headache.

Interpretation of Responses

HUT is considered to be positive if syncopal or pre-syncopal symptoms reproducing the patients original symptoms are accompanied by hypotension, bradycardia (relative or absolute) or both. Delayed OH is defined as decrease of BP of at least 20 mmHg or diastolic BP of 10 mmHg after 3 min of standing (Table 12.1) [22]. Postural tachycardia syndrome is characterized by a sustained heart rate increment of more than 30 bpm within 10 min of standing or HUT, but is usually not accompanied by an important drop in systemic BP. For individuals aged 12–19 years the required increment is at least 40 bpm [22].

Experiences from tilt testing showed that a decrease in systolic BP to 80 mmHg or lower at heart level is associated with symptoms of

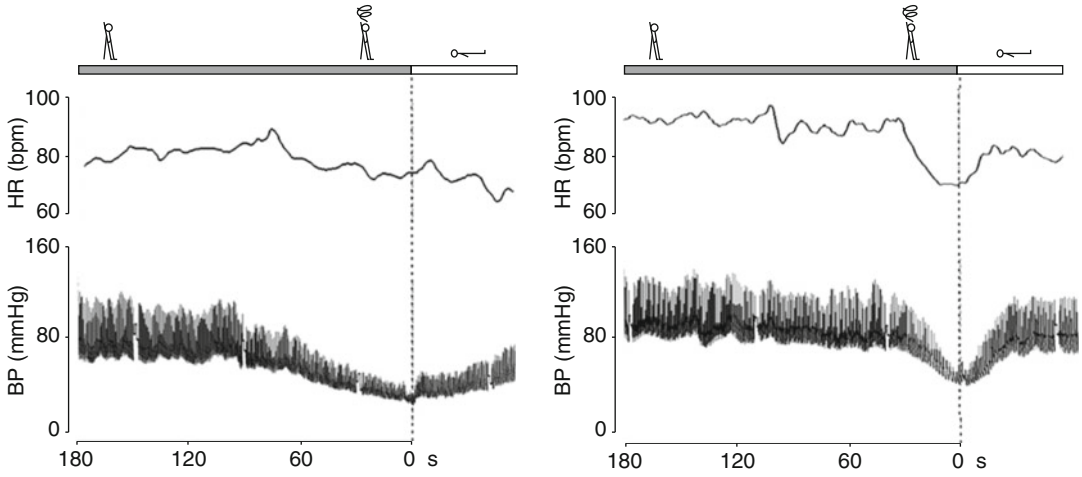

Figure 12–3. Different head-up tilt test patterns. Changes in finger arterial pressure and heart rate during passive movement to the upright position in a 69-year old patient with reflex syncope (*left panel*) and a 31-year old patient with reflex syncope (*right panel*). Note the much steeper fall in blood pressure in the younger subject compared with the older subject. *BP* blood pressure, *HR* heart rate, *bpm* beats per minute (Revised after Verheyden et al. [35])

impending syncope and 60 mmHg or lower is associated with syncope. Different BP and heart rate patterns can be associated with a positive HUT test (Fig. 12.3). One of the more common patterns, especially in the younger otherwise healthy vasovagal fainter is the "classic" response. It comprises an initial phase of rapid reflex adaptation to upright position with apparent stabilization of blood pressure and heart rate, suggesting a normal baroreflex function. The seemingly stable state is maintained until abrupt onset of the vasovagal reaction, which is characterized by a rapid fall in both BP and heart rate, causing the prodromes. The fall in heart rate varies in severity, ranging from a slight heart rate decrease up to prolonged asystole, often 10–20 s in duration, but sometimes much longer. Asystolic episodes up to 70 s have been recorded [36], always with spontaneous resumption of normal cardiac rhythm. Another relatively common pattern in especially older patients with concomitant diseases is characterized by the inability to obtain a steady-state hemodynamic adaptation to upright position. After a variable period of relative stability, there is a progressive fall of BP and a limited (positive or negative) heart-rate response, suggesting some degree of chonotropic restraint [37].

The results of most studies suggest that HUT testing discriminates relatively well between symptomatic patients and asymptomatic control subjects [31, 38–40]. Specificity of tilt testing is estimated at 85 %, depending on the steepness of the tilt angle used [40]. Sensitivity, estimated at 50–75 % [31, 39], is harder to evaluate, considering the lack of a golden standard for establishing the diagnosis of vasovagal syncope. Both drug-free and isoproterenol or nitroglycerin tilt tests show reduced sensitivity in elderly patients [41–43]. Tilt test reproducibility of an initial negative response (85–94 %) is higher than the reproducibility of an initial positive response (31–92 %) [44, 45]. The poorer reproducibility of the positive responses weakens the usefulness of tilt testing for assessing treatment-effectiveness.

Comparable to OH, the vulnerability to presyncope caused by head-up tilt has a strong endogenous circadian rhythm [46]. This highlights the importance of performing tilt-table tests at similar circadian times when comparing responses of different individuals or the same person before and after treatments for syncope. Additionally, a higher sensitivity may be achieved by performing tilt-table testing during early morning hours or at night-time.

Several studies on follow-up failed to show any correlation between the severity of the HUT test response and the syncope recurrences [47] suggesting that the mechanism of tilt-induced syncope is frequently different from that of the

Table 12–2. Indications for head-up tilt testing [6]

	Class	Level
Unexplained single episode in high risk settings (e.g. occurrence of, or potential risk of physical injury or with occupational implications)	I	B
Recurrent episodes in the absence of organic heart disease, after cardiac causes of syncope have been excluded	I	C
To demonstrate susceptibility to reflex syncope to the patient, when its of clinical value	IIa	C
To discriminate between reflex- and orthostatic hypotension syncope	IIb	C
To differentiate syncope with jerking movements from epilepsy	IIb	C
To evaluate patients with unexplained falls	IIb	C
To evaluate patients with frequent syncope and psychiatric disease	IIb	C

spontaneous syncope, reducing the role of tilt testing in defining the optimal treatment in individual patients [48–50].

Indications and Contraindications

HUT testing is widely used for the evaluation of patients with suspected reflex syncope or in who it is of clinical value to determine the susceptibility of reflex syncope (Table 12.2) [6]. It can also distinguish vasovagal reflex syncope from OH [51], psychiatric [52] or neurologic [53] syncope, and may be useful in the assessment of elderly patients with recurrent unexplained falls [54]. In patients with a known structural or primary heart disease HUT testing can be used to evaluate other causes of syncope if cardiac syncope is excluded by thorough evaluation [6]. Additionally, HUT testing can enhance patient confidence that the physician has witnessed their symptoms and is thereby better able to provide advice and treatment recommendations. It permits the patient to become familiar with typical premonitory symptoms indicating the need to initiate potential evasive manoeuvres [55].

Patients in whom the diagnosis of reflex syncope can be confirmed by initial evaluation and patients who have a single or rare cause of situational syncope, HUT testing is unnecessary. Also, HUT testing is not recommended to assess treatment efficacy due to its low reproducibility [56].

HUT testing is generally safe. Relative contraindications include clinically severe left ventricular outflow obstruction, critical mitral stenosis and patients in whom low organ perfusion pressure may compromise end artery supplied tissue, as in severe proximal coronary artery and cerebrovascular stenosis [33]. Only in patients with ischemic heart disease [57] or sick sinus syndrome [58] adverse events were reported with the use of isoproterenol in the drug provocation phase. Parasympathetic-mediated atrial fibrillation has been reported during or after a HUT, but is usually self-limited [59]. Despite the low risk, advanced resuscitation equipment should be immediately available at all times [6].

Conclusion

The active lying-to-standing test using continuous BP measuring or cuff BP measuring and the HUT are widely accepted as diagnostic tools for evaluation of orthostatic adjustment. HUT testing is especially useful for those cases in which vasovagal syncope is suspected, but the historical features are not sufficiently "classic" to establish the diagnosis confidently based on history, physical examination and ECG alone. Moreover, by itself, all tests may have a "therapeutic" effect in preventing recurrences [60] as the uncertainty about the aetiology of disturbance may lead to a degree of anxiety that can facilitate recurrence. Finally, identification of clinical prodromes during active lying-to-standing testing and HUT testing can help patients to recognize the incipient syncope, thus decreasing its severity and possibly preventing it with measures such as counterpressure manoeuvres.

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13
Signal Averaged ECG

Gioia Turitto, David M. Benson, Brian C. Wong, and Nabil El-Sherif

Abstract

The signal averaged electrocardiogram (SAECG) is one of several proposed methods for non-invasive risk stratification for sudden cardiac death (SCD). The term SAECG refers to techniques improving the signal-to-noise ratio, thus allowing analysis of signals that are too small to be detected by routine measurement. Among such signals are those arising from areas of slow and inhomogeneous conduction in diseased ventricular myocardium, which may represent a substrate for malignant reentrant ventricular tachyarrhythmias. A recently published AHA/ACC/HRS Consensus Document acknowledged that an abnormal SAECG may identify patients with prior myocardial infarction at risk of SCD. Given its high negative predictive accuracy, the SAECG could be useful for identification of low-risk patients. However, the document noted that routine use of the SAECG to identify patients at high risk for SCD is not adequately supported by existing data and further studies would be required to assess the utility of this test. It is possible that improved risk stratification may be accomplished if the SAECG is utilized as part of an algorithm in conjunction with other risk stratifiers. Large prospective studies to develop a robust prediction model are still warranted.

Keywords

Signal averaging • Sudden cardiac death • Ventricular tachycardia • Ventricular fibrillation • Risk stratification

G. Turitto, MD (✉), D.M. Benson, MD • B.C. Wong, MD
Division of Cardiology, Department of Medicine,
New York Methodist Hospital,
506 Sixth Street, Brooklyn, NY 11215, USA
e-mail: git9006@nyp.org; drdavidbenson@yahoo.com;
bricwong@gmail.com

N. El-Sherif, MD
Division of Cardiology, Department of Medicine,
New York Harbor Veterans Administration
Healthcare System, 800 Poly Place, Brooklyn,
NY 11209, USA
e-mail: nelsherif@aol.com

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Introduction

The term "signal averaged electrocardiogram" (SAECG) encompasses any technique that results in an improvement of the signal-to-noise ratio, thus allowing analysis of signals that are too small to be detected by routine measurement. Among such signals are those arising from areas of slow and inhomogeneous conduction in diseased ventricular myocardium [usually referred to as late potentials (LPs)]. These potentials are small because the activation front is slow and fractionated, or the mass of tissue undergoing depolarization is small, or both. LPs are of clinical relevance because they may identify a substrate for reentrant ventricular excitation [1].

Important technical advances in the field of SAECG were made in the early 1980s and included the introduction and refinement of filtering techniques, the selection of bipolar orthogonal leads and their combination into a vector magnitude for maximal sensitivity, as well as the use of computer algorithms to identify QRS offset and provide numerical values for signals in the terminal part of the QRS [2, 3]. In 1991, a Task Force of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology published standards for acquisition and analysis of LPs and attempted to define clinical indications for the SAECG [4]. The Task Force original recommendations were updated by an American College of Cardiology Expert Consensus Document [5]. The recommended applications consisted of risk stratification for future arrhythmic events and sudden cardiac death (SCD) in survivors of myocardial infarction (MI), and prediction of malignant ventricular tachyarrhythmias in patients with coronary artery disease and syncope, or asymptomatic non-sustained ventricular tachycardia (VT). Other groups of patients with organic heart disease in whom the SAECG has been utilized for risk stratification for SCD include patients with idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, right ventricular cardiomyopathy. More recently, the prognostic value of SAECG was examined in a statement prepared by a Joint ACC/AHA/Heart Rhythm Society Writing Group on noninvasive risk stratification techniques for identifying patients at risk of SCD [6]. This Expert Consensus Document acknowledged that an abnormal SAECG may identify patients with prior MI at risk of SCD. Given its high negative predictive accuracy, SAECG could be useful to screen low-risk patients. However, the document noted that routine use of the SAECG to identify patients at high risk for SCD is not adequately supported by existing data and further studies would be required to assess the usefulness of this test.

Technical Aspects of the SAECG

Time-Domain Analysis

ECG data acquisition consists of several steps: proper recording, amplification, digitization, identification and alignment of the signal of interest, time-ensemble averaging, and filtering [7, 8]. Typically, 200–600 cardiac cycles are acquired. The QRS selection process uses a cross-correlation algorithm, where each detected QRS is compared to a pre-selected template. A correlation coefficient of >0.98 is typically required for a good match; this allows rejection of abnormal QRS such as ventricular premature complexes or noisy beats. Time-ensemble averaging is used because the signal of interest, i.e. the QRS, is repetitive while much of the interfering noise (environmental noise, electromyographic noise, etc.) is random. Thus, time-ensemble averaging results in an improved signal-to-noise ratio. Filtering is also applied to reduce the residual noise and improve identification of LPs. A bidirectional Butterworth filter has been recommended for analysis of LPs [2]. By using this filter, the first part of the QRS is bandpass filtered, and then the second part of the QRS as well as the ST segment are filtered in reverse time, starting from the end of the data and moving towards the middle of the QRS. A bipolar orthogonal lead system is used to optimize the recording of LPs because of their unknown distribution on the body surface. The three leads are processed separately, and then combined into a vector magnitude of the form $\sqrt{X^2+Y^2+Z^2}$ and used for subsequent analysis. Bandpass filtering of the SA

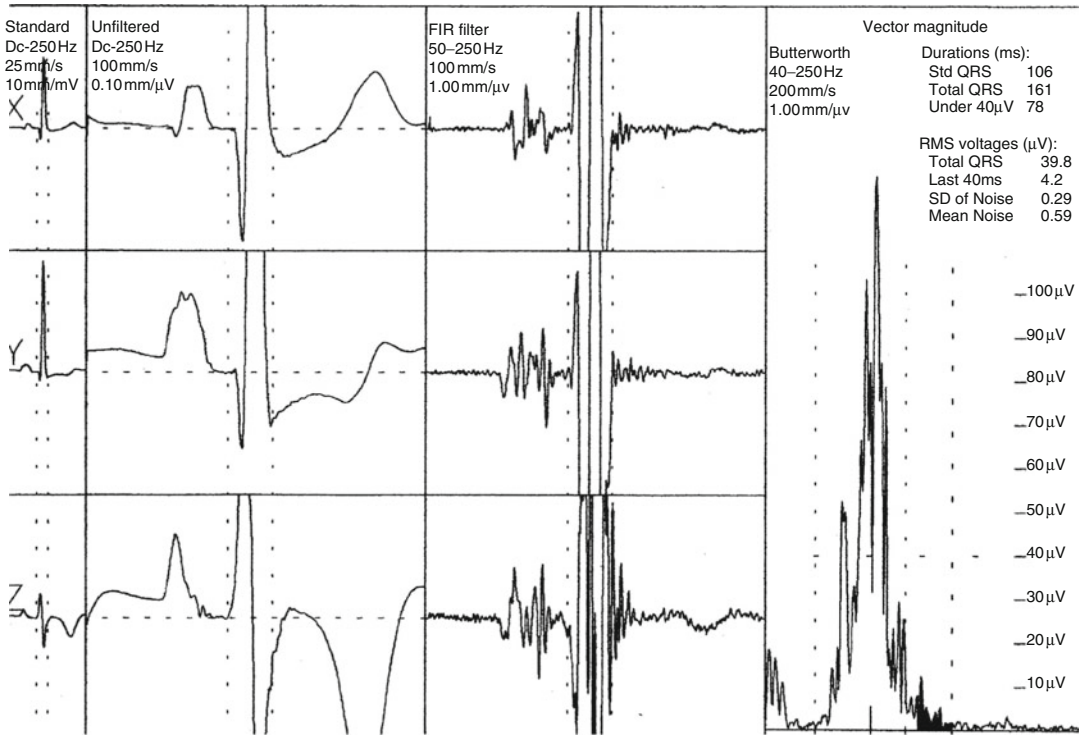

Figure 13–1. Example of abnormal time-domain analysis of the SAECG. Filtered QRS duration and duration of low amplitude signals are prolonged, while voltage of the terminal QRS is decreased, at a filter setting of 40–250 Hz. *Total QRS* high-frequency QRS duration, *Under 40 μV* duration of low-amplitude signals <40 μV, *RMS* root mean square, *Last 40 ms* RMS voltage of the terminal 40 ms of the QRS

vector magnitude may further discriminate LPs from noise. Early studies of the frequency signature of LPs showed that they contained predominantly high frequencies, and filters that eliminate low frequencies may expose LPs more clearly. Commercial SAECG systems apply bandpass filtering with a low-pass setting of 250 Hz and a high-pass setting of 25–40 Hz. Computer algorithms are utilized to identify QRS onset and offset. These algorithms depend on the signal-to-noise ratio [2]. Once the QRS offset is defined, time-domain analysis of the SAECG mainly consists of the determination of three parameters: the duration of the filtered QRS complex (QRSD), the duration of low-amplitude signals of <40 μV, i.e. the time that the filtered QRS voltage remains below 40 μV (LAS40), and the root mean square voltage of the terminal 40 ms of the QRS (RMS40). The ad hoc Task Force recommended that, for adequate LP analysis, a low noise level of <1 μV with a 25-Hz high-pass cutoff or <0.7 μV with a 40-Hz high-pass cutoff be obtained [4]. The Task Force also recognized that the definition of a LP and the scoring of a SAECG as normal or abnormal have not been standardized. Representative criteria include that a LP exists (using a 40-Hz high-pass filter) when: (1) QRSD is >114 ms; (2) LAS40 is >38 ms; and (3) RMS40 is <20 μV[4] (Fig. 13.1). Time-domain analysis remains the mainstay for SAECG analysis, due to its proven diagnostic accuracy and high reproducibility [8].

The ambulatory ECG has been proposed to record and examine the SAECG for risk stratification of post-MI patients [9, 10]. The prognostic value of SAECGs obtained from ambulatory (Holter) ECG recordings was found to compare favorably to that of conventional SAECGs.

Frequency-Domain Analysis

Techniques for frequency domain analysis were devised to overcome some of the limitations of

time-domain analysis, namely the inability to detect abnormal and delayed conduction within the QRS complex, or in the presence of intraventricular conduction defect. The rationale for frequency-domain analysis is the observation that the QRS, LP, and ST segment waveforms in the SAECG have different spectral characteristics. Various techniques have been described under different names, including spectro-temporal mapping, spectral turbulence analysis, wavelet decomposition analysis, and acceleration spectrum analysis [11–16]. At the present time, none of these techniques has gained widespread acceptance, due to their lack of standardization, sub-optimal reproducibility, and the lack of convincing evidence that frequency-domain analysis results in a greater diagnostic and prognostic accuracy than conventional time-domain analysis.

Clinical Applications of the SAECG

Post-infarction Patients

The prevalence of an abnormal SAECG in normal subjects, and in patients with prior MI with or without ventricular tachyarrhythmias is shown in Table 13.1 [1]. The reported wide range in the prevalence of LPs following MI may be related to differences in the diagnostic criteria for LPs, as well as in the time of recording of the SAECG [17–19], and the site of MI [20]. El-Sherif et al. showed that the prevalence of an abnormal SAECG recording varied widely in the first 60 days after MI [18, 19]. An abnormal recording 6–30 days after MI had the most significant relation to arrhythmic events occurring in the first year post-MI [19]. LPs became progressively less frequent following hospital discharge [17, 18]. In a study by Gomes et al., LPs were more common in patients with inferior MI compared to patients with anterior MI [20]. This could be related to the fact that the infero-posterior segments of the left ventricle depolarize later than the antero-septal and anterior segments. Thus, in patients with inferior MI, delayed regional activation is likely to outlast normal ventricular depolarization and appear as LPs after the QRS offset. On the other hand, in patients with anterior MI, the abnormal myocardial region is activated early during the QRS complex, resulting in partial obscuring of LPs.

Risk stratification of survivors of MI has been successfully performed with time-domain analysis of the SAECG. Several prospective studies have confirmed the increased likelihood of malignant ventricular tachyarrhythmias and SCD in post-MI patients with an abnormal SAECG [19–30]. A previous review analyzed studies in which the SAECG was performed in approximately 5,000 patients within 1 month of MI (usually at the time of hospital discharge), with an average follow-up of 13 months [31]. The SAECG was abnormal in 29 % of patients, while arrhythmic events occurred in 7 % of patients. The positive predictive accuracy of the SAECG was low (mean: 17 %, range: 8–29), while its negative predictive accuracy was high (mean: 96 %, range: 81–99). Because of the low predictive accuracy of the test, no intervention is justified in post-MI patients based solely on the presence of an abnormal SAECG [5]. The prognostic value of the SAECG in post-MI patients was also reviewed by Bailey et al., in a meta-analysis of almost 10,000 patients [30]. This showed the high sensitivity and specificity of the test, as well as its low positive predictive accuracy (Table 13.2) [30].

A multicenter NIH-sponsored substudy of the Cardiac Arrhythmia Suppression Trial (CAST)

Table 13–1. Prevalence of an abnormal SAECG in normal subjects and in post-infarction patients with or without malignant ventricular tachyarrhythmias

Study groups	Prevalence (%) Time-domain	Frequency-domain
Normal subjects	0–10	4
Recent MI (<2 weeks), no VTA	14–29	26
Remote MI (≥1 month), no VTA	18–33	23
Remote MI (≥1 month), VTA	52–90	73–92

From Cain [5]. Reprinted with permission from Elsevier
MI myocardial infarction, *VTA* ventricular tachyarrhythmias

Table 13–2. Prognostic value of the SAECG for serious arrhythmic events after myocardial infarction

Studies (n)	22
Patients (n)	9,883
Follow-up (months)	22
Arrhythmic events (%)	7.2
Sensitivity (%)	62
Specificity (%)	77
Positive predictive accuracy (%)	19
Relative risk	4.8
Odds ratio	5.7

From Bailey et al. [30]. Reprinted with permission from Elsevier

Table 13–3. Prognostic value of the SAECG after myocardial infarction in the CAST substudy

Variable	χ^2	Probability
QRSD/25 Hz	32.4	.0000
RMS40/25 Hz	4.1	.0433
LAS/25 Hz	23.8	.0000
QRSD/40 Hz	**37.1**	**.0000**
RMS40/40 Hz	4.5	.0344
LAS/40 Hz	10.3	.0001

From El-Sherif et al. [27]. Reprinted with permission from Elsevier
LAS duration of low-amplitude signals of <40 μV, *QRSD* high-frequency filtered QRS duration, *RMS40* root mean square voltage of the terminal 40 ms of the QRS. All parameters were measured at high-pass filter settings of 25 and 40 Hz
Bold = Most significant parameter

was conducted to define the best predictive criteria of time-domain SAECG in the post-MI period [27]. A total of 1,158 patients was recruited and followed for an average of 10 ± 3 months. Forty-five patients (4 %) suffered serious arrhythmic events (nonfatal VT or SCD). A Cox regression analysis with six SAECG variables indicated that a filtered QRSD at 40 Hz ≥120 m was the most predictive criterion of arrhythmic events (Table 13.3). An abnormal SAECG, defined as QRSD at 40 Hz ≥120 ms, was present in 12 % of the study population. The positive, negative and total predictive accuracy of an abnormal SAECG was 17, 98, and 88 %, respectively [27].

Several studies have shown that the predictive value of the SAECG could be increased by combining its results with other clinical data, such as left ventricular ejection fraction (LVEF), degree of ventricular ectopy, heart rate variability [19–23, 26, 28, 30, 32]. Bailey et al. surveyed the literature to estimate prediction values for five common tests for major arrhythmic events (MAE) after MI [30]. They identified 44 studies on SAECG, heart rate variability, ventricular arrhythmias on ambulatory ECG, LVEF, and electrophysiology study. Their meta-analysis used receiver-operating characteristic curves to estimate mean values for sensitivity and specificity for each test and 95 % confidence limits (Fig. 13.2). According to these Authors, it may be feasible to stratify as many as 90 % of post-MI patients into "high risk" (>30 %) and "low risk" (<3 %) categories using combinations of four noninvasive tests (Table 13.4) [30]. With this approach, the first step would be performance of both SAECG and LVEF. If the two tests were both negative or both positive (as would be true for 64.2 % of the patients), further testing would not be done, as the 2-year probability of a MAE would be very low in the former situation (2.2 %), and high enough in the latter situation (38.7 %) to warrant consideration of ICD implantation. The second step would be performance of a 24-h ambulatory ECG in the 35.8 % of patients who had only a positive SAECG or only a low LVEF, resulting in an intermediate risk for a MAE (10.6 % over 2 years). If the ambulatory ECG and heart rate variability were both normal or both abnormal (25.9 %), no further testing would be needed, because in the former situation, the posterior probability would still be below the original prior probability, despite having either an abnormal SAECG or a low LVEF, and in the latter case, the posterior probability would again be high enough to warrant consideration of ICD implantation. As a result of this non-invasive approach, approximately 90 % of patients would be accurately risk stratified into low-risk (80 %) and high-risk (10 %) groups for MAE, while the unstratified group would include only 10 % of post-MI patients.

A limitation of risk stratification studies in post-MI patients may be the reduced ability to predict arrhythmic events in the era of aggressive treatment of MI, including reperfusion or revascularization strategies, and pharmacotherapy (i.e. beta-blockers) [33–35]. In this setting, the prognostic value of LPs may be diminished [33–35]. However, the recently published Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study confirmed the ability of the SAECG to predict arrhythmic events after MI [36]. A total of 312 patients with a mean LVEF of 31 ± 6 % was

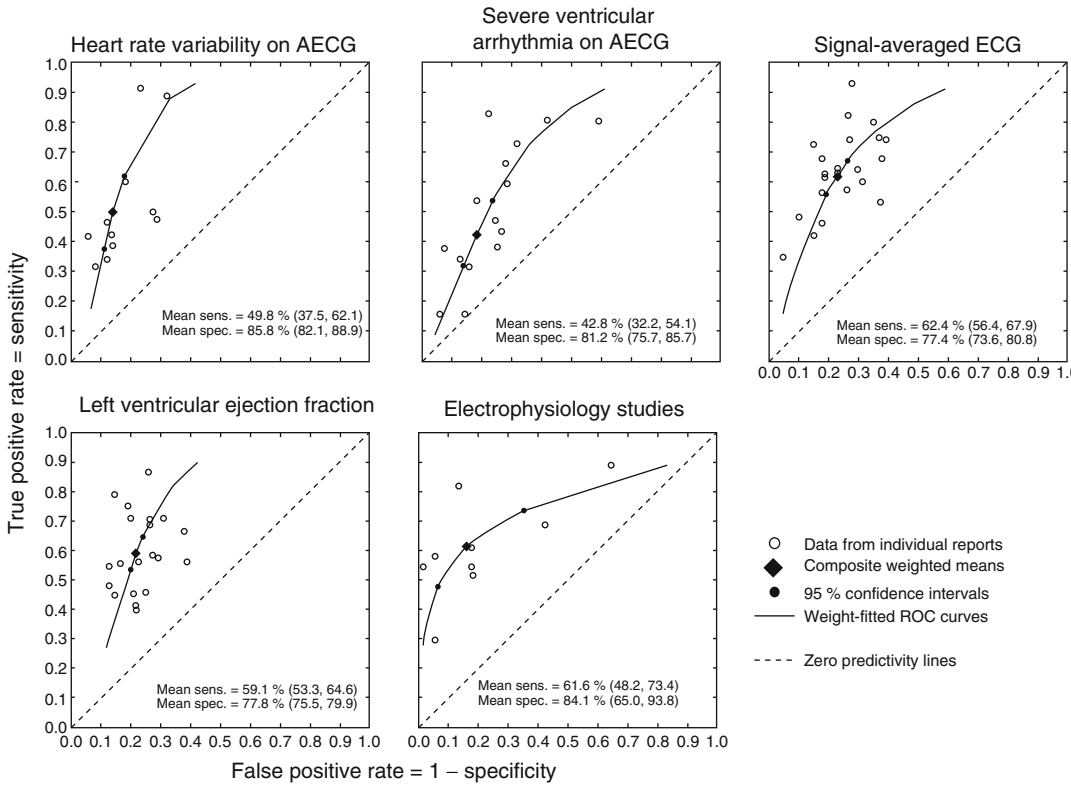

Figure 13–2. Receiver operator curves (*ROC*) for five risk stratifiers for major arrhythmic events after myocardial infarction. Mean values for sensitivity and specificity and 95 % confidence intervals for each test are shown. *AECG* ambulatory electrocardiogram (From Bailey et al. [30]. Reprinted with permission from Elsevier)

Table 13–4. Staged application of tests for prediction of major arrhythmic events following myocardial infarction

Test combination	Results of tests	Proportion of population (%)	Probability of MAE over 2 years (%)
Stage 1 = SAECG and LVEF	Both negative	56.6	2.2
	Only one positive	35.8	10.6
	Both positive	7.6	38.7
Stage 2 = AECG (SVA and HRV) performed on "only one positive" patient of stage 1	Both negative	23.3	4.7
	Only one positive	10.8	17.5
	Both positive	2.6	48.2

From Bailey et al. [30]. Reprinted with permission from Elsevier
Based on a 2-year prior probability of 7.9 %
AECG ambulatory (Holter) ECG, *HRV* heart rate variability, *LVEF* left ventricular ejection fraction, *SVA* serious ventricular arrhythmias on ambulatory (Holter) ECG

included in this study. Heart rate variability and turbulence, ambient arrhythmias on 24-Holter recordings, SAECG, T-wave alternans, and programmed electrical stimulation were performed 6 weeks after MI. The primary endpoint was ECG-documented ventricular fibrillation or symptomatic sustained VT. To document these arrhythmic events, the patients received an implantable ECG loop recorder. There were 25 primary endpoints (8 %) during a follow-up of 2 years. QRSD on the SAECG was a significant predictor of the primary endpoint, along with several heart rate variability measures (Fig. 13.3). A QRSD >120 ms on the SAECG had a sensitivity, specificity, and positive and negative predictive values for arrhythmic events of, respectively, 44, 85, 20, and 95 % [36].

The Occluded Artery Trial – Electrophysiological Mechanisms (OAT-EP) tested the hypothesis that opening a persistently occluded infarct-

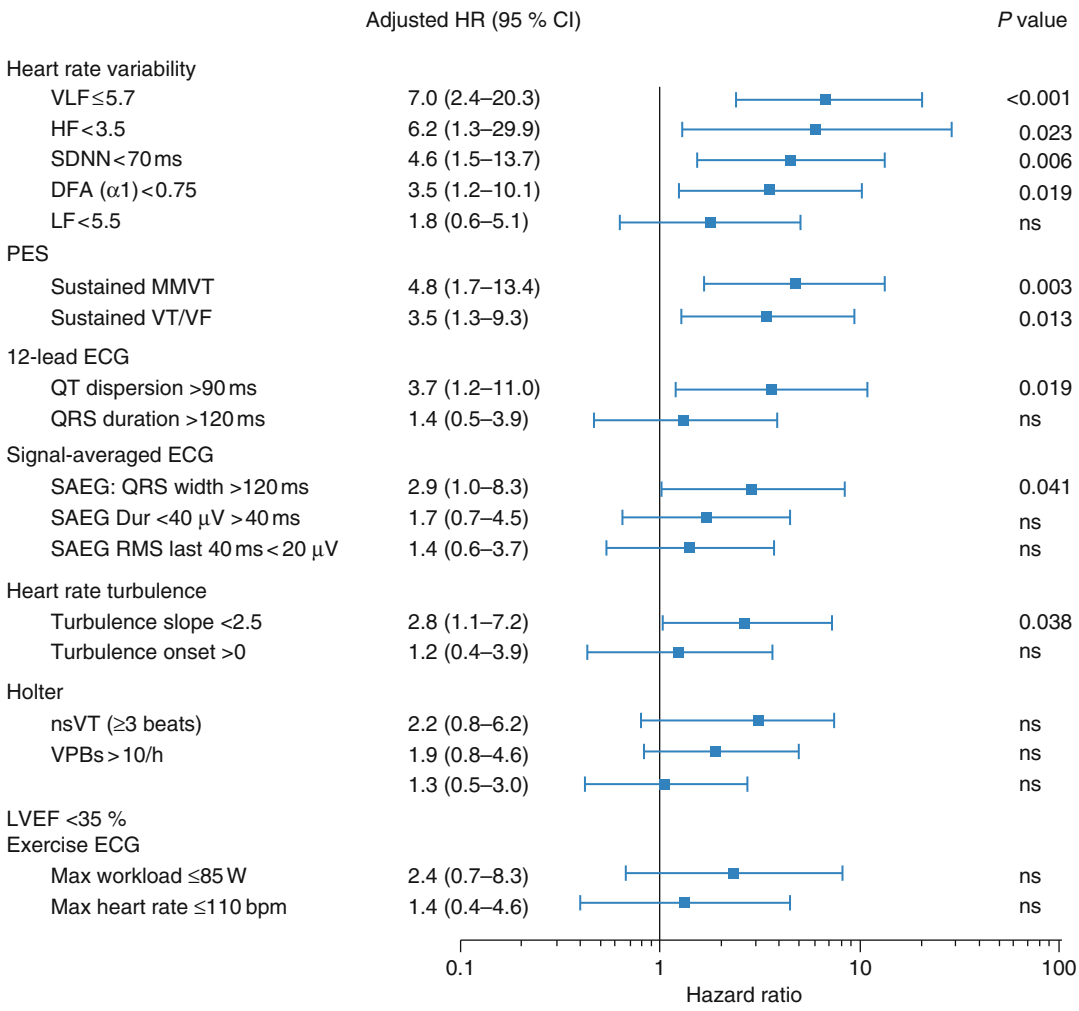

Figure 13–3. Adjusted hazard ratios (HRs) with 95 % confidence intervals of predictors of primary endpoint (ECG-documented ventricular fibrillation or symptomatic sustained VT) in 312 out of 5,869 screened post-infarction patients, who had LVEF ≤40 %. HRs are calculated from predefined threshold values of continuous variables. HRs are adjusted for age, prior MI, history of congestive heart failure, and diabetes. The variables are listed in descending order starting with the highest HR for each risk stratification method. *DFA* fractal scaling exponent of heart rate variability, *HF* high frequency, *LF* low frequency, *MMVT* monomorphic ventricular tachycardia, *PES* programmed electrical stimulation, *SDNN* standard deviation of N–N (R–R) intervals, *VF* ventricular fibrillation, *VLF* very low frequency, *VPBs* ventricular premature beats (Reproduced from Huikuri et al. [36], with permission from the European Society of Cardiology and Oxford University Press)

related artery by percutaneous coronary intervention and stenting after the acute phase of MI compared to optimal medical therapy alone reduces markers of vulnerability to ventricular arrhythmias. In this study, 300 patients with an occluded native infarct-related artery 3–28 days after MI were randomized to coronary intervention or medical therapy. Ten minute digital Holter recordings were obtained prior to randomization, at 30 days, and at 1 year. Holter data were analyzed for heart rate variability parameters, SAECG variables, and T-wave variability. The major findings of this study were that coronary intervention on a persistently occluded infarct-related artery compared to medical therapy alone had no significant effect on measures of heart rate variability, SAECG, or T-wave variability during the first year after MI. Although late coronary patency was achieved in 83 % of study patients and at least moderately retained viability was present at baseline in 69 %, percutaneous coronary intervention had no

significant effect on changes in the major determinants of arrhythmia vulnerability: the autonomic nervous system (heart rate variability), impulse conduction (SAECG), and ventricular repolarization (T-wave variability) [37].

This review of the literature suggests that sensitivities and specificities for the most commonly used non-invasive tests for risk stratification of SCD in post-MI patients, including the SAECG, are relatively low. No one test is satisfactory alone for accurately predicting risk. Combinations of tests in stages may result in an improvement of the positive predictive accuracy of non-invasive risk stratifiers.

Patients with Non-sustained Ventricular Tachycardia

The SAECG was initially utilized to predict the outcome of programmed ventricular stimulation in patients with coronary artery disease and asymptomatic non-sustained VT [31]. In a study from Turitto et al., LPs proved to be the single most accurate predictor for the induction of sustained monomorphic VT in 105 patients with non-sustained VT [38]. In this study, concordance between the results of programmed stimulation and those of the SAECG was observed in 84 % of cases. The largest subgroup consisted of patients who had a normal SAECG and no induced sustained monomorphic VT (70 %). In these patients, the spontaneous arrhythmia may be due to mechanisms other than reentry. The group with both abnormal SAECG and induced sustained VT accounted for 14 % of cases. The results of the two tests were discordant in the remaining 16 % of cases. This may be explained by electrophysiologic limitations of both programmed stimulation and SAECG techniques [38]. Subsequent studies have shown that the SAECG may also predict the results of programmed stimulation in patients with non-ischemic dilated cardiomyopathy [39–42].

The most compelling data on the predictive accuracy of the SAECG in patients with coronary artery disease, prior MI, left ventricular dysfunction, and asymptomatic non-sustained VT originated from the SAECG substudy of the Multicenter UnSustained Tachycardia Trial (MUSTT) [43]. In this large, prospective, multicenter study, SAECG data from 1,268 patients were entered in a Cox proportional hazards modeling to examine individual and joint relations between SAECG parameters and arrhythmic death or cardiac arrest (primary end point), cardiac death, and total mortality. In all patients, SAECG quantitative variables were processed at 40–250 Hz and included filtered QRSD, RMS40 and LAS40. First, in order to assess the prognostic content of a "normal" versus "abnormal" SAECG, the SAECG parameters were analyzed as continuous variable and as dichotomized at standard cut points. A QRSD >114 ms was the single most powerful independent predictor of the primary end point and cardiac death, and was, thus, defined as an abnormal SAECG (Table 13.5) [43]. The SAECG variables remained significant predictors after adjustment for prognostic clinical and treatment factors. Second, to illustrate the ability of the SAECG to stratify risk, patients were divided by QRSD (>114 ms [abnormal SAECG] versus ≤114 ms [normal SAECG]) and Kaplan-Meier survival curves were generated for each outcome (Fig. 13.4) [43]. With an abnormal SAECG, the 5-year rates of the primary end point (28 % versus 17 %, P = 0.0001), cardiac death (37 % versus 25 %, P = 0.0001), and total mortality (43 % versus 35 %, P = 0.0001) were significantly higher. The combination of LVEF <30 % and abnormal SAECG identified a particularly high-risk subset that constituted 21 % of the total population. Thirty-six percent and 44 % of patients with this combination experienced arrhythmic events or cardiac death, respectively, during a 5-year follow-up. On the other hand, 13 and 20 % of patients without this combination experienced arrhythmic events or cardiac death, respectively, during a 5-year follow-up. The Authors concluded that an abnormal SAECG (defined as a filtered QRS duration >114 ms) is a strong predictor for both arrhythmic events and cardiac mortality in patients with ischemic cardiomyopathy [43].

Patients with Non-ischemic Dilated Cardiomyopathy

Studies investigating the prognostic value of the SAECG in non-ischemic dilated cardiomyopathy are relatively scarce [42, 44–46]. In some early studies, the SAECG was found to be a predictor of survival [44, 45]. The heterogeneity

Table 13–5. Multivariate analysis of SAECG quantitative values as predictors of outcome in the MUSTT SAECG Substudy

Predictor	Arrhythmic death/cardiac arrest χ^2	*P*	Cardiac death χ^2	*P*
Continuous variables				
Filtered QRS duration	29.2	<0.001	34.0	<0.001
RMS voltage	14.3	0.004	17.0	<0.001
Duration of LAS	0.3	0.59	0.2	0.62
Dichotomous variables				
Filtered QRS duration (>114 vs. ≤114 ms)	23.1	<0.001	20.8	<0.001
RMS voltage (<20 vs. ≥20 μV)	0.3	0.59	0.1	0.73
Duration of LAS (<38 vs. ≥38 ms)	1.6	0.21	0.3	0.58

From: Gomes et al. [43]. Reprinted with permission from Wolters Kluwer Health

LAS low amplitude signals of <40 μV, *RMS* root mean square voltage of the terminal 40 ms of filtered QRS. SAECG parameters were analyzed at 40–250 Hz filter setting

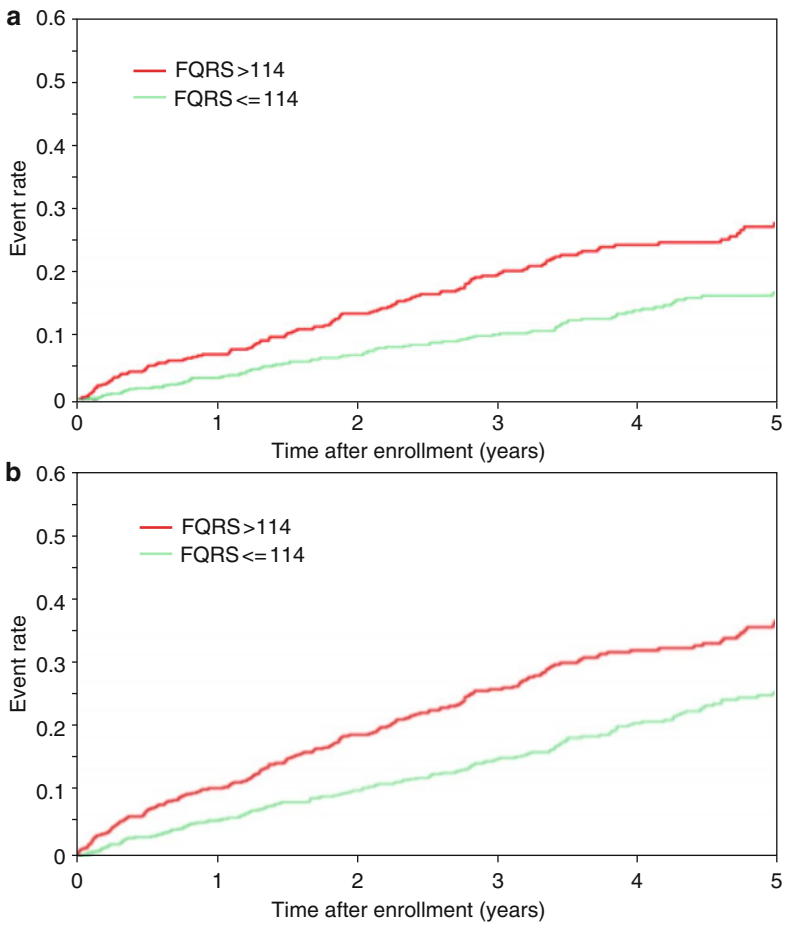

Figure 13–4. Kaplan-Meier estimates of arrhythmic death or cardiac arrest (**a**) and cardiac death (**b**) by SAECG result in the MUSTT substudy. P < 0.001 between groups; *fQRS* high-frequency QRS duration (From Gomes et al. [43]. Reprinted with permission from Wolters Kluwer Health)

of the study population with respect to the presence of spontaneous ventricular tachyarrhythmias and bundle branch block, as well as the empirical use of antiarrhythmic drugs, which could have influenced both the results of the SAECG and clinical outcome, may explain the discrepancies between these reports and other series, which did not find any correlation

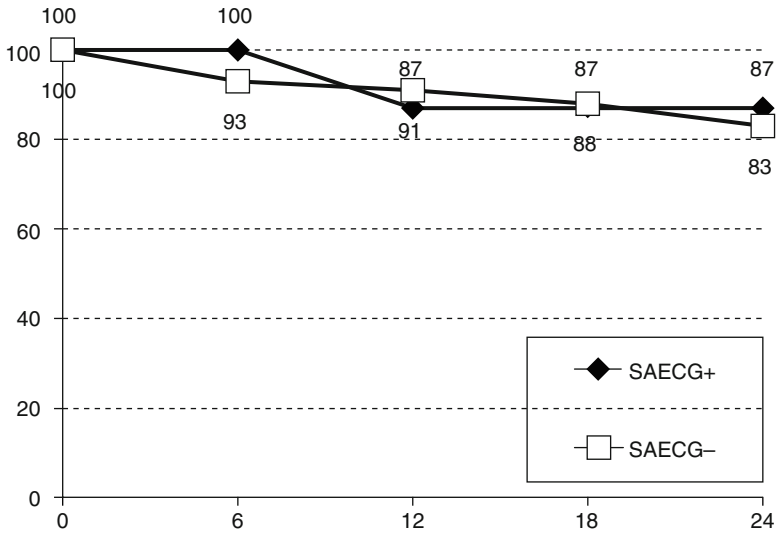

Figure 13–5. Two-year actuarial survival curves for arrhythmic events in 80 patients with non-ischemic dilated cardiomyopathy classified by SAECG results. *SAECG+* abnormal recording, *SAECG–* normal recording. Data are expressed as mean value ± standard error (From Turitto et al. [42]. Reprinted with permission from Elsevier)

between an abnormal SAECG and prognosis in patients with dilated cardiomyopathy [42, 46].

Turitto et al. performed SAECG and programmed ventricular stimulation in a group of 80 subjects with non-ischemic dilated cardiomyopathy and spontaneous non-sustained VT, who had a mean follow-up of 22 months [42]. Survival analysis with Cox proportional hazards model demonstrated that no test result was significantly associated with arrhythmic events or total cardiac mortality [42]. When 2-year survival analysis was based on the results of the SAECG, there were no significant differences in arrhythmia-free survival or cumulative survival between patients with or without an abnormal SAECG (Fig. 13.5). An important finding in this study was that the presence of a normal SAECG and lack of inducibility of sustained monomorphic VT did not portend a favorable prognosis, in patients with non-ischemic dilated cardiomyopathy and spontaneous non-sustained VT [42].

In the Marburg Cardiomyopathy Study, arrhythmia risk stratification was performed prospectively in 343 patients with idiopathic dilated cardiomyopathy [46]. This included analysis of LVEF by echocardiography, SAECG, arrhythmias on ambulatory ECG, QTc dispersion, heart rate variability, baroreflex sensitivity, and T-wave alternans. During 52 ± 21 months of follow-up, major arrhythmic events, defined as sustained VT, ventricular fibrillation, or SCD, occurred in 46 patients (13 %). On multivariate analysis, LVEF was the only significant arrhythmia risk predictor in patients with sinus rhythm, with a relative risk of 2.3 per 10 % decrease of ejection fraction (95 % CI, 1.5–3.3; P = 0.0001). In patients with atrial fibrillation, multivariate Cox analysis identified LVEF and absence of beta-blocker therapy as the only significant arrhythmia risk predictors. SAECG, baroreflex sensitivity, heart rate variability, and T-wave alternans did not appear to be helpful for arrhythmia risk stratification in this population [46]. These results strongly support the recommendation that novel risk stratification strategies be sought in patients with non-ischemic dilated cardiomyopathy.

Miscellaneous Applications

Hypertrophic Cardiomyopathy

There are limited data on the prevalence and prognostic value of the SAECG in patients with hypertrophic cardiomyopathy. In two studies from the group of McKenna, there was low prevalence of abnormal SAECG and lack of correlation with SCD [47, 48].

Arrhythmogenic Right Ventricular Cardiomyopathy/Disease (ARVC/D)

An abnormal SAECG is frequently seen in patients with right ventricular cardiomyopathy, and LPs have been listed as a minor diagnostic criterion for this disease [49]. They were also

incorporated in the most recent revision of the Task Force criteria for the diagnosis of ARVC/D [50, 51]. The Multidisciplinary Study of ARVC/D reexamined the value of the SAECG in a large population of genotyped ARVC/D probands [52]. The study included 87 ARVC/D probands (age 37 ± 13 years, 47 males) diagnosed as affected (n = 62) or borderline (n = 25) by Task Force criteria without using the SAECG criterion. Conventional time-domain analysis was obtained using a high-pass filter at 40 Hz. A recording was deemed to be abnormal according to the ad hoc Task Force criteria [4]. In this study, the SAECG and its components QRSD, LAS40, and RMS40 were highly associated with the diagnosis of ARVC/D. The sensitivity of using SAECG for the diagnosis of ARVC/D was increased from 47 % using two of the three criteria to 69 % by using any one of the three criteria, while maintaining high specificity of 90–95 %. Abnormal SAECG as defined by these modified criteria was strongly associated with dilated right ventricular volumes and decreased right ventricular ejection fraction detected by cardiac magnetic resonance imaging. SAECG abnormalities did not vary with clinical presentation or reliably predict spontaneous or inducible VT, and had limited correlation with ECG findings.

Primary Electrical Disease

This term refers to ventricular tachyarrhythmias occurring in the absence of documented structural heart disease. The exclusion of unrecognized ARVC/D is important especially in patients with right-sided VT (left bundle branch block configuration). The role of the SAECG as a screening test in patients with cardiac arrest in the absence of evident structural heart disease was assessed in two recent studies [53, 54]. The Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER) enrolled patients with apparently unexplained cardiac arrest and no evident cardiac disease (normal cardiac function on echocardiogram, no evidence of coronary artery disease, and a normal ECG). Sixty-three patients were enrolled and underwent systematic testing, including cardiac magnetic resonance imaging, SAECG, exercise testing, drug challenge, and selective electrophysiological testing. This systematic evaluation resulted in unmasking of the cause of apparently unexplained cardiac arrest in 35 patients (56 %): long-QT syndrome in eight, catecholaminergic polymorphic VT in eight, ARVC/D in six, early repolarization in five, coronary spasm in four, Brugada syndrome in three, and myocarditis in one. The diagnosis of ARVC/D in six patients was based on a combination of an abnormal SAECG in three, genetic testing in two, an abnormal voltage map in two, a diagnostic biopsy in one, and right ventricular premature complexes during adrenaline infusion in one. A similar investigative strategy utilized in families with sudden arrhythmic death syndrome confirmed the high prevalence of inherited heart diseases in this category of patients and the value of the SAECG as a screening test for ARVC/D [54].

A few studies suggested that LPs may be of value for risk stratification of patients with the Brugada syndrome [55–57]. In a study enrolling 43 Chinese patients with Brugada syndrome (24 with symptoms and 19 without symptoms), there was a high prevalence of a positive SAECG (92 % in the symptomatic group and 37 % in the asymptomatic group). During a mean follow-up of 34 ± 9 months, the incidence of arrhythmic events was 73 % (21/29) in LP-positive patients compared with 14 % (2/14) in LP-negative patients. A multivariate Cox proportional hazard analysis including historical variables and the results of an invasive electrophysiological evaluation revealed that the presence of LPs had the most significant hazard ratio of 10.9, with sensitivity, specificity, positive predictive value, negative predictive value, and total predictive accuracy of 96, 65, 76, 93, and 82 %, respectively. The results of this study may support the role of LPs detected by SAECG in arrhythmic risk stratification of Brugada syndrome patients.

Conclusions

The SAECG is an established noninvasive test for risk stratification for SCD, especially in survivors of MI. It has a very high negative predictive accuracy but a relatively low positive predictive accuracy. Improved risk stratification may be accomplished if this test is utilized as

part of an algorithm in conjunction with other risk stratifiers. For this purpose, new ambulatory monitoring devices utilizing digital recordings with high sampling rate may permit the simultaneous analysis of several non-invasive parameters (e.g., LPs, heart rate variability, T-wave alternans) from the same recording. Large prospective studies to develop a robust prediction model are still warranted.

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14
Surface Mapping and Magneto-Electrocardiography

Satsuki Yamada and Akihiko Kandori

Abstract

The heart generates magnetic fields that can be detected by body surface mapping utilizing superconducting interference device sensors giving magnetocardiograms (MCGs). The advantages of MCGs over traditional electrocardiograms (ECGs) include increased sensitivity to small signals, less interference by tissue conductivities, and presentation of direct component signals and primary currents. This section highlights the basic principles, recent advancements, and clinical application of MCGs, especially in individuals whose ECGs are not diagnostic. Indeed, MCGs have unique value in diagnosis of prenatal electrical abnormalities, baseline shift in ischemic heart disease, His potential recording, mechanisms and foci of arrhythmias. State of the art technologies for 2D and 3D reconstruction of cardiac electrical activity combined with other cardiac imaging modalities are also discussed.

Keywords

Electrical currents • Magnetic fields • SQUID • Prenatal diagnosis • Reentrant circuits • Arrhythmogenicity

Introduction

Major progress in non-pharmacological therapies for the management of cardiac electrical disorders has been achieved over the past decades. Device therapy is a necessary palliative approach for advanced stage heart failure, however, a prophylactic approach for electrical abnormalities in failing myocardium has not yet been established. One of the limitations is due to lack of clinical parameters which could detect disease substrate thus predicting a risk for arrhythmic events. Reduced systolic function of the left ventricle is the most reliable predictor for poor outcome, but this parameter does not specify myocardial electrical properties. The

S. Yamada, MD, PhD (✉)
Division of Cardiovascular Diseases,
Department of Medicine, Molecular Pharmacology and Experimental Therapeutics, and Medical Genetics,
Mayo Clinic, Stabile 5, 200 First Street, SW, Rochester, Minnesota 55905, USA
e-mail: yamada.satsuki@mayo.edu

A. Kandori, PhD(Eng), PhD(Med)
Central Research Laboratory,
Life Science Research Center,
Hitachi Ltd, 1-280 Higachi-koigakubo,
Kokubunji-shi, Tokyo 185-8601, Japan
e-mail: akihiko.kandori.vc@hitachi.com

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electrocardiogram (ECG) is widely used as a standard diagnostic tool, but it also harbors certain limitations, as some ECGs may not provide sufficient information required for clinical decision-making, such as in patients with baseline ECG abnormalities, e.g., with ventricular hypertrophy, ischemic heart disease, or those using certain medications. Moreover, patients with a normal or nonspecific ECG, in spite of latent cardiac disease, are less likely to be hospitalized and may consequently suffer adverse events, including increased mortality [1]. Therefore, it is essential to have additional diagnostic tools to increase the probability of detecting individuals who are likely to suffer from adverse cardiac events.

Ongoing efforts to overcome limitations of conventional 12-lead ECG include novel methodologies for (1) signal detection (e.g., magnetocardiography), (2) signal processing (e.g., signal average electrocardiogram, heart rate variability, and T wave alternans), (3) 2D and 3D reconstruction of body surface electrical potentials combined with cardiac imaging modalities [2, 3], (4) induction test to unmask arrhythmogenicity (e.g., noninvasive- and invasive-programmed stimulation), and (5) genetic test (e.g., long QT syndrome and Brugada syndrome). A magnetocardiogram (MCG), the first noted novel methodology, is a body surface mapping technique that detects cardiac magnetic fields and especially weak electrophysiological phenomena that could be missed by an ECG. Advantages of MCGs over traditional ECGs are increased sensitivity to small signals, lack of distortion from conductivity in body tissues, and presentation of direct current (DC) component signals and primary currents. This review highlights the basic principles and recent advantages of magnetocardiography, and clinical application of an MCG for detecting arrhythmic substrates related to sudden cardiac death. Areas of future basic and clinical research are also discussed.

Basic Principles of Magnetocardiograms

Biomagnetic Fields

A changing electrical field produces a magnetic field, as Hans C. Ørsted found that a compass needle placed by chance near a wire carrying electrical current swings (Table 14.1). This principle, electromagnetism, also applies to currents associated with the electrophysiological phenomena in human body. Action potentials originating in myocardial cells create electrical currents and thus both electric and magnetic fields occur. At the body surface, cardiac electric fields are measured by ECGs and by body surface potential mappings, while cardiac magnetic fields may be measured by MCGs. Although the cardiac magnetic field (adult heart 10^{-10} tesla (T), fetal heart 10^{-12} T) is the strongest of all biomagnetic fields, it is still a million times weaker than the earth's magnetic field (10^{-5} T) and a thousand times weaker than magnetic fields

Table 14–1. History of magnetocardiogram

Year	MCG	ECG and others
Eleventh century	Compasses in China (detection of the earth's magnetic field)	
1820	Discovery of electromagnetism (Ørsted)	ECG in human (Waller 1887) ECG system by Einthoven (1903) Fetal ECG (Cremer 1906) ECG in sinus rhythm, AF, and VF (Lewis 1909–1911) Percutaneous transfemoral catheterization (Seldinger 1953) Echocardiogram (Edler and Hertz 1953)
1963	Detection of the cardiac magnetic fields (Baule)	
1970	Single-channel MCG system using SQIOD (Cohen)	EP study [4] MR [5]
1980s	Multi-channel MCG system using DC-SQUID	
1990s	High-temperature-SQUID MCG system without a magnetically shielded room	Catheter ablation in WPW syndrome by radiofrequency current [6]

AF atrial fibrillation, *DC* direct current, *ECG* electrocardiogram, *EP* electrophysiological, *MCG* magnetocardiogram, *MR* magnetic resonance, *SQUID* superconducting quantum interference device, *WPW syndrome* Wolff-Parkinson-White syndrome, *VF* ventricular fibrillation

associated with urban noise (approximately 10^{-7} T) (Fig. 14.1) [7, 8]. Therefore, detecting these weak physiological signals in a noisy environment is one of the primary issues pertaining to MCG studies. To improve signal-to-noise ratio, current MCG systems use superconducting quantum interference devices (SQUIDs, minimal detection threshold of 10^{-15} T), a gradiometer, a magnetically shielded room, filtering, and signal averaging.

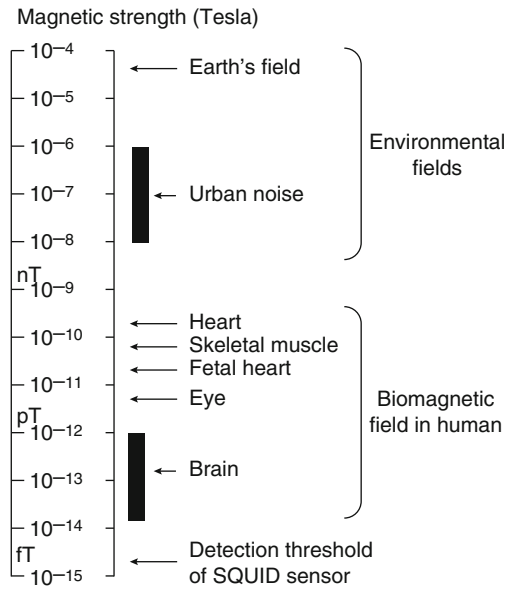

Figure 14–1. Biomagnetic fields. *fT* femtotesla, *nT* nanotesla, *pT* picotesla, *SQUID* superconducting quantum interference device

Advantages of Magnetocardiograms Over Electrocardiograms

ECGs and MCGs provide information originating from the same phenomena, cardiac electrophysiological activity, by using different methods, i.e., ECGs detect the electrical fields using electrodes, while MCGs measure the magnetic fields using SQUID sensors. Therefore, signals show similar patterns in these two forms of electrophysiological mapping (Fig. 14.2). Waveforms of atrial activation, ventricular depolarization, and ventricular repolarization are called P, QRS, and T waves, respectively, in both. In addition, conduction time also shows significant linear correlation between ECGs and MCGs.

While MCGs and ECGs share many similarities, MCGs have some distinct advantages over ECGs (Table 14.2), related to several signal-modifying variables between the heart and sensors at the body surface [9]. First, MCGs constitute a completely noninvasive system measuring spontaneous magnetic fields that accompany the heartbeat. There is no need for electrodes, radiation, or stimulation procedures in MCGs, whereas ECGs require patch or needle electrodes. No necessity for direct body contact in turn confers a second advantage – skin electrode interference does not exist in MCGs. A third advantage is that MCGs are less affected by conductivities of body tissues than are ECGs. Fluids and fat surrounding the heart reduce

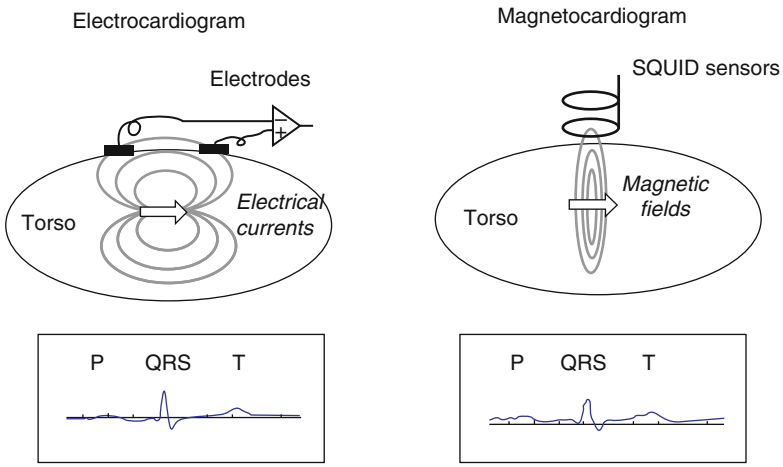

Figure 14–2. Relationship between signals and sensors in electrocardiography and that in magnetocardiography. One heart beat was simultaneously recorded by electrocardiography (lead II, *left bottom*) and magnetocardiography (approximately V1 position, *right bottom*) in the same subject, a 60-year old healthy male. *SQUID* superconducting quantum interference device

Table 14–2. Advantages of magnetocardiogram

	12-lead ECG	BSPM	MCG	EPS
Advantage				
1. Effects of body tissues on conductivities	High	High	Low	Low
2. Contact to skin or heart required	Yes, noninvasive	Yes, noninvasive	No	Yes, invasive
3. Skin-electrode or tissue-electrode interference	Yes	Yes	No	Yes
4. Components of volume currents	High	High	Low	Low
5. Direct-current filtering required	Yes	Yes	No	No
6. Use for fetal study	Yes, low	Yes, low	Yes, high	No
7. Spatial resolution	Low	Intermediate	Intermediate	High
8. Imaging technology	Low	High	High	High
9.Diagnosis/treatment	Diagnosis	Diagnosis	Diagnosis	Diagnosis/treatment
Disadvantage				
1. Environmental noise	Low	Low	High	Low
2. Portability	Yes, high	Yes, intermediate	No	No
3. Costs	Low	Intermediate	High	High
4. Clinical evidence	High	Intermediate	Low	High

BSMP body surface potential mapping, *ECG* electrocardiogram, *EPS* electrophysiological study, *MCG* magnetocardiogram

signal strength in ECGs but not in MCGs. Together, these three advantages make MCGs uniquely valuable in fetal diagnosis. Finally, DC components are not filtered in MCGs, an advantage over ECGs that makes them valuable for analyzing baseline shifts in cardiac ischemia. With respect to their spatial components, cardiac magnetic fields are measured as vectors in MCGs, while cardiac electrical fields are scalar values in ECGs. The DC components plus vector analysis make the baseline value of zero closer to "absolute zero" in MCGs compared to the baseline in ECGs. Because of these advantages, MCGs can provide unique and additional information when ECGs are not practical or not sensitive enough. Examples of phenomena successfully examined using MCGs are fetal arrhythmias (see the section on "Fetal Magnetocardiograms"), differentiation between primary and secondary ST-T changes, at-rest abnormalities in stable angina pectoris (see the section on "Ischemic Heart Disease"), and His potentials recording (see the section on "Arrhythmias"). In addition to the advantages of MCGs over ECGs (at the same recording position), current MCG systems have multiple channels (up to 64) and a variety of computer based analyzing methods [9, 10].

Measurements of Cardiac Magnetic Fields

Magnetocardiogram System

The MCG system is composed of sensors, computers for data processing, and a magnetically shielded system. Sensors are placed in a cooling system called a "Dewar" (or "cryostat"; arrow in Fig. 14.3a) to maintain superconductance. Because MCG systems have not been internationally standardized, their gradiometers (a first order or up to a third order), sensors, number of measuring points (from 1 up to 64), measuring areas, and shielding systems (with or without a shielding room, or a passive or active shield) differ between laboratories. In Japan, a 64-channel MCG system (Hitachi High-technologies MC-6400 model, Japan; Fig. 14.3) was officially approved by the Japanese Ministry of Health, Labor, and Welfare in 2002, and was commercialized in 2003 as the first system in Japan.

Measurements

Spatial Components of the Cardiac Magnetic Fields

Cardiac magnetic fields are measured as vector markers consisting of three spatial components,

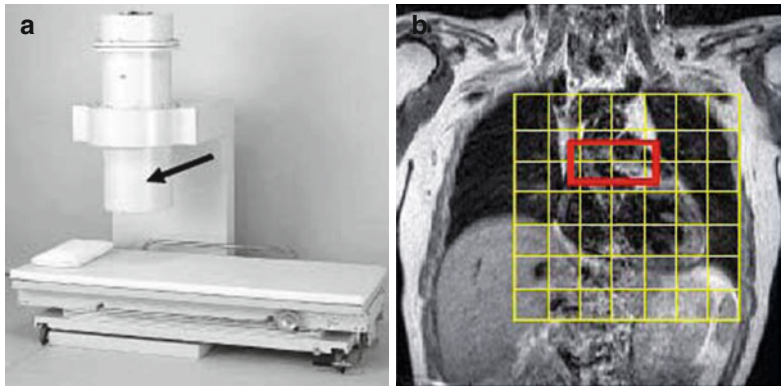

Figure 14–3. A 64-channel magnetocardiographic system. (**a**) Overview of the system (*arrow* indicates a Dewar). (**b**) A measuring area of 8 by 8 matrix (sensor interval, 2.5 cm; a measuring area, 17.5 by 17.5 cm) superimposed on a magnetic resonance image. (**c**) Signals (normal-component cardiac magnetic fields) at 3 (*red area* in b) out of 64 channels. *pT* picotesla

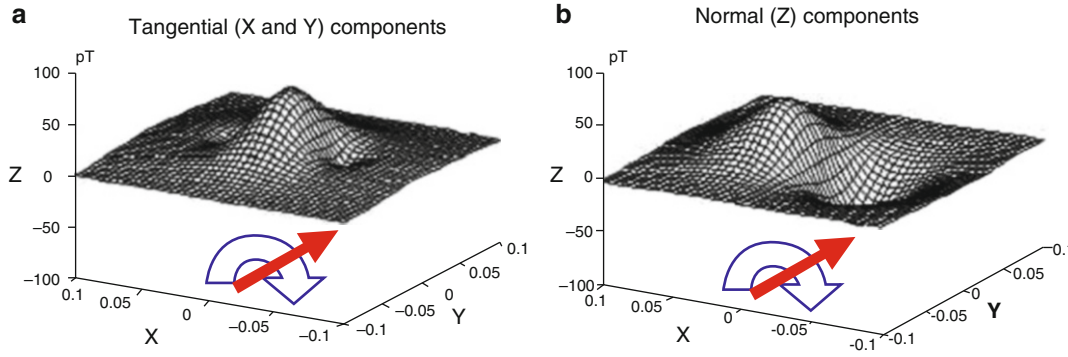

Figure 14–4. Spatial components of cardiac magnetic fields. Magnetic fields (*curved arrow*) show clockwise rotation along the electrical currents (*straight arrow*). The magnetic strength just above the magnetic source is the maximum in the tangential (or X and Y) components (**a**), while it is "zero" in the normal (or Z) components (**b**). *pT* picotesla [11]

called the X, Y, and Z components, corresponding to horizontal, longitudinal, and vertical components, respectively, in the anterior–posterior view (Fig. 14.4). As magnetic fields show clockwise rotation along electrical currents, the magnetic strength just above the magnetic source is maximum in the tangential (X and Y) components (Fig. 14.4a), while it is "zero" transitioning from positive to negative in the normal (or Z) components (Fig. 14.4b), as the electrical voltage above the electrical source is zero in ECGs or in body surface potential mappings. The normal-component MCG was developed first, but now both normal- and tangential-component MCGs are commercially available. Advantages of the normal-component MCG are (1) less disturbance by volume (or secondary) currents, (2) it is a compact system because sensor numbers can be halved, compared with the tangential system, and (3) it is easy to compare with ECG or body surface potential mapping. The main advantage of the tangential-component MCG is

that foci and mechanisms of electrophysiological phenomena can be directly analyzed without mathematical models (see the section on "Arrhythmias").

Measurements of the Cardiac Magnetic Fields Using Magnetocardiograms

Special attention must be paid to reduction of environmental noise when measuring biomagnetic fields. Ideally, MCG systems should be set up in a room that is magnetically shielded and isolated from major sources of environmental noise. The detection limit was less than a few femto (10^{-15}) T/√Hz when the cardiac magnetic fields were measured in a magnetically shielded room at subway level [12]. Cardiac magnetic fields, like body surface potential mappings, can be monitored/measured in anterior-posterior and posterior-anterior projections at-rest or under stress conditions.

Analysis

Measured data are sent to network computers and are analyzed by several methods: grid maps investigating cardiac magnetic fields spatial distribution (Fig 14.3c), overlapped waveforms, isomagnetic field maps (see the section on "Arrhythmias", Figs. 14.5 and 14.6), and integral values (see the section on "Ischemic Heart Disease"). Filtering (standard filter: 0.1–100 Hz), baseline correction, signal averaging (see the section on "Arrhythmias", Fig. 14.5b), and time frequency analysis (see the section on "Arrhythmias", Fig. 14.7) are used according to the noise level. Beyond traditional waveform analysis, cardiac magnetic fields detected by multi-channel systems can be reconstructed in 2D/3D current arrow maps [16, 17], subtraction maps [18], whole-heart electrical-activation diagrams [19, 20], and superimposition on 2D/3D cardiac imaging [9].

Spatial and Temporal Accuracy of Magnetocardiograms

MCG accuracy is affected by many factors: signal-to-noise ratio, numbers and intervals of sensors [13], distance from the magnetic source to the sensor, the clinical or simulated study, models, and the comparison tools. In general, the spatial error of MCGs is one-third to one-half

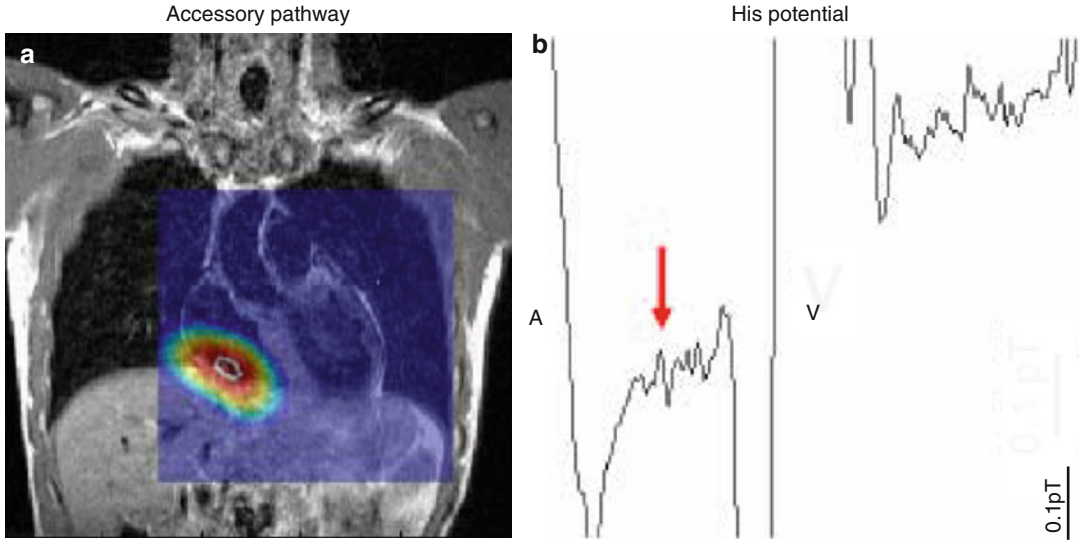

Figure 14–5. Clinical application of magnetocardiograms: arrhythmias. (**a**) A location of an accessory pathway diagnosed by magnetocardiography was superimposed on magnetic resonance imaging. (**b**) His potential (*arrow*) was recorded between atrial (*A*) and ventricular (*V*) potentials. *pT* picotesla [12, 13]

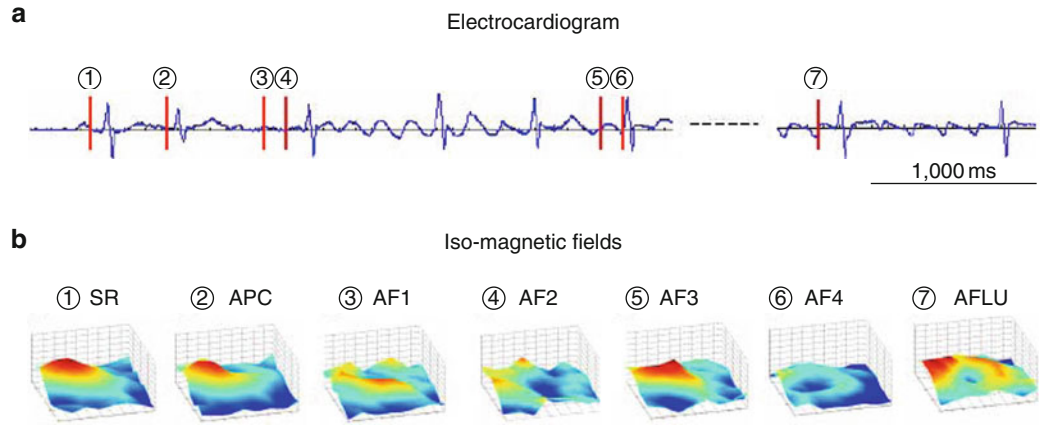

Figure 14–6. Paroxysmal atrial flutter. Initiation of paroxysmal atrial flutter was simultaneously recorded by electrocardiography (**a**) and magnetocardiography (**b**). The cardiac magnetic fields (*red* or *yellow areas* in b) showed a single peak during sinus rhythm (*SR*, *1* in b) or atrial premature complex (*APC*, *2* in b), a large circuit during atrial flutter (*AFLU*) due to macroreentry along the tricuspid annulus (*7* in b), and a disorganized pattern during atrial fibrillation (*AF*, *3* and *4* in b). When AF shifted to AFLU, the disorganized pattern fused to a single pattern (*5* in b), and then evolved into a circle (*6* in b) [14]

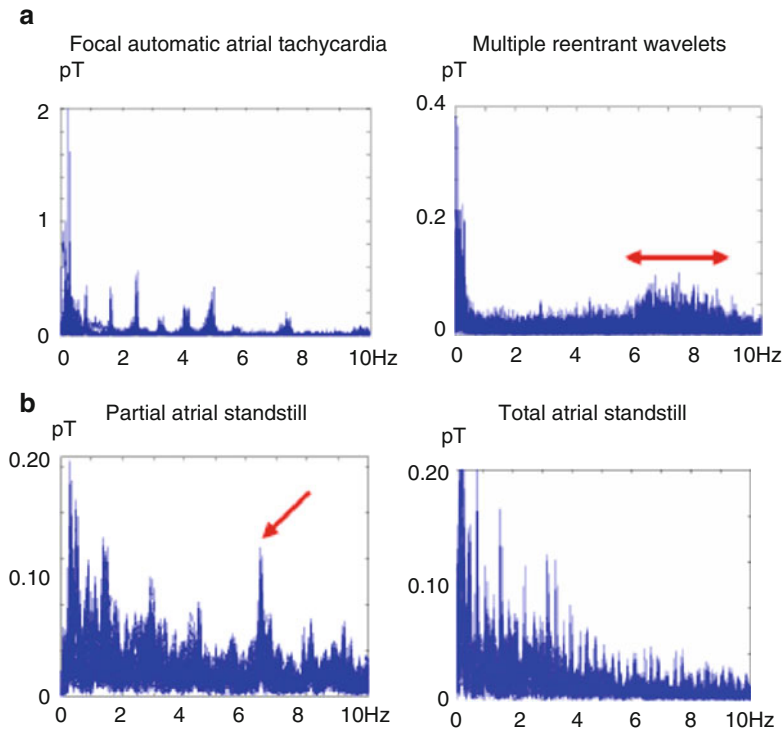

Figure 14–7. Magnetocardiographic time-frequency components. A disorganized pattern in isomagnetic field maps during atrial tachyarrhythmias was classified by time-frequency components as regular signals are amplified through time-frequency analysis, while irregular signals are reduced. Time-frequency analysis showed multiple peaks, which were clearly isolated from other peaks in a patient with focal automatic atrial tachycardia (**a** *left*), and showed a broad distribution at a range of 6–10 Hz at a low field strength (*arrow* in **a** *right*) in a patient with multiple reentrant wavelets. Among chronic atrial fibrillation with no f wave on the electrocardiogram, the magnetocardiogram detected a high-frequency component (6 Hz, *arrow* in **b** *left*) in a patient with partial atrial standstill, but did not in a patient with total atrial standstill (**b** *right*). *pT* picotesla [9, 15]

that of ECGs [9]. The spatial accuracy of a 64-channel system (sensor arrangement: an 8-by-8 matrix in a 2.5-cm interval, with a total measuring area of 17.5 by 17.5 cm (Fig. 14.3b); minimum sampling interval: 0.5 ms, 2 kHz) is 1.4 ± 0.7 mm in simulation, whereas it is approximately 1 cm in clinical cases [13]. Conduction times on MCGs have a linear correlation with those on intracardiac electrode recordings [12].

Clinical Utility for Detecting High-Risk Patients for Sudden Cardiac Death

Fetal Magnetocardiograms

Fetal death (≥20 weeks gestation) annually affects 27,000 cases in the United States, or approximately 7.0 per 1,000 live births. Fetal arrhythmias, such as atrioventricular conduction block, supraventricular tachycardia, and long QT syndrome, especially complicated with hydrops fetalis, are a significant risk for fetal death. Indeed, atrioventricular nodal reentry or atrioventricular reciprocating tachycardia in individuals without structural heart disease, which is not life-threatening in adults, can be fatal in a fetus or neonate, because fetuses and neonates are more vulnerable to tachycardia-induced heart failure. However, the natural course of fetal arrhythmias is still not completely understood. There has been no reliable tool for detecting fetal arrhythmias and no placebo-controlled study for the treatment of fetal arrhythmias.

One of the most promising areas for MCGs is prenatal diagnosis of electrophysiological abnormalities in congenital cardiac diseases [21, 22], because the advantages of MCGs, such as no need for electrodes and less interference by tissue conductivities, become more valuable (Table 14.2). Fetal MCGs are unaffected by vernix caseosa and by amniotic fluid and are reliable throughout the second and third trimesters of pregnancy, whereas fetal ECGs measured on the maternal abdomen are reliable only before week 27 of gestation [23]. Fetal MCGs can also be applied to cases with poor echocardiographic imaging [24, 25]. Moreover, fetal MCGs can provide (1) direct information on ventricular repolarization abnormalities [26] and (2) clear differentiation between atrial and ventricular components, thus (3) enabling diagnosis of arrhythmic mechanisms with accuracy similar to postnatal ECGs [27], while a fetal ECG or echocardiogram focuses mainly on diagnosis of heart rhythm. Fetal MCGs have three main goals: (1) observation of fetal well-being, normal development, or growth restriction, (2) detection and diagnosis of arrhythmias, and (3) evaluation of the efficacies of therapies, if needed.

Normal Cardiac Development Evaluated by Fetal Magnetocardiograms

In fetal MCGs, electrical activity of the fetus can be measured at the maternal abdominal wall from week 15 of gestation in some cases to week 20 with approximately 100 % reliability [28]. Echocardiographic screening before MCG measurement helps to understand the position of the fetus and to identify the optimal recording point. Normal values of fetal MCGs change according to gestational age [29]. A multicenter study with a registration of 582 healthy fetuses reported that P wave and QRS complex durations increase linearly with gestational age (whereas the PQ interval and T wave are independent of fetal age), suggesting concomitant increases in cardiac mass and cardiac dimension [28].

Fetal Arrhythmias

Prenatal diagnosis by MCGs is not only of academic interest, but is also useful for management of high-risk pregnancies. Clinical cases of long QT syndrome [30–33], Wolff-Parkinson-White syndrome [34, 35], supraventricular tachycardia [27], atrial flutter [36, 37], atrioventricular conduction block [38], and cardiac hypertrophy [39] have all been prenatally diagnosed using MCGs.

Supraventricular Tachycardia in the Fetus

The etiology of supraventricular tachycardia is different between newborns and adults. In neonates, atrioventricular reciprocating tachycardia in Wolff–Parkinson–White syndrome is more common, and atrioventricular nodal reentry is

less common, compared to adults. Although the etiology of supraventricular tachycardia in the fetus is considered to be similar to neonates, the differential diagnosis between the two tachycardias is difficult in neonates through conventional tools. Using MCG, Wakai et al. [27] analyzed 96 episodes of supraventricular tachycardias in eight fetuses (17–31 weeks of gestation, two with and six without delta waves) using MCG. Their study showed that MCG could differentiate P, QRS, and T waves during both sinus rhythm (100–155 bpm) and tachycardia (185–305 bpm), and thus could diagnose their mechanisms with the same accuracy as postnatal ECGs. They also reported unique properties of fetal arrhythmias suggesting autonomic influences: (1) a variety of initiation and termination patterns, (2) reentrant premature atrial complexes as the most common pattern of initiation, compared with a spontaneous atrial premature complex in adults, (3) transient bradycardia as the most common pattern of the termination, spontaneous block in adults, and (4) a strong association between episodes of supraventricular tachycardia and fetal trunk movement.

Long QT Syndrome in the Fetus

Although QT prolongation and certain T wave abnormalities are well recognized risk factors for ventricular tachyarrhythmia and sudden cardiac death at all ages after birth [40], their incidence and association with fetal death have not been established. Using fetal MCG, Zhao et al. [26] assessed the QT interval and T wave alternans in 120 fetuses (78 normal pregnancies, 43 fetal arrhythmias, 14–39 weeks gestation). Their study showed that rate corrected QT intervals (= QT/√RR interval) in normal sinus rhythm match Bazzet's formula for adults, independent of gestational age. However, QT prolongation was prominent in fetuses with poor outcomes and often accompanied by T wave alternans. They reported a case of *in utero* pharmacological treatment for a hydropic fetus with torsades de pointes and atrioventricular conduction block associated with long QT syndrome, suggesting that MCG-guided pharmacological treatment might be a therapeutic option for fetal arrhythmias [31].

Ischemic Heart Disease

Ischemic heart disease is the number one cause of death worldwide (World Heart Organization, the top 10 causes of death updated in June 2011). In this section, we will focus on MCG challenges to develop highly sensitive detection of cardiac injury or arrhythmic substrates in ischemic heart disease.

Detection of Baseline Shift in Cardiac Ischemia

MCGs and ECGs differ in the concept of the baseline or zero level. One of the reasons is that direct currents are filtered in ECGs but not in MCGs. The ECG baseline is determined as the PR segment [41] or the TP segment [42], while the MCG baseline is determined on an absolute scale measured by the SQUID sensors. In other words, amplitudes in ECGs are based on an external voltage standard rather than an absolute scale [42]. Proposing that MCG would be better than ECG for determining the baseline value, Cohen and colleagues investigated the mechanism of ST changes during cardiac ischemia [43–45]. Subendocardial ischemia causes depression of the ST segment in ECGs, while transmural ischemia causes ST elevation. But it is not clear when ST elevation occurs or whether an injury current flows only during the ST segment or during both baseline and ST segments. Cohen et al. first investigated ST elevation after coronary occlusion in dog models in 1975 [43] and then investigated ST depression during exercise in patients with stable angina pectoris in 1983 [45]. They found that cardiac ischemia changed both baseline and ST segments, shifting them in opposite directions. During acute coronary occlusion, the extent of the baseline shift was approximately equal to that of the ST segment change, but in angina pectoris the magnitude was about 70 % of the ST segment shift. An MCG baseline shift was not observed in left bundle branch block or early depolarization, a normal variant of ST change [44]. It was concluded from these results that ST elevation during acute coronary occlusion is a secondary result of a primary injury current that is interrupted during the ST interval [43].

Measuring DC components to directly identify injury currents is challenging, but would enable detection of cardiac damage in individuals with baseline cardiac disease, i.e., new myocardial infarction in cardiac hypertrophy, in bundle branch block, or in manifest Wolff–Parkinson–White syndrome. Cohen et al. reported that MCG has the potential to measure DC components [43–45], but has not succeeded in clinical situations due to difficulty in separating DC components of cardiac magnetic fields from low-frequency noises near DC.

Currently, other MCG parameters, such as current density vector, signal morphology, conduction time, amplitude ratio, and dipole analysis, have been proposed to detect cardiac ischemia, primarily during stress tests. The sensitivity and specificity of QT prolongation or QT dispersion on MCG are 85 and 68 %, respectively [46], and that of vector analysis in acute coronary syndrome are 93 and 95 % [47]. A combination of several MCG parameters might improve diagnostic accuracy.

At-Rest Phase Abnormalities in Angina Pectoris

About half of patients with new onset myocardial infarction have no symptoms prior to onset. ECG abnormalities are observed in 70–90 % of angina pectoris patients during exercise tests, but in only about 50 % of angina pectoris patients at rest [48]. Clinical tools to identify ischemic heart disease in at-rest individuals and in the asymptomatic phases are thus limited, providing another potential application for MCG measurements.

MCG integral value was measured in ischemic heart disease at rest phase [49–53] based on the hypotheses that (1) MCG is sensitive for detecting baseline shift (see the previous section "Detection of Baseline Shift in Cardiac Ischemia") and (2) a combination of two parameters, ST changes (voltage) and QT intervals (conduction time) would be more sensitive in detecting ventricular repolarization abnormalities [54], compared with a single parameter. Comparing angina pectoris patients with controls, MCG integral values of angina pectoris patients were smaller than those of the controls, while ECG parameters (QT interval, QT dispersion, and ST changes) did not differ [9, 49, 51]. This revealed that the MCGs of unstressed and asymptomatic individuals with angina pectoris have potential abnormalities. Moreover, MCG integral values decreased more in a myocardial infarction group without myocardial viability than in the angina pectoris group, and these values increased after coronary intervention, indicating that MCG integral values reflect both myocardial viability and treatment effects [51–53].

A Future Risk of Arrhythmic Events in Myocardial Infarction

Implantable cardioverter defibrillators represent a major advance in preventing cardiac death among patients with left ventricular dysfunction. However, low accuracy of current risk-stratification strategy and demanding costs of device-based therapy suggest an urgent need for new predictors of disease outcomes, perhaps including MCG-based parameters [55]. Korhonen et al. [56] showed that intra-QRS fragmentation in MCG, which correlates with slow conduction in intra-operative cardiac mapping [57], increased in patients with an old myocardial infarction with prior history of ventricular tachycardia. Based on these findings, they utilized intra-QRS fragmentation in MCG as a predictor of future cardiac events. Among 158 patients with acute myocardial infarction and left ventricular dysfunction (mean follow-up of 50 months), increased MCG intra-QRS fragmentation predicted both arrhythmic events and all-cause mortality, whereas QRS duration in ECG predicted only all-cause mortality. Moreover, in multivariate analysis, intra-QRS fragmentation in MCG was the strongest predictor of arrhythmic events with a hazard ratio of 5.1 (95 % confidence interval 1.7–15.9), whereas left ventricular ejection fraction less than 30 % resulted in a hazard ratio of 3.1 (95 % confidence interval 1.1–8.8). The combined criteria of intra-QRS fragmentation and low ejection fraction had 50 % positive and 91 % negative predictive values for arrhythmic events, suggesting that MCG analysis could provide prognostic information beyond assessment of ventricular dysfunction [56].

Ventricular Abnormalities in Nonischemic Heart Disease

Case studies in individuals with cardiac hypertrophy due to pressure overload [58] or due to congenital heart disease [59], cardiomyopathy [60], Kawasaki disease [61], diabetes mellitus [62], or heart transplantation [55] have been reported using MCGs. As a trial for noninvasive detection of graft rejection after heart transplantation, high sensitivity and specificity were reported in MCGs (an increase in current dipole strength attributed to changes in intra-myocardial impedance: sensitivity 91 % and specificity 93 % for acute rejections; an increase in an approximately 90-Hz component during QRS complex: sensitivity 83 % and specificity 84 % for chronic rejections) [55].

Arrhythmias

To delineate arrhythmic substrates, MCGs and electrophysiological (EP) studies are compared in this section, which first discusses detection of arrhythmic foci. As previously described (see the section on "Analysis"), spatial accuracy of the multichannel MCG system is 0.5–2.0 cm in analysis of the location of accessory pathways in Wolff–Parkinson–White syndrome (Fig. 14.5a). This result is applied to an electrophysiological phenomena that can be approximated by a single-dipole model, such as a premature complex [13], an accessory pathway [13, 63, 64], and a His potential (Fig. 14.5b). To reduce noise, signal averaging was done in these analyses, but signal averaging can obscure physiological signals. The latter part of this section addresses beat-to-beat analysis using tangential components in MCGs [11, 14]. This analytical method covers the entire sequence of a heart beat and all mechanisms of arrhythmias, from automaticity to reentry.

His Potential Recording in Magnetocardiograms

The origin of atrioventricular conduction block cannot be determined without an invasive EP study because the amplitude of a His potential is too small to record on standard ECGs. Using MCG, a spike potential was recorded between the atrial and the ventricular components on MCG by using 2-min signal averaging (101 ± 36 beats; Fig. 14.5b) [12]. His ventricular intervals in the noninvasive MCG significantly correlated with those in the EP studies ($R = 0.81$, $P < 0.01$).

Conduction Delay

A conduction delay predisposes the heart to cardiac arrhythmias, but ECGs provide less information about atria in comparison to ventricles. We previously reported that MCGs are superior in detecting local conduction delays in the early stage of paroxysmal atrial fibrillation, whereas ECGs detect conduction delays originating from broader areas in advanced stages of paroxysmal atrial fibrillation [65]. Based on these data, patients with ischemic heart disease and no prior history of atrial fibrillation were prospectively followed [66]. They were divided into two groups according to P wave duration on MCG (patients with P wave <115 ms and those with ≥115 ms). Although there was no significant difference in ECG parameters between the two groups, prolonged P wave duration on MCG identified individuals with a low ejection fraction and ventricular dilatation. During a mean follow-up of 2.1 years, prolonged P wave patients detected by MCG had a higher incidence of atrial fibrillation (18 % versus 0 %) and heart failure hospitalization (45 % versus 9 %), compared with the control group.

Atrial Fibrillation

Atrial tachyarrhythmias are divided into three clinical diagnoses (atrial tachycardia, atrial flutter, and atrial fibrillation) and have three mechanisms (reentry, automaticity, and triggered activity). The clinical diagnosis of arrhythmic mechanisms is currently based on EP studies because ECG based diagnosis does not show a 1:1 correspondence with the mechanisms. To identify mechanisms noninvasively, we designed a two-step algorithm using MCG. The first step is continuous visualization of electrical currents through an MCG animation. Reentrant circuit numbers (single or multiple)

and size (macro- or microreentry) are screened through the animation. The second step is a time frequency analysis that can reveal regular activity under a random pattern. This two-step algorithm was applied to the most common arrhythmia (atrial fibrillation) scenarios [9, 14].

Mechanisms of Tachyarrhythmias: Automaticity, Macroreentry, or Microreentry

For the first step of algorithm design, we animated MCG by editing isomagnetic field maps (the tangential components of the cardiac magnetic fields) with a minimal interval of 1 ms [14]. Cardiac magnetic fields (red areas in Fig. 14.6) exhibited a single peak during sinus rhythm or premature atrial complex, a large circuit during atrial flutter due to macroreentry along the tricuspid annulus, and a disorganized pattern during atrial fibrillation. When atrial fibrillation shifted to atrial flutter, the disorganized pattern fused to a single pattern, and then evolved into a circle. During common atrial flutter, atrial activation showed counterclockwise rotation in the animation. This study showed how the cardiac magnetic field pattern reflects distinct types of atrial activation in the right atrium: a circular pattern for atrial flutter and a disorganized pattern for atrial fibrillation. Notably, MCG acquisition provided unique information as the magnetic fields show three patterns (disorganized multiple peaks, a single peak, and a weak circular pattern) when atrial fibrillation shifts to common atrial flutter. Further MCG studies are required to differentiate atrial activation in the right atrium from that in the left atrium and to classify additional patterns of atrial flutter. Finally, MCG animation can also be applied to analyze reentrant circuits during ventricular tachycardia. The magnetic sources show a circular pattern during atrial flutter because its macro-reentrant circuit is almost round and parallel to the SQUID sensors, while those during ventricular tachycardia in ischemic heart disease may show a more complicated pattern because of its smaller and three-dimensionally complex reentrant circuit.

Mechanisms of Tachyarrhythmias: Reentry with or Without Focal Automaticity

In the second element of algorithm design, disorganized patterns of atrial tachyarrhythmias on isomagnetic field maps were further classified by time frequency analysis hypothesizing that regular signals are amplified, while irregular signals are reduced. Time frequency analysis showed multiple peaks at a high field strength (0.2–0.6 pT), which were clearly isolated from the other peak in the MCG of a patient with focal automatic atrial tachycardia (Fig. 14.7a left), and showed a broad distribution at a range of 6–10 Hz at a low field strength (0.1–0.15 pT) in the MCG of a patient with multiple reentrant wavelets (arrow in Fig. 14.7a right). These two patterns could not be differentiated as a quantitative parameter by ECG or MCG animation. Time frequency analysis also reveals differential patterns between partial atrial standstill [15] and total atrial standstill (Fig. 14.7b). The studies reviewed in this section suggest that MCGs could be used to detect local atrial conduction delay, risk for new onset atrial fibrillation with subsequent heart failure hospitalization, mechanisms of atrial arrhythmias, and degree of atrial electrical remodeling. Thus MCGs may provide key information for determining which strategies to use in the treatment of atrial fibrillation, e.g., pharmacological or non-pharmacological therapy, rhythm control or rate control.

Future Direction of Magnetocardiograms

Understanding and measurement of magnetic fields are centuries old. Indeed, early navigators used the earth's magnetic fields to guide them in navigating the earth and sea (Table 14.1). The cardiac magnetic field was detected much later and was first described by Baule and McFee in 1963 [67]. Over the years, advances have been made in the field of magnetocardiography

[68–71] and it has been developed as a potentially useful diagnostic tool with multichannel recordings. Recent reports provide further evidence confirming MCG as a practical and useful tool for optimal patient care by providing supplemental information to other diagnostic modalities including ECG [21].

The most important advantage of MCGs is their sensitivity to small signals. The studies reviewed here suggest that MCGs could be used to detect ischemic heart disease in asymptomatic individuals lacking ECG abnormalities, and to noninvasively obtain information useful for determining treatment strategies (existence of cardiac ischemia or viability in ischemic heart disease, risk for future cardiac events, mechanisms of tachyarrhythmias, degree of electrical remodeling, etc.). If this is the case, MCGs can be a powerful tool in preventing sudden cardiac death.

One factor limiting the clinical use of MCGs is that their utility has not yet been established. There are very few translational studies [72] and few clinical studies in a large population or from a prospective approach. The potential benefits of MCGs and the most effective way to apply them in clinical medicine have therefore not been fully realized. A second limiting factor is that MCG systems and parameters have not been standardized [73]. Finally, the cost effectiveness of MCG must also be improved if it is to become more widely adopted.

The search for future uses of MCGs remains ongoing. One potential application is in 3D diagnosis combined with electrophysiological, anatomical [9], and metabolic information [74]. These kinds of information are currently obtained in different images, but a combined image helps provide a comprehensive understanding of a given pathophysiology. Another approach is a therapeutic one. EP studies using nonmagnetic catheters under MCG monitoring [75, 76] might reduce radiation time allowing for less invasive ablation procedures to treat arrhythmias.

In conclusion, MCGs, body surface mapping of the cardiac magnetic fields measured using SQUID sensors, can be used in clinical diagnosis when ECGs are not practical or informative, such as in fetal cardiac assessment, ischemic heart disease, and arrhythmias. Establishing MCG utility, however, will require further studies in both basic and clinical approaches.

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15
Ambulatory Monitoring: (Holter, Event Recorders, External, and Implantable Loop Recorders and Wireless Technology)

Rajesh N. Subbiah, Pow-Li Chia, Peter Leong-Sit, Lorne J. Gula, Allan C. Skanes, Raymond Yee, George J. Klein, and Andrew D. Krahn

Abstract

The cornerstone for the evaluation of unexplained syncope or palpitations is a comprehensive clinical evaluation combined with cardiac monitoring to establish an accurate symptom-rhythm correlate. There are many modalities of ambulatory outpatient monitoring, ranging from non-invasive Holter monitoring to implantable loop recorders. The choice of modality should be tailored to individual patients based on nature and frequency of symptoms.

Keywords

Syncope • Palpitations • Arrhythmia • Ambulatory cardiac monitoring • Holter monitor • Loop recorder

R.N. Subbiah, MBBS, PhD
Department of Cardiology,
St. Vincent's Hospital,
University of New South Wales,
Darlinghurst, Sydney,
NSW, 2010, Australia
e-mail: rajeshnsubbiah@gmail.com

P.-L Chia, MBBS, MMed
Department of Cardiology,
St. Vincent's Hospital,
Sydney, NSW, Australia

P. Leong-Sit, MD • L.J. Gula, MD • A.C. Skanes, MD
R. Yee, MD • G.J. Klein, MD
Division of Cardiology,
University of Western Ontario,
London, ON, Canada
e-mail: lgula@uwo.ca; ryee@uwo.ca; gklein@uwo.ca

A.D. Krahn, MD (✉)
Division of Cardiology,
Gordon and Leslie Diamond Health Care Centre,
University of British Columbia,
2775 Laurel Street, Vancouver,
BC V5Z 1M9, Canada
e-mail: akrahn9@gmail.com

Introduction

Delineating the underlying cause of arrhythmia-related symptoms such as palpitations or unexplained syncope often constitutes a clinical conundrum. The most important aspect of the diagnostic challenge is to obtain a comprehensive history and physical examination [1, 2]. The ideal but often unattainable test for elucidating a cause is a standard electrocardiogram during spontaneous symptoms. Short of that goal, establishing an accurate symptom–rhythm correlation can often provide a diagnosis. Increased emphasis on outpatient diagnosis and evolving technologies have yielded a wide array of monitoring options that facilitate obtaining an electrocardiogram during symptomatic episodes in an ambulatory patient. These monitoring modalities differ in duration of monitoring, quality of recording, convenience, and invasiveness.

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Holter Monitoring

The Holter monitor is a portable battery-operated device that connects to the patient using bipolar electrodes and provides recordings from up to 12 electrocardiographic leads. Data are stored in the device using analog or digital storage media. The data are transformed into a digital format and analyzed using interpretive software. Additional markers for patient-activated events and time correlates are included to allow greater diagnostic accuracy. Continuous electrocardiographic monitoring is possible for 24 h to a maximum of 72 h (see Fig. 15.1). This allows the documentation of symptomatic and/or asymptomatic events. Holter monitoring is useful if the clinical history is suggestive of an arrhythmic etiology and the symptoms are frequent enough to be detected within the period of monitoring.

Holter monitoring has several drawbacks. Patients may not experience symptoms or cardiac arrhythmias during the Holter recording of 72 h or less. In patients with syncope, the likelihood of another syncopal episode occurring during the monitoring period is the major limiting factor. Presyncope is a more common event during ambulatory monitoring, but is less likely to be associated with an arrhythmia [3, 4]. Additionally, the ubiquity of presyncope as a symptom in the community makes its utility as a surrogate for syncope relatively uncertain. The physical size of the device may hinder the ability of patients to sleep comfortably or engage in activities that precipitate symptoms. Patients are further inconvenienced because the devices have to be removed while showering. The observations on Holter monitoring must be correlated with the clinical context, as findings may not be clinically significant if detected in the absence of symptoms. There is often significant variability in patient documentation of activated events, such that accurate symptom–rhythm correlation is undermined.

It is therefore not surprising that Holter monitoring has a low diagnostic yield. In several large series of patients utilizing 12 h or more of ambulatory monitoring for investigation of syncope, only 4 % had recurrence of symptoms during monitoring [5–7]. The overall diagnostic yield of ambulatory or Holter monitoring was 19 %. These studies reported symptoms that were not associated with arrhythmias in 15 % of cases. The causal relationship between the arrhythmia and syncope was uncertain. Uncommon asymptomatic arrhythmias such as prolonged sinus pauses, atrioventricular block (such as Mobitz type II block), and non-sustained ventricular tachycardia can provide important contributions

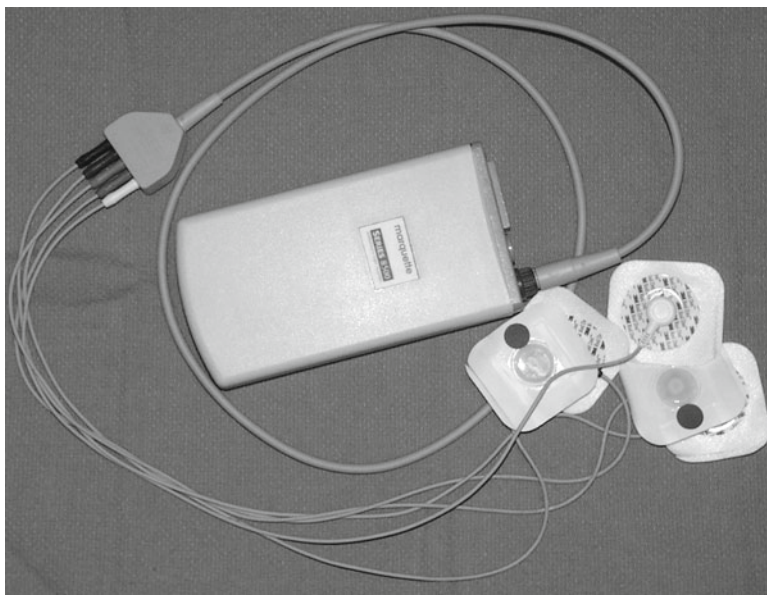

Figure 15–1. Holter monitor. The recording device (*center*) is worn by the patient using a shoulder strap or belt loop, attaching to 3–5 skin electrodes for continuous monitoring. An event button (not shown) at the top of the housing of the device is pressed in the event of symptoms to mark the recording. See text for discussion

to the diagnosis, often instigating further investigations to rule out structural heart disease and other precipitating factors. While these observations necessitate prompt attention, it is important to interpret the results in the clinical context of the syncopal presentation so common causes of syncope such as neurocardiogenic syncope are not unduly excluded.

It is also important to understand that a normal Holter monitoring report does not exclude an arrhythmic cause for syncope, and in fact is typically the case. If the pretest probability is high for an arrhythmic cause, further investigations such as more prolonged monitoring or cardiac electrophysiological studies are required. In a study which evaluated extension of ambulatory Holter monitoring duration to 72 h [6], there was an increase in the number of asymptomatic arrhythmias detected, but not the overall diagnostic yield.

In our institution we typically use Holter monitoring for 48 h. It is a noninvasive test that provides information to establish a rhythm profile in patients and the diagnosis in those with frequent symptoms. The more frequent the symptoms, the higher the diagnostic yield of Holter monitoring. The apparent modest yield of Holter monitoring presumably reflects the primary care use of the device in patients with frequent symptoms facilitating a symptom–rhythm correlation. This leads to selection bias in the referral population, leading to an apparent nearly futile yield in referred patients who, by definition, have failed short-term monitoring.

External Event Recorders

External event recorders are external devices attached to patients via one to three electrodes with the ability to provide a longer period of monitoring than the standard Holter monitor. They may be patient activated or autotriggered, The three main types of external event recorders are transtelephonic monitors, external cardiac loop recorders and mobile automated cardiac outpatient telemetry (MCOT) monitors.

Transtelephonic monitors are a form of noncontinuous ambulatory recording. During symptomatic episodes, the patient activates the device, which then records electrocardiographic signals. The recorded event must be directly transmitted by an analog telephone line to a receiving centre (Fig. 15.2). The received signal is then converted to an interpretable recording that is displayed or printed as a single lead rhythm strip. There are two specific types of devices. The first does not save a recording of the rhythm for later playback and requires the patient to transmit the data "live" to the base station where it can be analyzed. The second type of device, with solid-state memory capacity allowing recording and storage of

Figure 15–2. Transtelephonic Monitors. The device is lightweight and portable, easily placed in a handbag or pocket. Four recording electrodes are present on the back of the device to permit single lead rhythm strip capture. A record button (*top left*) is pressed in the event of symptoms, and the recorded event is transmitted to a base station over an analog phone line

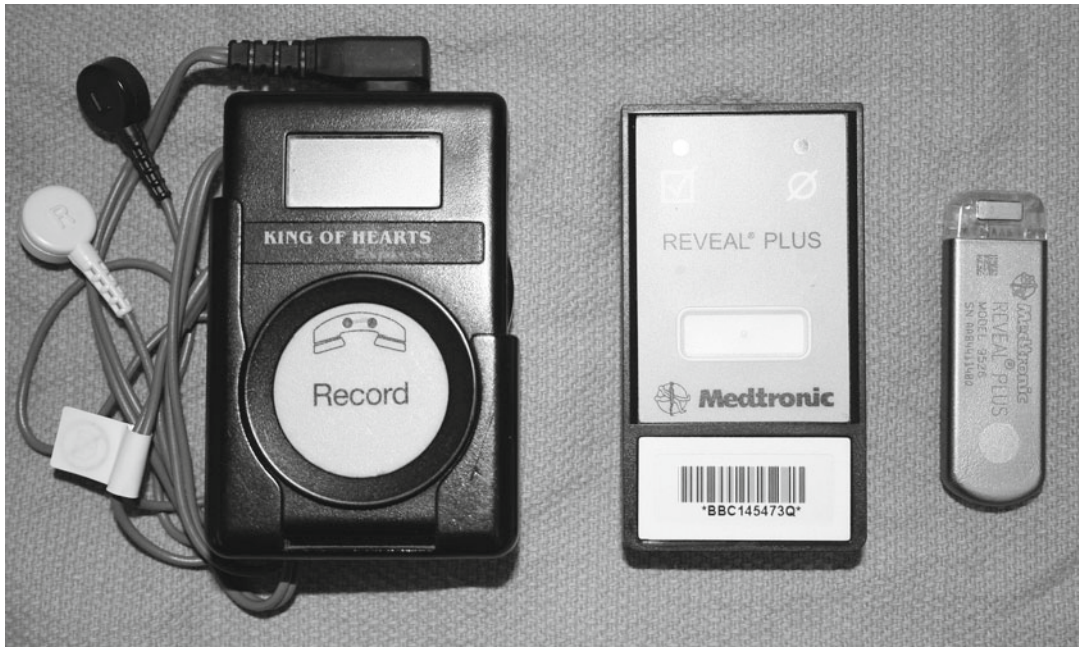

Figure 15–3. Loop recorders. An external loop recorder (*left*) with cables that attach to the patient. The record button is pressed in the event of symptoms to store the previous 9 min, and the ensuing 1-min. The phone receiver is also placed over this button to transmit data over an analog phone line. An implantable loop recorder (*right*) and patient activator (*center*). The patient activator is used to "freeze" symptomatic events that are retrieved with a pacemaker programmer. Automatic events can also be captured (see text for discussion)

electrocardiographic signals during symptoms, has replaced the non-recording units. The electrocardiographic signals are collected prospectively for 1–2 min upon patient activation. The major disadvantages of this device are the patient-activated nature, asymptomatic arrhythmias will be missed, the symptoms must persist long enough for the device to record the event, and the inability to record the events that surround the onset of symptoms.

An external cardiac loop recorder continuously records and stores an external single modified limb lead electrogram with a 4- to 18-min memory buffer (Fig. 15.3, left). After the onset of spontaneous symptoms the patient activates the device, which stores the previous 3–6 min of recorded information as well as the following 1–2 min. The device memory is then "frozen." In lay terms, it answers the question: "What just happened?" The captured rhythm strip can subsequently be uploaded and analyzed (Fig. 15.4). This system can be used for weeks to months provided weekly battery changes are performed. The recording device is attached with two leads to the chest wall of the patient and needs to be removed for bathing. Long-term compliance with this device can be challenging because of electrode and skin-related problems and waning of patient motivation in the absence of symptom recurrence. To allow detection of asymptomatic arrhythmias, external loop recorders with an automatic trigger (autotrigger) algorithm have been introduced.

The most recent advancement in external ambulatory arrhythmia monitoring is MCOT [8]. Patients wear two to three chest leads attached to a portable sensor that continuously records rhythm strips and transmits the electrocardiographic data of pre-specified arrhythmias in real-time to a hub at the patient's home. If the algorithms in the hub detect a significant arrhythmia as per physician-predesignated thresholds or if the patient activates the sensor to report symptoms, the monitor automatically transmits the patient's electrocardiographic data to the central station using wireless communications. The data may be screened 24 h a day by central station technicians, with potential immediate or

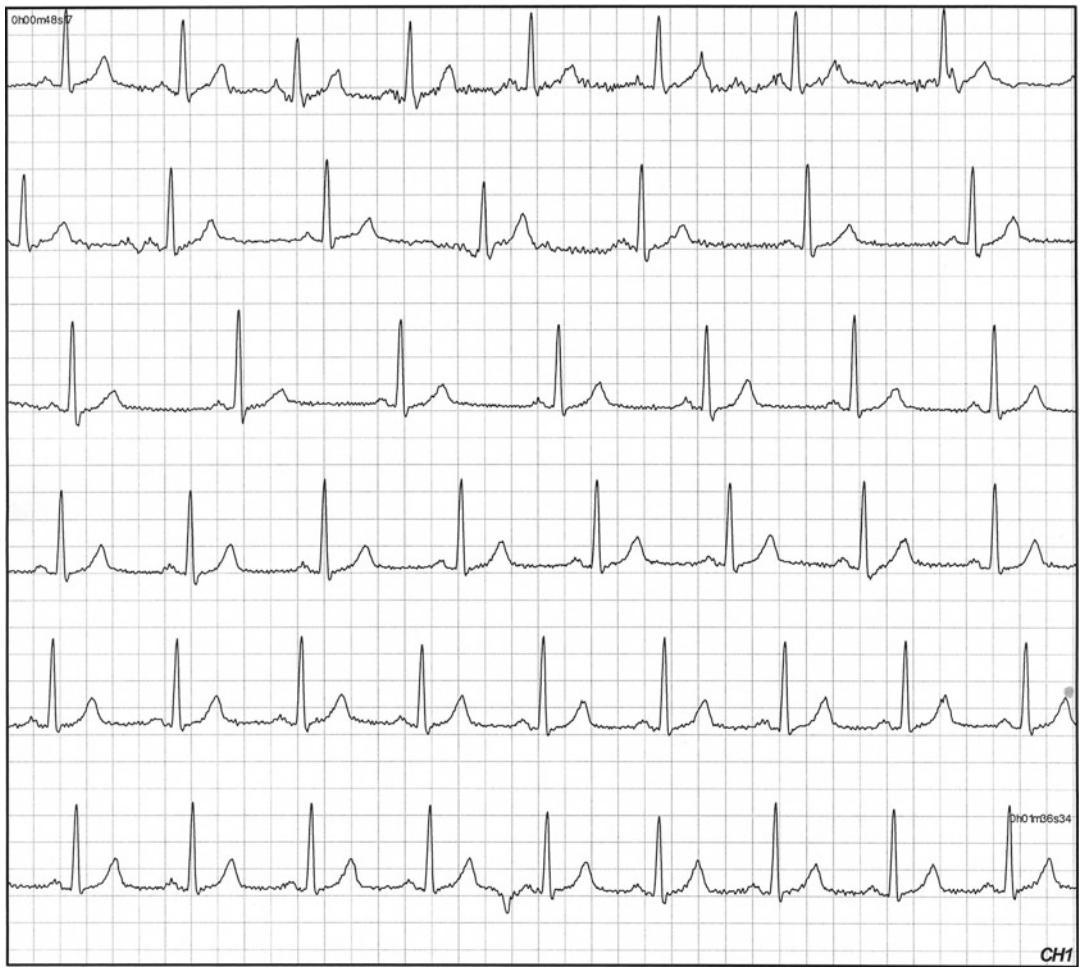

Figure 15–4. External loop recorder tracing. Sinus rhythm during presyncope is recorded in a 43-year-old female with recurrent unexplained syncope and presyncope. The fluctuation in heart rate is suggestive of neurocardiogenic syncope

deferred referral to the attending physician for evaluation of symptoms, rate and/or rhythm changes. The major drawback of this modality is patient compliance to wearing the device.

Linzer et al. reported the use of patient-activated loop recorders in 57 patients with syncope and nondiagnostic findings on history, physical examination, and 2-h Holter monitoring [9, 10]. A diagnosis was obtained in 14 of 32 patients who had recurrence of symptoms. Device malfunction, patient noncompliance, or inability to activate the recorder was responsible for the lack of diagnosis in the remaining 18 patients. Other studies have also reported similar findings [10, 11] and demonstrated that loop recorders are complementary to 24-h ambulatory electrocardiographic monitoring. The diagnostic yield for external loop recorders in these three studies [5, 10, 11] ranged from 24 to 47 %, with the highest yield in patients with palpitations.

A prospective randomized clinical trial compared the utility of external loop recorders to conventional Holter monitoring in a community-based referral population with syncope and presyncope [12]. Not surprisingly, the ability to obtain a symptom–rhythm correlation increased from 22 % for Holter monitoring to 56 % for the external loop recorder ($p < 0.001$), which allowed an increased duration of monitoring from 48 h to 4 weeks. A higher diagnostic yield was also obtained among patients randomized to Holter monitoring who remained undiagnosed and

crossed over to use of a loop recorder. This trial suggests that loop recorders should be considered as first line technology when attempting to establish a symptom–rhythm correlation in the initial workup of patients with syncope. Unfortunately, patient or device-related failed activation occurred in 24 % of loop recorder patients, limiting their usefulness in some patients [12]. Analysis of factors pertaining to use of external loop recorders has revealed a particularly low diagnostic yield among patients who are unfamiliar with technology, live alone, or have low motivation for achieving a diagnosis [13]. More recently, Reiffel et al. retrospectively compared the results obtained by Holter monitoring, loop recording, and autotriggered loop recording in 600 patients from a database of approximately 100,000 patients. The autotriggered loop recording approach provided a higher yield of diagnostic events (36 %) compared to loop recording (17 %) and Holter monitoring (6.2 %) [14].

Rothman et al. [15] performed a prospective multi-center randomized study to compare the relative value of a MCOT system with a patient-activated external loop recorder for symptoms believed to be due to arrhythmias. The study analyzed findings from 266 patients randomized to either the loop recorder or MCOT for up to 30 days. A diagnosis was made in 88 % of MCOT subjects compared with 75 % of loop recorder subjects ($p = 0.008$). In a subgroup of patients presenting with syncope or presyncope, a diagnosis was made in 89 % of MCOT subjects versus 69 % of loop recorder subjects ($p = 0.008$). MCOT was superior in confirming the diagnosis of clinical significant arrhythmias, detecting such events in 55 of 134 patients (41 %) compared with 19 of 132 patients (15 %) in the loop recorder group ($p < 0.001$).

The external event recorders appear to have the greatest role in motivated patients with frequent symptoms in whom spontaneous symptoms are likely to recur within 4–6 weeks. Given that they are noninvasive and cost effective, they should be considered in all patients in whom an arrhythmic cause for syncope is suspected, keeping in mind that the major limitation of these devices is the need to continuously wear external electrodes.

Implantable Loop Recorders

Despite its introduction into clinical practice in the late 1990s, the implantable loop recorder (ILR) has only recently become the investigative tool of choice in recurrent unexplained syncope following negative initial investigations. The ILR permits prolonged monitoring without external electrodes. It is ideally suited to patients with infrequent recurrent syncope thought to be secondary to an arrhythmic cause. Similar to the external loop recorder, it is designed to correlate physiology with recorded cardiac rhythms, but unlike the external loop recorder, it is implanted and therefore devoid of surface electrodes and accompanying compliance issues. The ILR also monitors much longer time periods than an external loop recorder. Commonly available ILRs include the Medtronic Reveal® and the St Jude Medical Confirm™ series of ILRs. A typical ILR (Medtronic Reveal DX Model 9528) has a pair of sensing electrodes with 4-cm spacing on a small elongated recording device 6.2 cm long, 1.9 cm wide, and 0.8 cm thick, weighing 15 g (Fig. 15.3, right). The projected battery longevity is 36 months. The device can be implanted subcutaneously in the left chest wall with local anesthetic and antibiotic prophylaxis.

Prior to implantation, cutaneous mapping can be performed to optimize the sensed signal to avoid T wave oversensing, which can falsely be interpreted as a high rate episode. An adequate signal can usually be obtained anywhere in the left hemithorax [16]. Grubb et al. [17] described an anatomic-based approach to ILR placement in 63 patients that did not require cutaneous mapping. Each underwent implantation of ILR in the left upper chest area midway between the supraclavicular notch and left breast area. In all patients, adequate electrocardiographic tracings were obtained at implant without need for preoperative cutaneous mapping. The mean P wave amplitude was 0.12 ± 0.20 mV at implant and at follow-up (6–14 months postimplant), the amplitude was 0.11 ± 0.19 mV. The peak-to-peak QRS amplitude was 0.48 ± 0.15 mV at implant and 0.44 ± 0.16 mV at a follow-up of 6–14 months. This strategy has not been validated.

Table 15–1. ISSUE classification of detected rhythm from the ILR

Classification	Sinus rate	AV node	Comment
Asystole (RR >3 s)			
1A	Arrest	Normal	Progressive sinus bradycardia until sinus arrest probably vasovagal
1B	Bradycardia	AV block	AV block with associated sinus bradycardia probably vasovagal
1C	Normal or tachycardia	AV block	Abrupt AV block without sinus slowing suggests intrinsic AV node disease
Bradycardia			
2A	Decrease >30 %	Normal	Probably vasovagal
2B	HR <40 for >10 s	Normal	Probably vasovagal
Minimal HR change			
3A	<10 % variation	Normal	Suggests non-cardiac cause: unlikely vasovagal
3B	HR increase or decrease 10–30 %, not <40 or >120 bpm	Normal	Suggests vasovagal
Tachycardia			
4A	Progressive tachycardia	Normal	Sinus acceleration suggests orthostatic intolerance or non-cardiac cause
4B	N/A	Normal	Atrial fibrillation
4C	N/A	Normal	Supraventricular tachycardia
4D	N/A	Normal	Ventricular tachycardia

Adapted from Brignole et al. [18] with permission

HR heart rate, *N/A* not applicable

The recorded bipolar signal is stored in the device as 42 min of compressed signal. A compressed signal is generally used due to marginally better quality than the uncompressed signal, which maximizes memory capability. The patient, along with a spouse, family member, or friend, is instructed in the use of the activator at the time of implant. Once an episode is recorded (i.e., a presyncopal or syncopal event occurs) the memory is "frozen" by the patient or a relative by applying a nonmagnetic hand-held activator (Fig. 15.3 center). The episode is then uploaded for interrogation to a pacemaker programmer (Medtronic 2090). Though heart rate is usually easily discerned, p waves can occasionally be difficult to interpret. The most recent version of the ILR has programmable automatic detection of tachycardia-bradycardia (so-called tachy-brady) arrhythmias, pauses and allows for comprehensive remote monitoring without an office visit. The Medtronic CareLink® Home Monitor allows patients to send data from their Medtronic Reveal® ILRs over a standard phone line for review by their physician. The St Jude Medical Confirm™ ILRs also has transtelephonic monitoring capability, enabling timely and accurate data to be transmitted. This enhances the utility of these devices, particularly if patients have frequent saved events or live in remote areas where travel to a dedicated clinic is time consuming and costly.

Because of the heterogeneity of findings and the wide variety of rhythm disturbances recorded with the ILR at the time of syncope, Brignole et al. [18] have proposed a classification system (Table 15.1) that assigns the mechanism of syncope according to the arrhythmia recorded during spontaneous syncope. This classification has become widely used and validated by others [19–21]. The classification has some pathophysiological implications that help to distinguish different types of arrhythmic syncope and have potentially different diagnostic, therapeutic, and prognostic implications. In types 1A (Fig. 15.5), 1B, and 2, the findings of progressive sinus bradycardia, most often followed by ventricular asystole due to sinus arrest, or progressive tachycardia followed by progressive bradycardia and, eventually, ventricular asystole due to sinus arrest, suggest that the syncope is probably neurally mediated. In type 1C (Fig. 15.6), the finding of prolonged asystolic pauses due to sudden-onset paroxysmal AV block with concomitant increase in sinus rate suggests intrinsic disease of the His–Purkinje system. In types 4B, 4C, and 4D, syncope is likely due to a primary cardiac

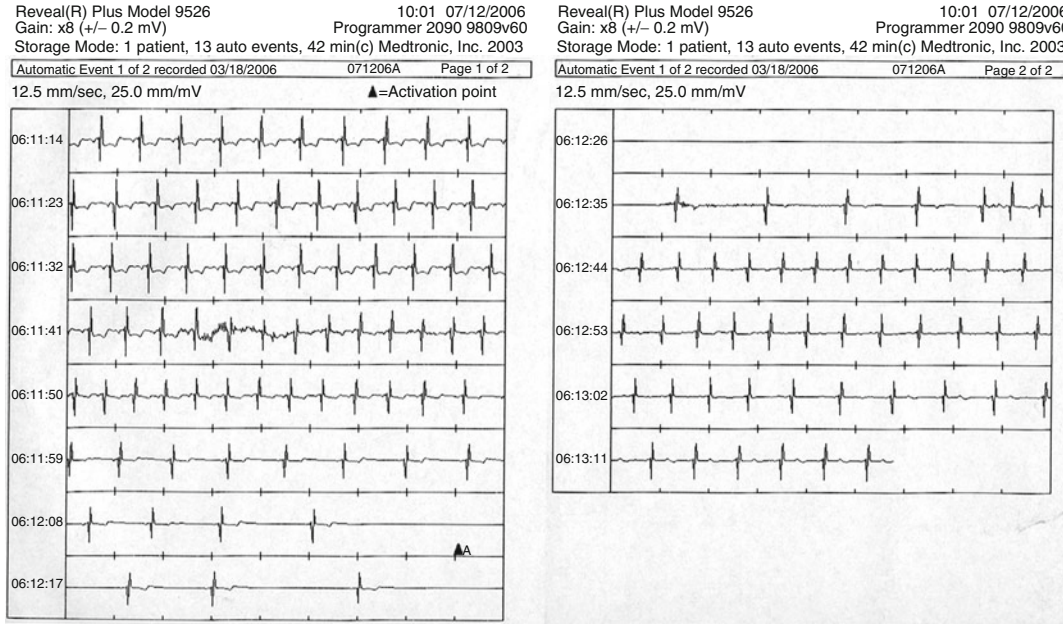

Figure 15–5. Automatic event detection from an ILR. This is a typical tracing of an event captured by an ILR during syncope in a patient. The *arrow* and letter A denotes automatic activation when the device detects a 3 s pause. Each line constitutes 10 s of a single lead rhythm strip. Note the slowing of the sinus rate prior to onset of a prolonged pause, which resulted in syncope. This is consistent with the diagnosis of neurocardiogenic syncope (ISSUE classification 1A)

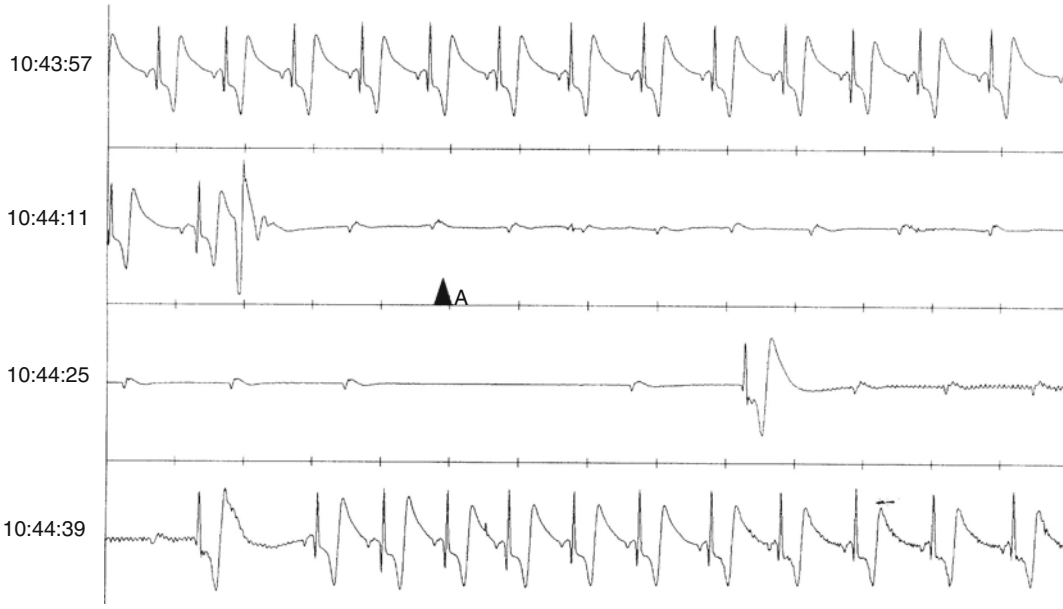

Figure 15–6. Manual event detection from an ILR. Manual activation during presyncope in a 73-year-old male with two previous episodes of unexplained syncope. Note that the trace reveals paroxysmal AV block. This is classified as a 1C response by the proposed ISSUE classification, suggesting intrinsic AV node disease

arrhythmia. In the other types, in which no arrhythmia is detected, the exact nature of syncope remains uncertain because of the lack of blood pressure recording. However, the finding of progressive heart rate increase and/or decrease at the time of syncope suggests a primary or secondary activation of the cardiovascular system and a possible hypotensive mechanism.

Several observational studies have been instrumental in establishing the role of ILR in the investigation and diagnosis of syncope [22–24]. The largest of these studies is a multicenter study of 206 patients [24]. The majority of patients had undergone noninvasive and invasive testing including head-up tilt testing and electrophysiological studies. The etiology of syncope was arrhythmic in 22 % of patients, sinus rhythm with exclusion of arrhythmia in 42 % of patients, and no further episodes occurred in 22 % of patients. Bradycardia was the most commonly detected arrhythmia (17 % vs. 6 % tachycardia), usually leading to pacemaker implantation. From this study, 4 % of patients failed to properly activate the device and thus did not establish a symptom–rhythm correlation. Multivariate modeling did not identify any significant pre-implant predictors of subsequent arrhythmia detection other than a weak association with advancing age and bradycardia. No age group had an incidence of bradycardia greater than 30 %, suggesting a limited role for empiric pacing in the unexplained syncope population.

Further studies have highlighted the potential utility of ILR in the diagnosis of syncope. In a group of patients with ongoing seizures despite anticonvulsant therapy, Zaidi et al. performed cardiac assessment including head-up tilt testing and carotid sinus massage in all patients, and implantation of an ILR in ten patients [25, 26]. Two of the ten patients with an ILR had marked bradycardia preceding a seizure: one was due to sinus pauses and the other was due to heart block. Importantly, this study suggested seizures that are atypical in presentation may have a cardiovascular cause in as many as 42 % of cases, and cardiovascular assessment including long-term cardiac monitoring with an ILR may play a role in select patients with atypical seizures.

In studies [27, 28] from the International Study on Syncope of Uncertain Etiology (ISSUE) investigators, ILRs were implanted in three different groups of syncopal patients to assess cardiac rhythm during syncope after conventional testing. The first study involved tilt tests in 111 patients with unexplained syncope, and loop recorders implanted after the tilt test, regardless of result [28]. Syncope recurred in 34 % of patients in both the tilt-positive and tilt-negative group, with marked bradycardia or asystole the most common recorded arrhythmia during follow-up (46 and 62 %, respectively). The heart rate response during tilt testing did not predict spontaneous heart rate response, with a much higher incidence of asystole than expected based on demographics or tilt response. This study suggests that observations during tilt testing correlate poorly with cardiac rhythm during spontaneous syncope, and that bradycardia is more common in this population than previously recognized. An example of the cardioinhibitory component of vasodepressor syncope is illustrated in Fig. 15.5.

In the second study, 52 patients with syncope, bundle branch block, and negative electrophysiological testing underwent ILR implantation [28]. Syncope recurred in 22 of the 52 patients with conduction system disease. Long-term monitoring demonstrated marked bradycardia mainly attributed to complete AV block in 17 patients, while it excluded AV block in 2 patients. Three patients did not properly activate the device after symptoms. This study confirmed that negative electrophysiological testing does not exclude intermittent complete AV block, and that prolonged monitoring or consideration of permanent pacing is reasonable in this population.

The third study examined the spontaneous rhythm in 35 patients with syncope, overt heart disease, and negative electrophysiological testing [29]. The underlying heart disease was predominantly ischemic or hypertrophic cardiomyopathy with moderate left ventricular dysfunction. Although previous studies have suggested that patients with negative electrophysiological testing have a better prognosis, there remains concern regarding risk of ventricular tachycardia

in this group. Symptoms recurred in 19 of the 35 patients (54 %), with bradycardia in 4, supraventricular tachyarrhythmias in 5, and ventricular tachycardia in only 1 patient. There were no sudden deaths during 16 ± 11 months of follow-up.

A prospective, multicenter observational study (ISSUE 2) investigated the efficacy of therapies based on ILR diagnosis of recurrent suspected neurocardiogenic syncope [30]. Patients were included in the study if they experienced three or more clinically severe syncopal episodes over 2 years without significant electrocardiographic or cardiac abnormalities. Patients with postural hypotension and carotid sinus syncope were excluded. After the first documented episode of syncope after ILR implantation, the device was interrogated and therapy was prescribed accordingly. The 1-year recurrence rate of syncope in 392 patients was 33 %. Among 103 patients with a documented episode, 53 patients received specific therapy: 47 received a pacemaker due to asystole and 6 received antitachyarrhythmia therapy (catheter ablation, four; implantable defibrillator, one; and antiarrhythmic drug, one) and the remaining 50 patients did not receive specific therapy. The 1-year recurrence rate among the 53 patients who received ILR guided therapy was 10 % compared with 41 % in the patients without specific therapy. The 1-year recurrence rate in patients with pacemakers was 5 %. It was concluded that a strategy based on diagnostic information from early ILR implant, with therapy delayed until documentation of syncope, allows safe, specific, and effective therapy in patients with neurocardiogenic syncope.

There have been two randomized trials that compared the role of the ILR with a conventional testing strategy for syncope. In the Randomized Assessment of Syncope Trial (RAST) [31], 60 patients (age 66 ± 14 years) with unexplained syncope were randomized to conventional testing with an external loop recorder, tilt test, and electrophysiological study versus prolonged monitoring with an ILR for 1 year. Patients were excluded if they had a left ventricular ejection fraction less than 35 %. If patients remained undiagnosed after their assigned strategy, they were offered crossover to the alternate strategy. A diagnosis was obtained in 14 of 27 patients randomized to prolonged monitoring, compared to 6 of 30 undergoing conventional testing (52 % vs. 20 %, $p = 0.012$). Overall, prolonged monitoring was more likely to result in a diagnosis than conventional testing (55 % vs. 19 %, $p = 0.0014$). Bradycardia was detected in 14 patients undergoing monitoring, compared to 3 patients with conventional testing (40 % vs. 8 %, $p = 0.005$). These data highlight the diverse etiology of syncope, and also illustrate the limitations of conventional diagnostic techniques. Although there is clear selection bias in enrollment of patients referred to an electrophysiologist for workup, this study suggests that tilt testing has a modest yield at best when applied to all patients undergoing investigation for unexplained syncope, and that electrophysiological testing is of very limited utility in patients with preserved left ventricular function.

The other randomized study is the Eastbourne Syncope Assessment Study (EaSyAS) [32]. Two hundred and one patients presenting to a single institution with recurrent syncope without a definite diagnosis following a basic clinical workup were randomly assigned to ILR implantation ($n = 103$) or conventional investigation and management ($n = 98$). Over a mean follow-up period of 276 ± 134 days, there were further syncopal events in 43 % of the ILR group compared with 33 % of the conventional strategy group. Thirty-three patients in the ILR group and four in the conventional strategy group received an electrocardiographic diagnosis (33 % vs. 4 %, HR 8.93, 95 % CI 3.17–25.2, $p < 0.0001$). Seventeen-month follow-up data from the same group of patients were reported in 2006 [33]. Forty-three percent of the ILR group and 6 % of the conventional testing strategy group received an electrocardiographic diagnosis (HR 6.53, 95 % CI 3.73–11.4, $p < 0.0001$).

The cost effectiveness of the ILR versus a conventional testing strategy in the evaluation of syncope was evaluated in both randomized trials. In the RAST study the prolonged monitoring strategy with crossover to conventional testing gave a diagnostic yield of 50 % at a cost of $2,937 ± 579 per patient and $5,875 ± 1,159 per diagnosis. Conventional testing followed by crossover to the ILR-based strategy gave a diagnostic yield of 47 % at a greater cost of

$3,683 ± 1,490 per patient (p = 0.013) and a greater cost per diagnosis of $7,891 ± 3,193 (p = 0.002) [34].

In the EaSyAs study, ILR resulted in a cost saving (not including the cost of the ILR itself, which was £1,350 at the time of the study) of £406 compared with £1,210 with the conventional strategy (mean difference £809, 95 % CI £123–£2,730). This meant that 60 % of the price of the device was recovered by the higher diagnostic yield.

The economic assumptions underpinning the conclusions of both studies are limited to investigation costs per diagnosis without considering the wider health economic costs such as lost income to patients, families and business associated with a delay in diagnosis. In addition, the EaSyAS study showed clearly that the cost of the device outweighs the cost savings on the reduced investigational burden. Thus, the clinical and economic case for ILR use is suggestive but far from definitive.

Due to their invasive nature and costs, ILRs play a lesser role in patients with recurrent unexplained palpitations when compared with those with syncope. Less invasive monitoring techniques typically provide a diagnosis in patients with palpitations, even when they are elusive (Fig. 15.7). They may be implanted in patients with infrequent palpitations (less than monthly) associated with troublesome symptoms when all other tests results are inconclusive. Few studies are available on the use of ILR in patients with unexplained palpitations [35]. In the Recurrent Unexplained Palpitations (RUP) study, 50 patients were enrolled with infrequent (≤1 episode/month) and sustained (>1 min) palpitations. Patients were randomized either to conventional strategy (24 h Holter recording, a 4-week period of ambulatory ECG monitoring with an external recorder, and electrophysiological study), or to ILR implantation with 1-year monitoring. A diagnosis was obtained in five patients in the conventional strategy group and in 19 subjects in the ILR group (21 vs. 73 %, p < 0.001). Despite the higher initial cost, the cost per diagnosis in the ILR group was lower than in the conventional strategy group [35]. After a diagnosis was reached, patients were followed up for at least 12 months. Palpitations were completely eliminated in 22 patients when an arrhythmic diagnosis treated with ablation, pacemaker, or drugs.

When to Choose Prolonged Monitoring

Table 15.2 summarizes the comparative advantages, limitations and indications for the various modes of ambulatory electrocardiographic monitoring. The literature, including guidelines and position paper from the European Society of Cardiology and European Heart Rhythm Association [36, 37], supports the early use of the ILR soon in an initial phase of the diagnostic work-up of patients with recurrent unexplained syncope. The optimal patient for prolonged monitoring with an external or ILR has symptoms suspicious for arrhythmia, namely abrupt onset with minimal prodrome, typically brief loss of consciousness, and complete resolution of symptoms within seconds to minutes. Episodes are not necessarily posture related, and may be associated with palpitations. After clinical assessment, including determination of left ventricular function, a decision must be made as to whether the underlying condition is potentially life threatening. We have historically used a left ventricular ejection fraction of 35 % as a cutoff for performing electrophysiological testing prior to employing a prolonged monitoring strategy. Primary and secondary prevention trials using implantable defibrillators support this practice. All reports using the ILR have suggested a low incidence of life-threatening arrhythmia or significant morbidity with a prolonged monitoring strategy. This suggests a good prognosis for patients with recurrent unexplained syncope in the absence of left ventricular dysfunction or with negative electrophysiological testing, and attests to the safety of a monitoring strategy. This finding was particularly striking in the negative electrophysiological testing arm of the ISSUE study (see discussion above).

Lastly, syncope resolves during long-term monitoring in almost one-third of patients even in the presence of frequent episodes prior to loop recorder implantation. This suggests that the cause of syncope in some instances is self-limited,

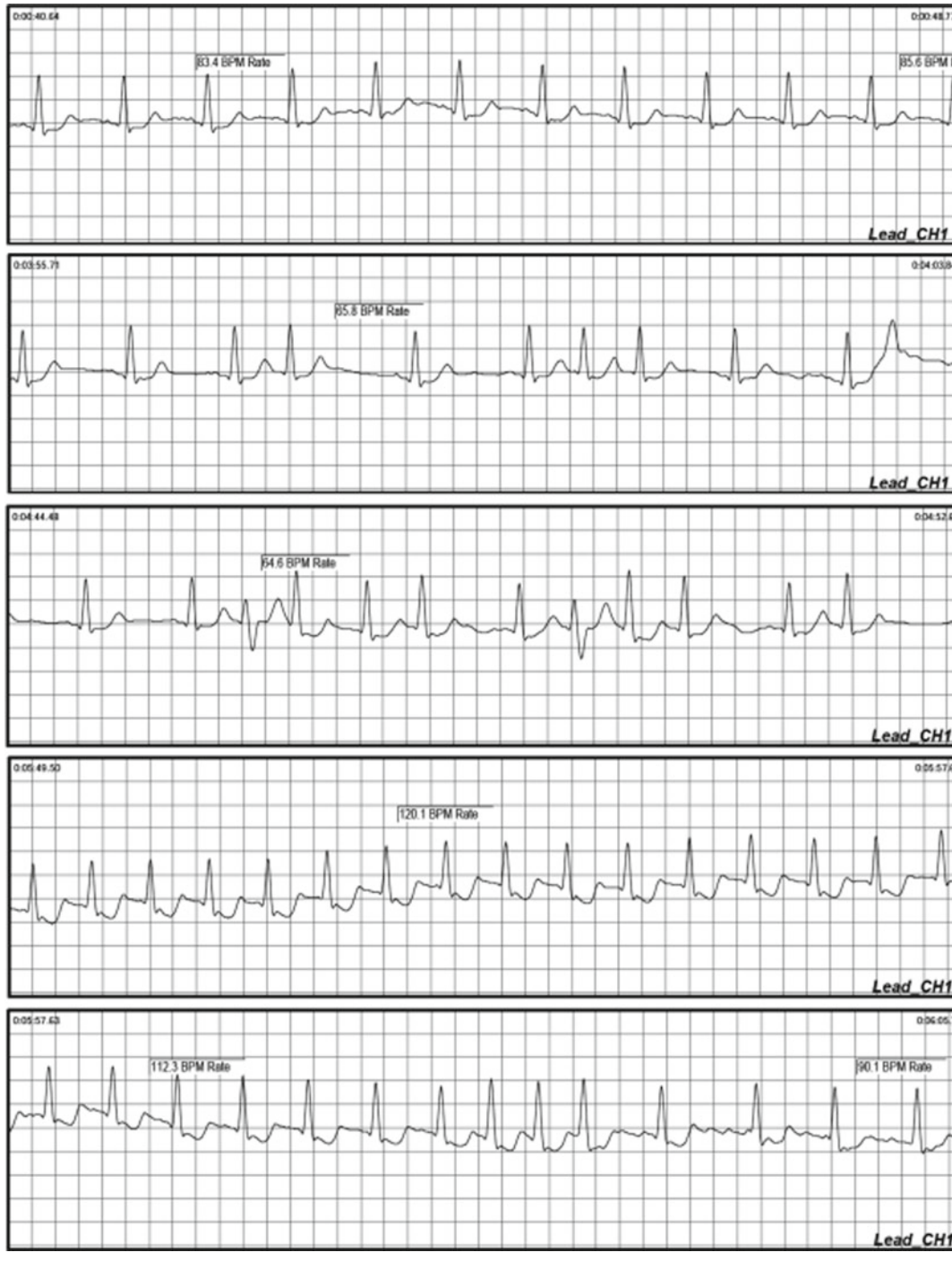

Figure 15–7. Manual event detection from an external loop recorder. Manual activation during presyncope and palpitations in an 83-year-old female with infrequent palpitations. The 5 rhythm strips represent non-consecutive select strips from a 10-min recording. Note the reference sinus rhythm, followed by progressively more complex atrial ectopy, transient regularity of the tachycardia (atrial tachycardia or flutter), followed by degeneration to atrial fibrillation

Table 15–2. Comparison of ambulatory electrocardiographic monitoring devices

	Holter monitor	Transtelephonic monitor	External loop recorder	Mobile cardiac outpatient telemetry	Implantable loop recorder
Advantages	Low cost; continuous monitoring	Low cost	Retrospective and prospective electrocardiographic records; possibility to record asymptomatic arrhythmias automatically	Continuous monitoring; patient activation to report symptoms	Prolonged monitoring without external electrodes; highest diagnostic yield
Limitations	Short duration of monitoring with low diagnostic yield	Poor electrocardiographic recordings; short lasting arrhythmias are not recorded; patient activation required; poor patient compliance to wearing device	Poor electrocardiographic recordings; poor patient compliance to wearing device; continual device maintenance required	Poor patient compliance to wearing device; continual device maintenance required; cost; not widely available	Invasive implantation with risk of local complications; high cost
Indications	Patients with very frequent symptoms (≥1 per week)	Compliant patients with inter-symptom interval ≤4 weeks	Compliant patients with inter-symptom interval ≤4 weeks	Compliant patients with inter-symptom interval ≤4 weeks	Early phase of evaluation of patients with recurrent syncope of uncertain origin who have absence of high-risk criteria that require immediate hospitalization or intensive evaluation and a likely recurrence within device battery longevity

or reflects a transient physiological abnormality. Long-term monitoring strategies may also have a role in the assessment of patients who have infrequent palpitations but are at risk of arrhythmias.

Conclusion

The identification of a cause for presyncope, syncope, or palpitations remains a significant challenge for clinicians despite advances in knowledge pertaining to mechanisms. A careful history and examination are mandatory in the assessment of these patients. However, the accurate correlation of symptoms to rhythm requires the judicious use of these monitoring tools. Ambulatory cardiac monitoring applied as either an external or implantable modality has provided a powerful means to elucidate the etiology of symptoms such as presyncope, syncope, or palpitations. The choice of ambulatory monitoring strategies is determined by the index of suspicion of cardiac arrhythmias, the frequency and nature of symptoms, and, ultimately, by the diagnostic yield of the particular monitoring strategy. For instance, implantable loop recorders have significantly improved the success of obtaining electrocardiographic rhythm data during spontaneous symptoms in patients with recurrent unexplained syncope. The clinician should consider early use of external and implantable loop recorders when an arrhythmia is suspected based on clinical presentation and initial noninvasive testing.

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16
Device Therapy for Remote Patient Management

Dwight W. Reynolds, Christina M. Murray, and Robin Germany

Abstract

Remote device (CIED) monitoring has become a mainstay of clinical practice involving implanted devices such as pacemakers, defibrillators, and implantable loop recorders. The aims of remote monitoring are to provide accurate, timely, and economical information about both device functions and disease status. Remote monitoring is an integral component of comprehensive CIED management and, as an extension, serves as an additional important tool in device performance surveillance.

While this chapter is unrevised from the 1st edition, and some of the statistics are out of date and some of the company systems have changed, the concepts and directions remain intact.

Keywords

Remote Monitoring • Device follow-up • Device interrogation • Device surveillance • Implantable monitors

Introduction

It is important that new medical technologies, including that of the present topic, remote monitoring and management of devices and diseases using implantable devices, provide answers to questions and help solve problems and not simply provide new and expensive "toys". We live in a world in which geographic proximity to advanced medical care is of major importance for those afflicted with many types of illness. And yet, there are vast areas of our world which do not have such proximity, so-called underserved areas. Additionally, even our most advanced medical facilities struggle with volumes of patients and the ability to provide timely care to all who need this care. We are also substantially challenged by the need to collect information about implantable device performance in a meaningful and comprehensive way. Finally, the cost, both in monetary terms and in human aggravation, of traditional in-hospital and in-clinic care using conventional approaches continues to escalate. Remote monitoring and management of chronic and even acute conditions using implanted devices offer substantial answers to each of the major

D.W. Reynolds, MD (✉) • C.M. Murray, MD, • R. Germany, MD
Medicine Department,
Cardiovascular Section,
University of Oklahoma Health Sciences Center and OU Medical Center,
920 Stanton L. Young Blvd., Rm WP3010,
Oklahoma City, OK 73104, USA
e-mail: dwight-reynolds@ouhsc.edu; christina-murray@ouhsc.edu; robin-germany@ouhsc.edu

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medical issues alluded to above. This chapter will describe what is surely only the beginning foray into this emerging technology and evolving concept.

Remote monitoring of intracardiac devices is a concept which has been reviewed in literature [1], but continues to evolve, and, at the time of this writing, appears to be gaining rather rapid momentum. While technology has allowed remote monitoring of implantable devices, especially pacemakers and more recently ICDs, for decades, the ability to acquire more extensive device and patient data using remote monitoring is a phenomenon that began in only the last few years. Twenty years ago we were able, using telephone line communications, to obtain information about heart rates, pacemaker output amplitude and duration, and ECGs. Today we can, using sophisticated but easily available computer linkages, obtain remotely virtually all information stored in the most sophisticated devices. This includes electrograms and information about remote and recent cardiac arrhythmic and even hemodynamic events. In the not too distant future, it is virtually certain that we will be remotely programming devices as the technology advances and professionals and patients (and regulators) become more comfortable in doing so. While much of the focus in this area has been on device monitoring, it is clear that, with the evolution of implantable physiological and now chemical sensors, monitoring of chronic and even acute illnesses will be possible. While there is an inevitable concern about the expense of developing and implementing these exciting technologies, it is likely that remote monitoring of implanted devices and diseases will actually reduce the cost of healthcare as fewer hospitalizations and both scheduled and unscheduled outpatient visits occur. There appears to be a substantial opportunity to use remotely acquired device information, logged into computer-based databases as an adjunct to other device performance surveillance systems.

In this chapter a summary of currently available remote monitoring by several different companies will be discussed. The reader is reminded, again, that because this area is changing rapidly, information here may soon need to be updated.

Current Uses and Goals for the Future

Rationale for Remote Monitoring

Patient Safety

Patient safety will inevitably drive much of the impetus toward closer monitoring and prompt notifications. Remote monitoring would allow more frequent device checks, with the potential for more timely trouble-shooting. The Heart Rhythm Society recommends that manufacturers of devices develop and utilize wireless and remote monitoring technologies, for the identification of abnormal device behavior as early as possible. This group has also recently stressed the importance of reducing the underreporting of device malfunction [2]. The ACC/AHA/NASPE Guidelines for Implantation of Cardiac Pacemakers and Arrhythmia Devices recommend close monitoring of devices (specifically ICDs), with frequency of follow-up dictated by the patient's condition. Intervals specified are 1–4 months, with in office visits supplementing transtelephonic evaluations no less than every 3 months [3]. Current practices have extended the times between follow-up visits.

Benefits Achieved Through Remote Monitoring

There is evidence for the benefit of some types of remote monitoring, in chronically ill patients such as those with advanced heart failure, thereby achieving morbidity and mortality benefits. Although not yet fully evaluated in randomized trials, it is anticipated that the same benefit may be obtained by remote monitoring of parameters measurable by implanted devices [4]. Interventions such as education and nurse telephone calls may reduce hospitalization by increasing disease awareness and compliance, along with therapy changes [5]. A mortality benefit was shown in the randomized, controlled WHARF trial, using a scale and symptom response system, with information transmitted via telephone. There was a 56 % reduction in mortality ($p < 0.003$) in the monitored group, speculated to be due to facilitated communication of important events to physicians [6]. These benefits have also been seen with a single home visit prior to discharge from the hospital [7] and with a more comprehensive

disease management program managed telephonically [8]. A recent European study compared automated telemonitoring (weight, blood pressure, heart rate, and rhythm) with nurse phone calls and usual care, finding reduced admission days and mortality in the telemonitored group [9]. Over the course of the 240-day follow-up period, hospital stays were reduced by 6 days, and mortality rates were 45 % in the usual care group, which was compared to 27 % in the nurse care group and 29 % in the telemonitored group, a significant reduction ($p = 0.032$).

Integration of Care

The centralized storage of remotely obtained data will permit improvements in integration of care. Information is available for both the heart rhythm specialist, as well as the heart failure physician or any other physician participating in the patient's care. If the observations of remote monitoring trials are correct, it should be possible to improve patient care by accessing this information. This may also facilitate communication regarding important patient care issues between subspecialists that often practice significant distances apart. Remotely obtained data may facilitate a multidisciplinary approach to patient care. It will also allow access of this data by physician extenders, such as physician assistants and nurse practitioners, who can aid in acting promptly on critical data.

Resource Conservation

Resource conservation may be one of the most compelling reasons to pursue remote monitoring. It is estimated that evaluation of remotely obtained data may take as little as 8 min [10] compared to 30 min for a traditional, in-office follow-up. Travel costs may be minimized. By reducing the interaction time required, more patients may be served. Time management and cost of follow-up care will be important considerations as the population ages and device indications grow.

Future Uses

As we move to more comprehensive, actually complete, device data availability remotely and as the implanted devices gather increasingly useful physiological information, new goals for remote care will likely emerge, changing the paradigm to one coupling modification of therapy with remote monitoring. It is easy to envision substantially improved clinical algorithms and modifications based on data obtained by this monitoring. Investigationally, using implanted devices, medical modifications have been made based on remote observations, including changes in agents such as beta-blockers, ACE inhibitors, and diuretics [4]. Future standards will almost certainly include remote programming of device settings. Programming to accomplish faster or slower pacing rates and AV interval modifications to minimize ventricular pacing could occur. In more technically challenging situations, changes could be made to more complex anti-tachycardia algorithms such as we do now in-clinic. In the future, home-based care might be possible that would otherwise necessitate hospitalization, with remotely available information such as hemodynamic parameters analogous to those obtained in the setting of a critical care unit.

Novel technologies will incorporate and likely improve on the remote monitoring, making a spectrum of routine to advanced care not only reliable, but possible financially advantageous for society. This may offer not only benefits with regard to resource conservation, but palliation of end-stage disease.

The History of Monitoring

Transtelephonic Monitoring

The early history of device monitoring began with trans-telephonic monitoring (TTM) of early pacemakers in the 1970s [11]. In the early era of pacemaker systems, battery longevity and lead performance were unpredictable. Early telemetry helped ensure patient safety, and provided a level of convenience for patients who were too ill to travel or lived substantial distances from clinics. Transtelephonic transmission was accomplished by connecting electrodes to the patient (wrists, ankles, etc., depending on system design) and to a transmitter, which was then coupled with the mouthpiece of the

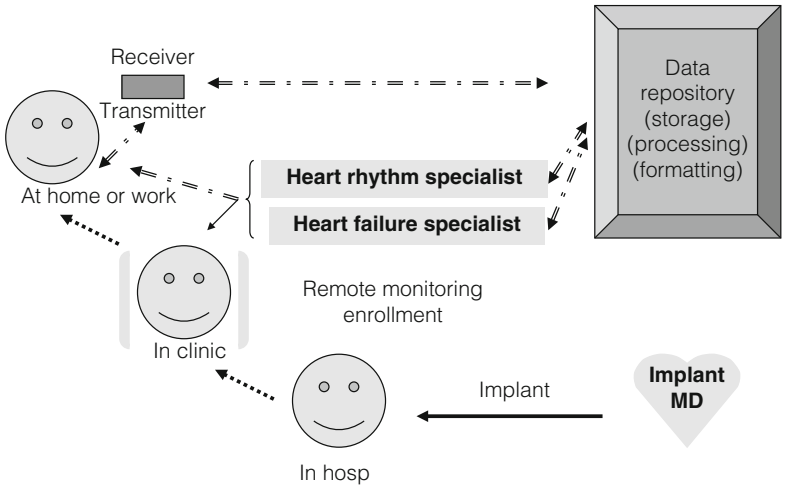


Figure 16–1. A schematic representation of a generic remote monitoring program. Other clinicians could be involved either directly or indirectly by receiving the remote monitoring report from the "data repository" or from one of the other clinicians

telephone. The only information available initially was rate determination with a reasonable evaluation of capture and sensing with the device as programmed. Interference artifacts often compromised the recordings obtained. Poor patient understanding of equipment use was also challenging [12]. ECG tracings were obtained in regular and magnet modes, and were required to be of 30 s duration, and a significant part of the medical record [13]. As technology progressed, threshold testing became available, via magnet induced reduction in pacemaker output.

Early Studies Using Transtelephonic Monitoring

Use of these systems became more sophisticated over time. A case report in 1984 described the use of TTM to monitor the use of an early device with anti-tachycardia therapy [14]. A trial published in 1992 confirmed symptoms of AF and SVT correlated with data obtained from transtelephonic ECG monitoring. There was significant correlation between symptoms and documented arrhythmia, with 70 % of calls related to symptoms showing PSVT or PAF attacks [15]. Use of TTM in following ICD patients was described in a report in 1995, in 18 patients, allowing identification of spontaneous arrhythmias, and assessment of the success of therapies delivered [16]. The feasibility of this type of monitoring had been well established. Expansion of device features and better internet technology lead to a greater sophistication for remote monitoring as well.

Current Examples of Remote Monitoring

Over the past several years, with improvement in device telemetry, remote communication and computer technology, major device manufacturers have developed and implemented increasingly sophisticated remote monitoring systems. While each device manufacturer's monitoring systems are restricted to their devices, and there are substantial differences among the systems, all are evolving and are aimed at greater patient safety and satisfaction as well as greater follow-up efficiency. This section explores examples of currently available technology. A general schematic of how most remote monitoring systems work is shown in Fig. 16.1. A synopsis of comparative features among the four systems discussed below is contained in Table 16.1.

Biotronik

The Biotronik remote monitoring system Home Monitoring™, uses wireless phone technology to transmit patient information, called to a centralized server, via a patient transceiver. Biotronik initially received a license to

Table 16–1. Historic manufacturer's monitoring systems

	Biotronik	Boston Scientific/Guidant	Medtronic	St Jude Medical
Name	Home Monitoring™	Latitude™	CareLink™	Housecall Plus™
Remote monitoring connection	Cellular or standard analog telephone line (not digital compatible)	Standard analog telephone line (not digital compatible)	Standard analog telephone line (not digital compatible)	Standard analog telephone line (not digital compatible)
Frequency/channel bandwidths of wireless components	Medical implant communications system (403 MHz); channel bandwidth 100 kHz	FCC license category used by any industrial, consumer, scientific or medical products (914 MHz)	Medical implant communication service band (402–405 MHz); multiple channel bandwidth 300 kHz	
Access	Secure internet network, internet access for multiple clinicians	Secure internet network; internet access for multiple clinicians; limited patient access	Secure internet network, internet access for multiple clinicians	Maintained in office or by service providers; no internet access
Data available	Battery voltage, pace and shock impedances, EGMs, arrhythmia and therapy data	Complete device data, EGMs, blood pressure and weight	Complete device data, EGMs, hemodynamic data	Complete device data, EGMs, surface ECG
Alerts	Internet, email, pager, cell phone or fax	Critical – call to physician and page to local representative; urgent – fax to office and information sent to internet website	Pager or voicemail notification, with patient information to be accessed on internet	Service center call to clinician
Manufacturer charges	At implant (hospital)	At implant (hospital)	At follow-up (clinic billed quarterly)	Clinic or third party (equipment purchase)

use the frequency in 2001 for wireless monitoring of pacemakers. ICD monitoring followed in 2002, with CRT-D monitoring initiated in 2006. Biotronik remote monitoring is, as of October 2006, in use by approximately 52,000 worldwide patients, with 12,000 of these in the United States.

Home Data Acquisition

Stored data is obtained wirelessly, automatically on a pre-determined schedule. A radio frequency transmitter is integrated into the implanted device circuitry, which communicates with the patient transceiver. Data can be acquired by the transceiver at a distance of 2 m from the implanted device. The transmitter is small, and can be worn or carried by the patient. The data is transmitted via GSM cellular telephone technology, and can also be used with a standard telephone land-line. Data is transmitted daily at programmed times. Patient triggered reports can be obtained as well. Transmission (unidirectional) occurs over the Medical Implant Communications System at 403 MHz with a channel bandwidth of 100 kHz. Data is transmitted to the Biotronik Service Center.

Data Obtained

Device related information obtained at interrogation includes such data as battery voltage, and pace and shock impedances. Routine remote device data acquisition using this system has the potential to identify significant events such as lead malfunction with sudden increase in pacing threshold (Fig. 16.2). For example, lead fracture which, in this case, was a result of patient manipulation (twiddler's syndrome) [17] was identified remotely (Fig. 16.3).

Patient related parameters reported, using this system, include atrial and ventricular arrhythmias, and therapies delivered for ventricular tachycardia and ventricular fibrillation. Intracardiac electrograms (IEGMs) are available for scrutiny of events, to determine whether therapy was appropriate. Other parameters can be remotely tracked, including mean heart rate, paced and intrinsic percentages, percent CRT pacing, ventricular ectopy and mode switching. Resting heart rate and patient activity level are also available.

Notifications

With the Biotronik System, as with others discussed later, critical patient and device data can be transmitted to physicians. Notification is made

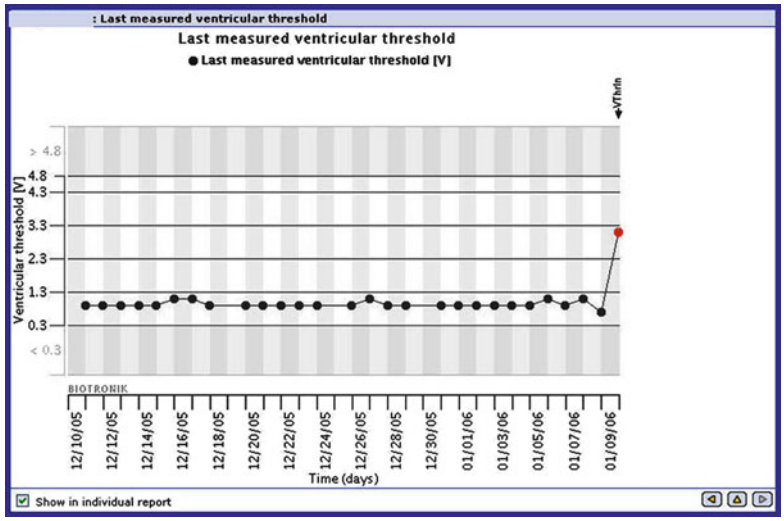


Figure 16–2. This data is an example of a remotely acquired report using the Biotronik Home Monitoring™ system. This report shows a sudden increase in pacing threshold (Courtesy of Biotronik)

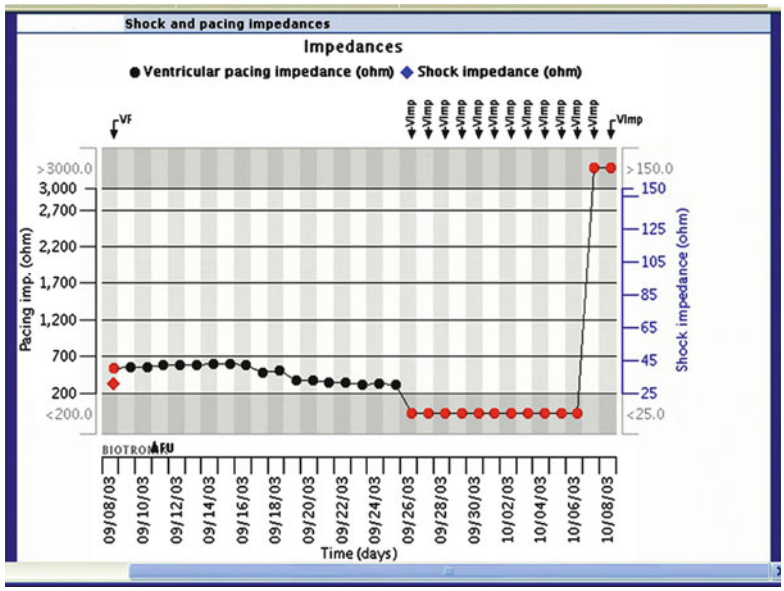


Figure 16–3. This is another example of a remotely acquired report of the Biotronik Home Monitoring™ system. This report shows an initial drop in impedance on a pacing lead over a several week period, indicating an insulation breach, followed by a dramatic increase in lead impedance indicating a fracture. This clinically was a result of "twiddler's syndrome" (Courtesy of Biotronik)

according to physician preference, including options of internet, email, pager, cell phone or fax. Notifications can be patient initiated in the case of symptoms. In such cases a patient can wave a magnet over the device, resulting in immediate transmission of data. If a patient receives therapy for certain events (ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia, etc.) the medical team can be notified immediately. If the physician so chooses, he/she can be notified of these events within 1 min of the event, by one of the methods mentioned above.

Cost

The manufacturer's charge for use of these added features, including the cellular service, is included at the time of device implantation. There are no additional charges for use for the life of the implanted device. The remote

monitoring charges by physicians to patients using this and other manufacturers' systems are currently under review and revision.

Boston Scientific/Guidant

The remote monitoring system offered by Boston Scientific, called Latitude™, was introduced to the market in 2006. It is, as of this writing, in use by approximately 6,500 patients. With the newest implantable devices, this technology permits not only remote monitoring but also "wireless" implant and "wireless" in-office follow up. This is accomplished by a new telemetry system in which the distance between the implanted device and the data acquisition device is substantially increased over earlier versions. There is also optional hardware, a Bluetooth enabled blood pressure cuff and scale, which can be used with the system.

Home Data Acquisition

Remote interrogations can be performed automatically on as much as a daily basis. Frequency and day of the week can be specified and modified. Interim follow-ups can be arranged, even on prespecified dates. Patient initiated interrogations are also possible (clinician enabled). Scheduling options exist for active monitoring notifications and can be changed according to physician and patient preference (daily or weekly). Data is transmitted from the patient's device to a wireless "communicator", a transceiver, kept in the home. This system currently requires a standard telephone line. Communication occurs via the Industrial, Scientific, Medical band at a frequency of 914 MHz.

Data Obtained

Downloaded information appears on an internet website, maintained on encrypted servers that comply with privacy rules. System information can be followed by multiple physicians. Although the physician viewed information is the same, schedules, alerts and notifications can be individualized for different physicians. At the time of data acquisition, critical information is deemed to fall into certain predetermined alert categories ("red" or "yellow"), in addition to standard patient care information.

A report is generated with features designed to assist with heart failure management (Fig. 16.4). Arrhythmias including atrial fibrillation and ventricular fibrillation and ventricular tachycardia are recorded. Weight, blood pressure (if scales and blood pressure cuffs are also included), activity, heart rate maximum, minimum and means are available. Autonomic parameters such as heart rate variability (HRV) determinations are incorporated in the report. Weight monitoring, as noted an optional feature, can highlight changes of 5 lbs in 1 week or 2 lbs pounds in a 1 or 2-day period.

The Boston Scientific system offers access to some non-traditional data via remote reporting. Patient quality of life issues can be addressed via self report questions that may be answered with the home monitor, a function programmable to either "on" or "off". Questions are asked weekly. Symptom queries include fatigue, dizziness, edema, orthopnea and PND (Fig. 16.5). The system also includes the ability to give patient access to limited information, via internet access. Patient-available data include dates of recent and scheduled interrogations, weight, blood pressure, battery status, and contact information.

Notifications

The relative importance of information may trigger physician contact, varying from a fax sent to the physician office to physician and local industry representative calls. If this feature is not enabled, the patient is notified. "Red" events are those that are considered critical to the continuing appropriate operation of the implanted system. Such events include battery end of life, impedance aberrancies, low right ventricular intrinsic (R wave) amplitudes, and high voltage detected on the shock lead during charge. When these criteria are met, the company calls the physician and contacts the local representative. "Yellow" alerts are noted on weekly checks. Alert events include such

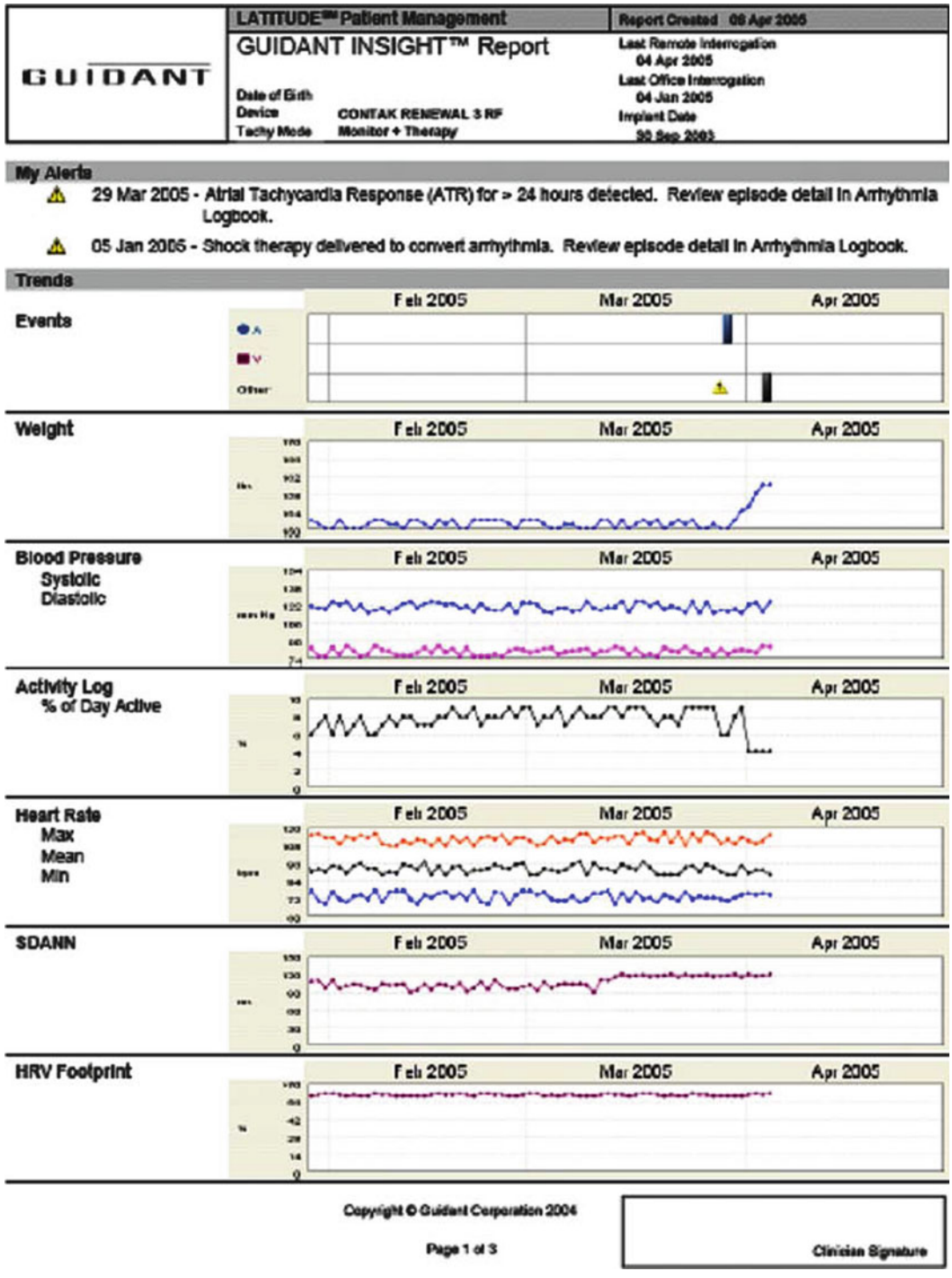
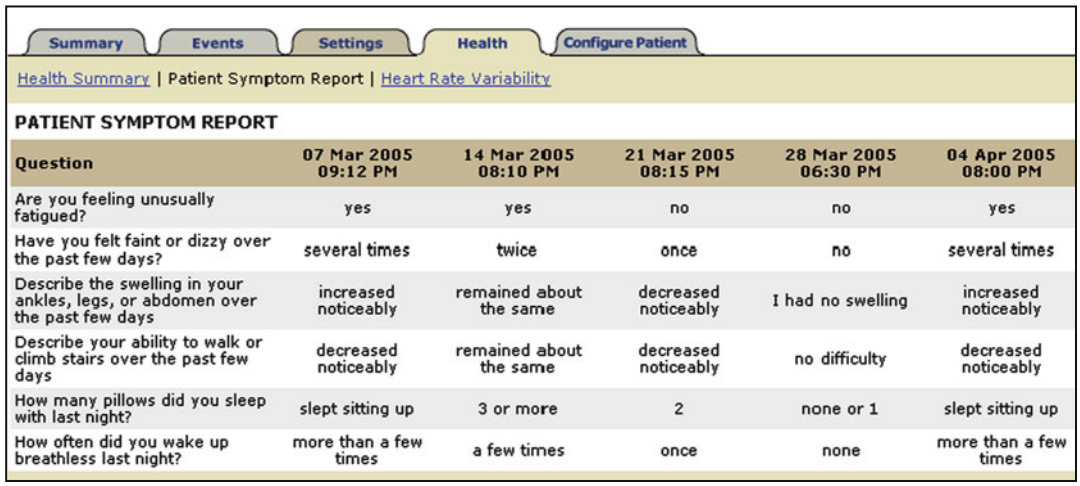


Figure 16–4. An example of a heart failure report generated on Boston Scientific's Latitude™ system. Note the inclusion of both blood pressure and weight data (Courtesy of Boston Scientific)



Summary | Events | Settings | Health | Configure Patient

Health Summary | Patient Symptom Report | Heart Rate Variability

PATIENT SYMPTOM REPORT

Question	07 Mar 2005 09:12 PM	14 Mar 2005 08:10 PM	21 Mar 2005 08:15 PM	28 Mar 2005 06:30 PM	04 Apr 2005 08:00 PM
Are you feeling unusually fatigued?	yes	yes	no	no	yes
Have you felt faint or dizzy over the past few days?	several times	twice	once	no	several times
Describe the swelling in your ankles, legs, or abdomen over the past few days	increased noticeably	remained about the same	decreased noticeably	I had no swelling	increased noticeably
Describe your ability to walk or climb stairs over the past few days	decreased noticeably	remained about the same	decreased noticeably	no difficulty	decreased noticeably
How many pillows did you sleep with last night?	slept sitting up	3 or more	2	none or 1	slept sitting up
How often did you wake up breathless last night?	more than a few times	a few times	once	none	more than a few times

Figure 16–5. An example of a patient symptoms report generated by the Boston Scientific Latitude™ system (Courtesy of Boston Scientific)

arrhythmic events such as shock delivery, type and timing of tachyarrhythmias, and patient triggered events. Significant weight changes are noted. Device specific parameters are noted, including battery status, and lead parameters including intrinsic amplitude and pacing lead impedance. These less critical "yellow" events are noted on the clinician accessible website, and a fax is sent to the physician office.

Cost

Weight scales and blood pressure cuff are available as optional components to the Latitude™ system. Manufacturer charges for use of the rest of the system are billed at the time of implant. As previously discussed, physician charges for remote follow-up are currently being reviewed and revised.

Medtronic

The remote monitoring system used by Medtronic called CareLink™ was launched in 2002. Approximately 85,000 patients (involving approximately 1,000 clinics) are using the network as of October 2006. Transmission captures device parameters, including diagnostics, and stored episodes of arrhythmia events. A prospective evaluation of the system was completed prior to market release, and demonstrated a high level of physician satisfaction with the system [18], with 96.5 % of physicians reporting that it was either somewhat easy or very easy to use. Patients also found the device easy to use, with 98.1 % reporting that the monitor was either somewhat easy or very easy to use. In addition to remote monitoring, Medtronic has recently introduced a new generation of devices that permit "wireless" implant, in-office follow-up, and automated remote follow-up, similar in function to that described with Boston Scientific's Latitude system. These systems which eliminate a "programming head" from the sterile field at the time of implant may have the additional advantage of reducing implant time by allowing activities such as pocket closure while doing final programming and interrogation. They also make clinic follow-up more streamlined, potentially. The most important advantage of the "long-distance" telemetry linkages, however, is that it allows automatic remote monitoring to occur, without the need for patients to take specific action to initiate a transmission.

Home Data Acquisition

Just as with the other systems, the monitors (transceivers) used in patient homes are FDA approved. These transceivers are portable and can be used outside of the home including internationally, and are patient specific. Downloaded information is stored on a secure internet system

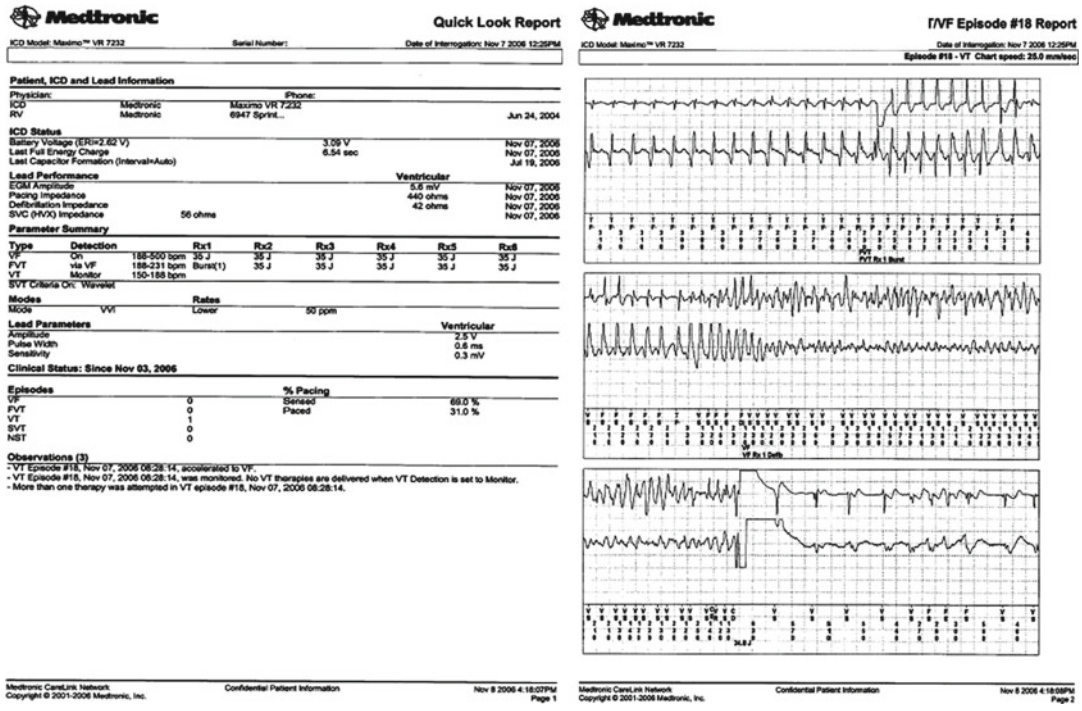


Figure 16–6. A Medtronic CareLink™ remote monitoring report on a patient with ventricular tachycardia that was accelerated by anti-tachycardia pacing resulting in ventricular fibrillation successfully defibrillated with a single internal shock

that is password protected. Telemetry is transmitted (bidirectionally) on the Medical Implant Communication Service Band, 402–405 MHz. Use of this band may have advantages in prevention of interference caused by other wireless devices such as cell phones that operate at other frequencies. With CareLink™, telemetry can occur on a variable, "clearest" MICS channel of up to 300 kHz (within the 402–405 MHz band), which helps ensure a strong signal. Telemetry range between implanted device and home receiver-transmitter is dependant on conditions including the model of the implanted device, but may be achieved at a minimum of 2–5 m with the most recently developed implantables. As above, "wireless" technology now allows automated interrogations, in addition to patient initiated downloads with older devices that do not possess the "long-distance" telemetry of newer implanted devices. Automated relay of information may allow for earlier monitoring of arrhythmias or device related issues. This automation may also simplify compliance issues for patients and physicians.

Data Obtained

A complete set of stored and real-time device information, just like that obtainable in-clinic, can be obtained at the time of remote interrogation, including both device and patient specific information including arrhythmia events data, with EGMs on therapy delivery (Fig. 16.6), and specialized heart failure management reports (Fig. 16.7). Even hemodynamic information now available from some implanted devices is available remotely. This remote monitoring system has been used with FDA approved systems [19] and still investigational implantable hemodynamic monitors [20–22] as well. The ability to monitor chronic conditions remotely such as heart failure promises to further hasten the development, implementation, and acceptance of this technology.

Notifications

Clinician alerts are initiated by device recognition of preset conditions. The system automatically

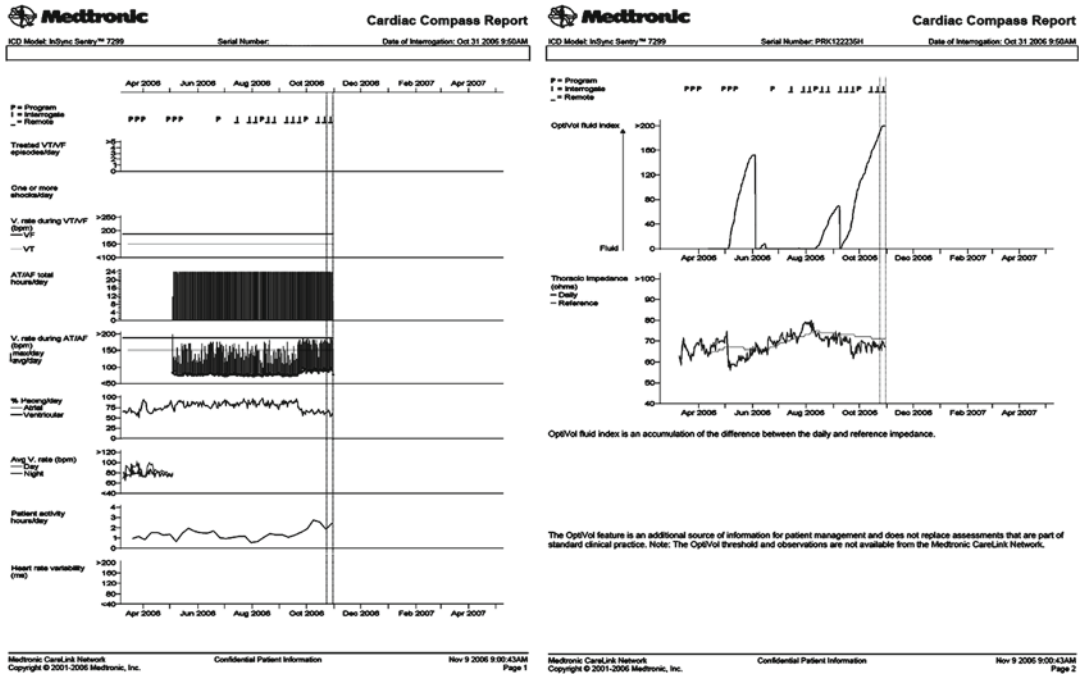


Figure 16–7. A Medtronic CareLink™ remote monitoring heart failure report on a patient using OptiVol, a measurement of transthoracic impedance as an indicator of heart failure status

sends a transmission when an alert is initiated. Alerts may be sent to the clinic or physician, to either voicemail or a pager. Information in the alert includes patient name and date of birth, type of alert, and a phone number to reach the patient.

Data obtained via alerts can be tailored according to physician preference. This allows for ongoing interaction with the system by different types of physicians. Device performance reports including all the standard information from interrogation, or heart failure management reports, may be sent to the heart rhythm specialist, or the heart failure physician, or both.

Cost

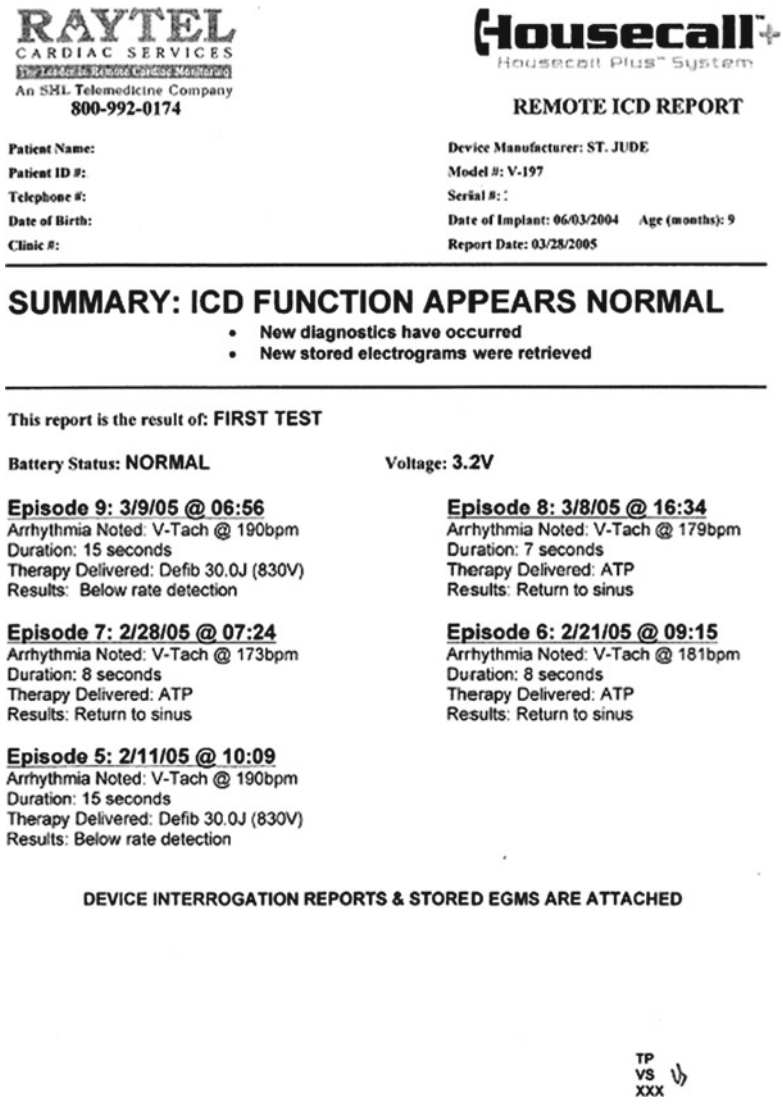
Manufacturer charges for the remote monitoring system are recurring, and are billed to the clinics where the monitoring takes place. Physician billing for these services is being reviewed and revised and there is significant variability, geographically, in third-party reimbursement for these, currently.

St. Jude Medical

The remote monitoring system marketed by St Jude Medical, Housecall Plus™, was introduced in October 2005, and has 7,000 patient enrollments as of October 2006. The system, different than the previous three discussed, utilizes live medical professionals (either in the patient's physician office or in service centers) to interface with patients during the transmission process. An early iteration of the system was evaluated in 124 patients, and found to have a high level of patient satisfaction, along with "safe and successful" monitoring [23].

Home Data Acquisition

Like the other systems described, data is obtained via a multi-part system. The device itself is the first part, the home transceiver in the patient's home a second part and the receiver is the final part, which may be owned and operated by service centers or by physicians. The home transceiver is equipped with



RAYTEL
CARDIAC SERVICES
The Leader in Remote Cardiac Monitoring
An SRL Telemedicine Company
800-992-0174

Housecall+
Housecall Plus™ System

REMOTE ICD REPORT

Patient Name:
Patient ID #:
Telephone #:
Date of Birth:
Clinic #:

Device Manufacturer: ST. JUDE
Model #: V-197
Serial #:
Date of Implant: 06/03/2004 Age (months): 9
Report Date: 03/28/2005

SUMMARY: ICD FUNCTION APPEARS NORMAL

- New diagnostics have occurred
- New stored electrograms were retrieved

This report is the result of: FIRST TEST

Battery Status: NORMAL Voltage: 3.2V

Episode 9: 3/9/05 @ 06:56
Arrhythmia Noted: V-Tach @ 190bpm
Duration: 15 seconds
Therapy Delivered: Defib 30.0J (830V)
Results: Below rate detection

Episode 8: 3/8/05 @ 16:34
Arrhythmia Noted: V-Tach @ 179bpm
Duration: 7 seconds
Therapy Delivered: ATP
Results: Return to sinus

Episode 7: 2/28/05 @ 07:24
Arrhythmia Noted: V-Tach @ 173bpm
Duration: 8 seconds
Therapy Delivered: ATP
Results: Return to sinus

Episode 6: 2/21/05 @ 09:15
Arrhythmia Noted: V-Tach @ 181bpm
Duration: 8 seconds
Therapy Delivered: ATP
Results: Return to sinus

Episode 5: 2/11/05 @ 10:09
Arrhythmia Noted: V-Tach @ 190bpm
Duration: 15 seconds
Therapy Delivered: Defib 30.0J (830V)
Results: Below rate detection

DEVICE INTERROGATION REPORTS & STORED EGMS ARE ATTACHED

TP
VS
XXX

Figure 16–8. A remote monitoring report from St. Jude Medical's Housecall Plus™ coupled with Raytel service center (Courtesy of St. Jude Medical)

two ECG wristbands, a telemetry wand to place right over the device and a built-in speakerphone, so patients can speak with the technician assisting with the download process. A standard telephone jack (with land-line) and power outlet are required. After the data is received and formatted, there is PDF export capability, to capture information for email, in office use such as in an electronic medical record, or other uses. Data can be maintained locally if a physician so chooses (and purchases the necessary equipment), or on servers controlled by service providers, currently the more commonly used approach.

Data Obtained

The data obtained, much like with the other systems discussed, is essentially the same as in-office reports obtained from a standard programmer. There are real time surface EGMs obtained from wristbands, along with stored electrograms from episodes where therapy was indicated and may have been delivered. Device specific information is assessed, including battery status, thresholds, and impedance measurements, along with other more specific programmed algorithms. Summaries of clinically relevant events may be obtained (Fig. 16.8), along with episode specific EGMs

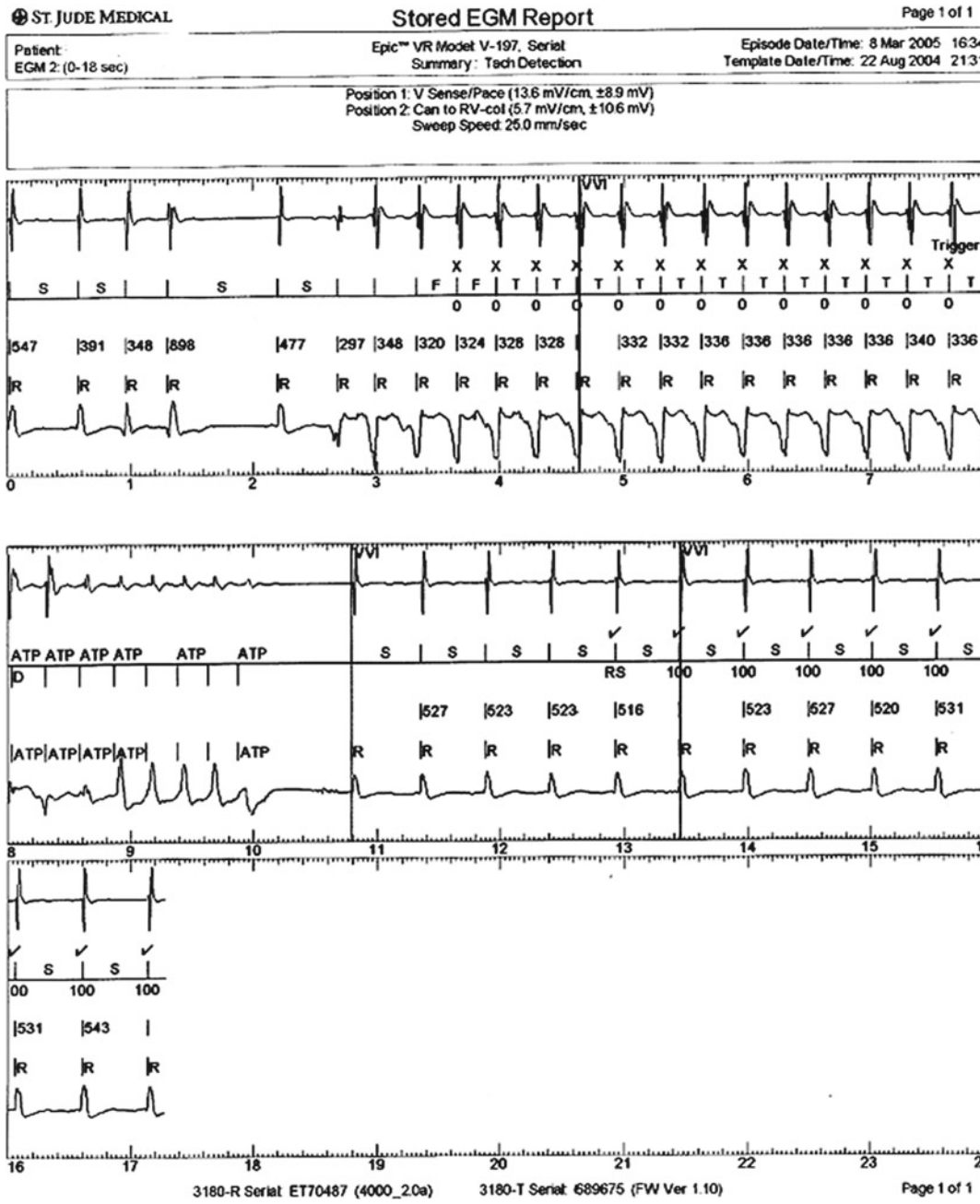


Figure 16–9. A St. Jude Housecall Plus™ remote monitoring report showing details of an arrhythmia event (ventricular tachycardia) successfully treated with anti-tachycardia pacing (Courtesy of St. Jude Medical)

(Fig. 16.9). In the service centers, data is evaluated by technicians who have become testamurs of NASPExAM (now referred to as IBHRE, International Board of Heart Rhythm Examiners).

Notifications

Critical issues are dealt with initially via the service center (if utilized). The physician may be notified in the case of pre-selected and customized notification criteria, such as therapy

delivery, battery compromise, or impedance changes. Under the physician maintained system, information is received by persons designated by the physician practice.

Cost

There are manufacturer charges for the receiver and the transmitter. Payment structures vary according to whether equipment is owned or leased, or how service centers are utilized. There are two service centers which can be used with the system, according to practice choice. There are no service fees associated with ongoing use of the system.

Billing for the services provided varies according to the model used, physician-maintained or by service providers, and involves variable billing of technical and professional fees associated with interrogation.

Challenges

Privacy

One of the challenges for remote monitoring is privacy protection. Technology has and will no doubt attempt to keep up with federal and international standards for protection of personal information, such as HIPAA, which dictates standards of protection of the privacy of personal health information. While technical challenges such as encryption of data and human challenges such as adequate training of personnel about privacy issues require careful attention, all involved, to date, appear committed to privacy protection.

Data Management

Management (and formatting for use) of great volumes of data involved in remote monitoring will be problematic. Large volume practices could potentially be challenged with the day to day data management of patients with more advanced illness and implanted devices being remotely monitored, such as those typically seen in tertiary care centers. While such data is likely to lead to improved patient care, it is also likely that care pathways will need to be developed in offices specifically to deal with remotely monitored devices and patients. It is probable that large practices will have implanted device remote monitoring "centers" where data will be maintained, formatted and parceled out to clinicians who can use the information for patient management. Smaller practices may rely solely on manufacturer or other "third-party" entities for data acquisitions, formatting, and management. It is important to point out that centralized data banks may be most important in improved device surveillance and reporting efforts.

Costs and Reimbursement

The direct and indirect costs of this technology will be significant. As has been discussed, direct costs are billed at the time of implant, or are recurring. There will be further expenses, both direct and indirect, in managing the data (physician time, added staff, etc.). At the time of this writing, reimbursement may be obtained in many states, by a variety of insurers for these services. The Centers for Medicare and Medicaid Services (CMS) issued a transmittal (Transmittal 979) in June 2006 authorizing reimbursement for remote monitoring of pacemakers and ICDs using in-office electronic analysis codes. While the initial forays into more sophisticated remote follow-up have targeted ICDs and CRT devices because of reimbursement issues, it is anticipated that over time, virtually all devices including pacemakers will be included.

Limitations

Limitations potentially imposed by this type of care will need to be addressed. Patient care teams will need to ensure that patients feel their care is being enhanced, rather than being compromised, by new technologies. These paradigm changes will likely require time to gain acceptance by the general medical community. Future trials will be designed to validate this approach to patient care and information, and also to investigate the potential economic aspects of remote care. As with any change in care paradigm, concerns will, no doubt, exist about not

only the feasibility of the new care style, but also patient acceptance.

Conclusions

It appears that we are on the brink of a new era in healthcare of patients with or at high risk of chronic, and even acute, diseases. Remote monitoring of both implanted devices and chronic illnesses using implanted devices has been developed, technologically, to a point of broad-based utility and availability. Most companies now marketing implantable electronic devices such as pacemakers and defibrillators have developed manufacturer-specific remote monitoring systems. While there are substantial differences in the technology and formatting of the different systems, there are common goals for all of the systems.

Rapid access by patients, even in geographies significantly remote from device and disease expertise, is facilitated by using remote monitoring systems. Patients in need can be more closely monitored using such systems and both the hassles and time for device and disease follow-up can be minimized, potentially at significant financial savings and certainly with improvement in patients and patients' families peace of mind and sense of wellbeing. From physicians' perspectives, with what will certainly be dramatic increases in patient volumes as our population ages as well as increases in absolute numbers, the improved efficiencies of remote monitoring will allow better human resource usage by minimizing unnecessary routine (and other) face to face visits with patients. It is likely that even hospitalizations can be reduced by remote monitoring systems as more consistent follow-up is done even for patients who otherwise would have difficulty achieving such follow-up because of geographic, physical, or economic restrictions. Remote monitoring and associated data-basing of device performance is an as yet untapped opportunity for dramatic improvement in device-performance surveillance.

While the future appears bright for this emerging discipline of remote monitoring, much work needs to be done to further expand what can be monitored remotely, especially in monitoring diseases, as well as other activities that can be accomplished such as remote programming of device function. Additionally, making certain that implementation of these new concepts, technology, and systems is accomplished in economically viable ways is a challenge of utmost importance.

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Invasive Electrophysiologic Testing: Role in Sudden Death Prediction

Jan Němec and Win-Kuang Shen

Abstract

Programmed ventricular stimulation has dramatically advanced understanding of ventricular tachycardia after myocardial infarction. It remains an important tool for sudden cardiac death risk assessment in certain groups of patients. Its role in patients without infarct-related scar is less clear. Current role of programmed ventricular stimulation, invasive assessment of accessory pathway properties and HV interval measurement is discussed in detail.

Keywords

Programmed ventricular stimulation • Risk stratification • Sudden cardiac death • Ventricular tachycardia

Abbreviations

AAD	Antiarrhythmic drugs
ARVD	Arrhythmogenic right ventricular dysplasia
AV	Atrioventricular
CAD	Coronary artery disease
CASCADE	Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation
CAST	Cardiac Arrhythmia Suppression Trial
CAST-II	Cardiac Arrhythmia Suppression Trial II
CL	Cycle length
DCM	Dilated cardiomyopathy
ERP	Effective refractory period
ESVEM	Electrophysiologic Study versus Electrocardiographic Monitoring Trial
HCM	Hypertrophic cardiomyopathy

J. Němec, MD, FACC (✉)
Department of Medicine
and Clinical Cardiac Electrophysiology,
Cardiovascular Institute, University of Pittsburgh,
200 Lothrop Street, Scaife 535,
Pittsburgh, PA 15213, USA
e-mail: nemecj@upmc.edu

W.-K. Shen, MD
Division of Cardiovascular Diseases,
Department of Medicine,
Mayo Clinic College of Medicine,
Mayo Clinic Arizona, Phoenix, AZ, USA
e-mail: wshen@mayo.edu

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ICD	Implantable cardioverter defibrillator
LV	Left ventricle left ventricular
LVEF	Left ventricular ejection fraction
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MADIT-2	Multicenter Automatic Defibrillator Implantation Trial II
MI	Myocardial infarction
MUSTT	Multicenter Unsustained Tachycardia Trial
PVS	Programmed ventricular stimulation
RFA	Radiofrequency ablation
RV	Right ventricle, or right ventricular
RVA	Right ventricular apex
RVOT	Right ventricular outflow tract
SCD	Sudden cardiac death
SMVT	Sustained monomorphic ventricular tachycardia
TOF	Tetralogy of Fallot
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White

Introduction

The placement of intracardiac catheters to assess risk of arrhythmias dates back nearly 40 years. The discovery by Wellens [1] in 1972 that clinical ventricular tachycardia (VT) in patients with prior myocardial infarction (MI) could be initiated by programmed ventricular stimulation (PVS) generated real enthusiasm about the technique. In the 1980s, many cardiologists would have labeled PVS the most precise and perhaps the most important tool for risk-stratification of patients at risk of sudden cardiac death (SCD). Selection of antiarrhythmic treatment based on suppression of ventricular tachycardia inducibility was reasonably believed to represent a scientific approach to management of life-threatening arrhythmias.

While we learned from subsequent studies that reality is more complicated and the role of invasive electrophysiologic testing is more circumscribed today, it remains a useful and widely used tool for risk stratification in many situations. The role of programmed electrical stimulation in risk-stratification is best defined in patients with prior MI and is the focus of this chapter. The available information on the role of PVS in other conditions is also reviewed, as well as two invasive electrophysiologic techniques unrelated to PVS – HV interval measurement and induction of atrial fibrillation in Wolff-Parkinson-White (WPW) patients – since they are occasionally used for prediction of potentially life-threatening arrhythmias.

Programmed Ventricular Stimulation

Coronary Artery Disease

Vast majority of VTs in the setting of prior MI is due to reentry. This statement is based on the ability to induce clinical sustained monomorphic ventricular tachycardia (SMVT) in most patients by PVS. The inducibility of life-threatening clinical arrhythmias in a controlled laboratory setting enhanced the understanding of the mechanisms leading to SCDs in these patients. The hypothesis formulated in the 1970s was that two factors need to be present for ventricular tachyarrhythmia to occur: a substrate and a trigger. In this concept, the substrate was believed to be a fixed anatomical obstacle (a scar after prior MI), allowing reentry to occur. The clinical trigger initiating the reentry was believed to be a ventricular extrasystole. In the catheterization laboratory, this role is played by a premature stimulus delivered by a catheter. In this paradigm, the substrate is relatively fixed, while the clinical trigger is stochastic, if not random.

The implications of this paradigm resulted in a widespread use of programmed ventricular stimulation, based on the following assumptions:

1. most instances of SCD after MI are related to ventricular tachyarrhythmia, either VT or ventricular fibrillation (VF), and many instances of VF result from degeneration of organized VT
2. the patients with the anatomical substrate allowing for sustained reentry VT can be identified by PVS, even if they never had a clinical arrhythmia; these patients are at higher risk of SCD than other post MI patients
3. once these patients are identified, effective antiarrhythmic drug treatment can be selected by testing VT inducibility on drug treatment.

By and large, the first and second assumption withstood the test of time with important amendments, while the last one was found to be incorrect. Nevertheless, they did provide a believable mechanistic framework for SCD risk stratification and for management of high-risk patients.

Clinical SMVT Can Be Reproduced by PVS

Multiple protocols can be used to induce VT by PVS. In the first PVS report, Wellens et al. [1] used a single extrastimulus from a single right ventricular (RV) site. It became soon apparent that the sensitivity of the method is increased by adding additional extrastimuli and an additional RV site. Josephson reported that in patients with coronary artery disease (CAD) presenting with SMVT, PVS can elicit the VT in 95 % of patients. About 10 % of VT can only be induced by stimulation from the left ventricle (LV) [2, 3].

At present, the details of the PVS continue to differ among different institutions, but protocol similar to the one used in the Multicenter Unsustained Tachycardia Trial (MUSTT) [4] is used most frequently (Fig. 17.1), since outcome data are available from this large study. Stimulation from both right ventricular apex (RVA) and right ventricular outflow tract (RVOT), but not from LV, would usually be performed. This would typically involve stimulation with 8 beat drive train (cycle length (CL) 600 and 400 ms), followed by 1, then 2 and finally 3 extrastimuli. The coupling interval of the last extrastimulus is gradually shortened until effective refractory period (ERP) is reached. A simplified variant, starting with 3 extrastimuli and simultaneously shortening all coupling intervals, has been proposed, but has not been widely adopted [5]. Other stimulation protocols have been used, including delivery of extrastimuli during sinus rhythm and use of short-long-short sequences [6]. Some authors have experimented with PVS during catecholamine infusion, but isoproterenol infusion does not appear to facilitate induction of reentry VT in CAD [7].

In approximately one third of patients, a non-clinical ventricular arrhythmia is induced during PVS. This may be either an SMVT of a different (usually shorter) CL than the VT observed clinically, or polymorphic VT or VF. The likelihood of induction of non-clinical SMVT and polymorphic VT/VF appears to be similar with PVS protocol utilizing 3 extrastimuli, but the latter is more likely to require the third extrastimuls (S4) [8] and short coupling intervals [9]. Since induction of polymorphic ventricular arrhythmia may be a nonspecific outcome (see below) and often requires direct current cardioversion, many operators do not test coupling intervals shorter than 180 or 200 ms in order to minimize induction of non-clinical arrhythmias. In fact, all clinical VTs were induced with coupling intervals of 180 ms or longer in one study of 52 patients with 57 documented clinical VTs [9].

Although it is customary to stimulate ventricular myocardium at twice the diastolic threshold (rectangular pulses of 1 or 2 ms duration), the increase of the stimulation current does not appear to substantially increase the sensitivity of the study [10–12]. The immediate and short-term reproducibility of PVS result appears to be excellent with respect to SMVT induction in most studies [13–16]. For example, Rosenbaum at al. [16] reported 98 % reproducibility of SMVT induction during the same study.

Risk of SCD Is Increased in Subjects with Inducible VT

The reproducible induction of clinically documented VT led to a question of arrhythmic risk in patients with inducible SMVT in the absence of prior clinical VT. These patients harbor the substrate for ventricular arrhythmia with respect to the substrate/trigger concept. It was natural to investigate the use of VT inducibility as a marker of cardiac arrest and effectiveness of AAD treatment. Several well-designed studies demonstrated that in patients with prior MI and decreased LV function, induction of SMVT during PVS is indeed associated with increased risk of future arrhythmic events and overall mortality. Moreover, this risk was found to be even higher in those patients in whom VT inducibility could not be abolished by antiarrhythmic drugs (AAD) administration.

Wilber et al. [17] studied 166 patients with prior resuscitated cardiac arrest, mostly in the setting of CAD, with PVS. Ventricular arrhythmia (sustained or non-sustained monomorphic VT, polymorphic VT or VF) was induced in 79 %.

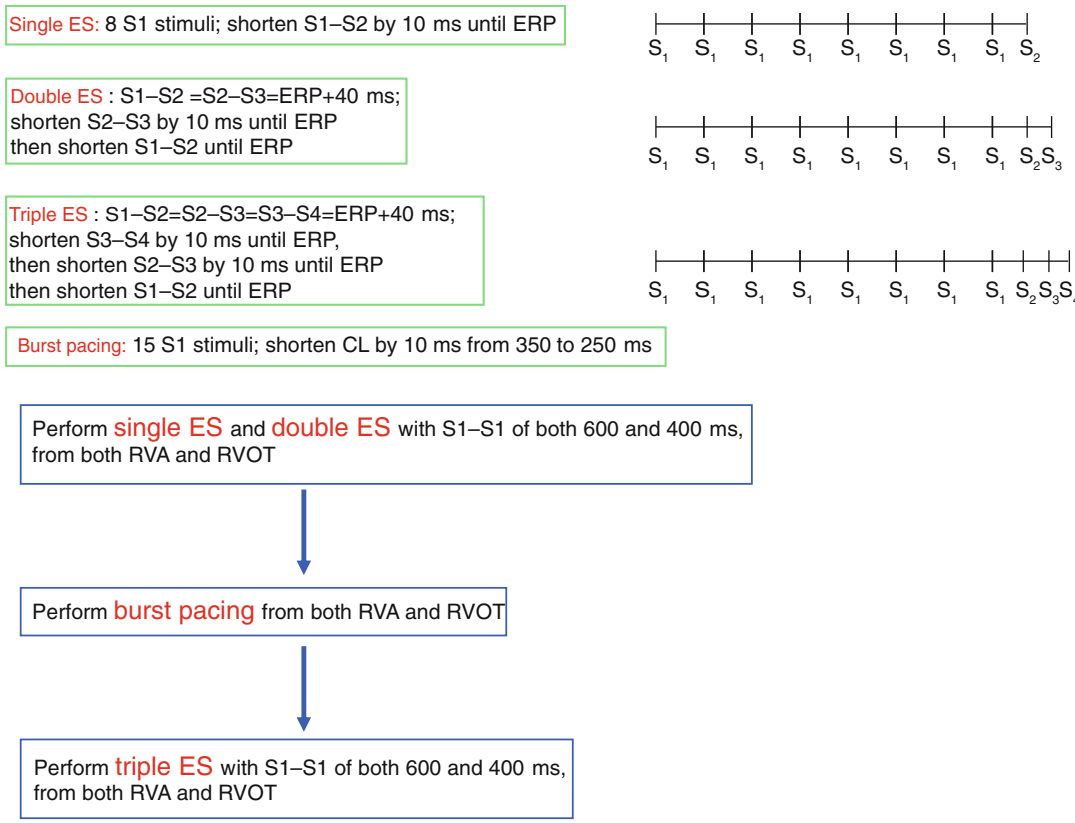

Figure 17–1. Simplified protocol of PVS employed in the MUSTT study. Variants of this protocol are commonly used in clinical practice (From Buxton et al. [4]. Reprinted with permission from Elsevier Limited)

In 72 % of these patients the arrhythmia was no longer induced on AAD treatment. The prognosis of these subjects was significantly better with respect to both arrhythmic and total mortality than in those in whom suppression of VT/VF induction was not accomplished (Fig. 17.2). This difference was especially marked in subjects with poor systolic LV function. Very similar results have been reported by Steinbeck et al. [18], who performed PVS in 170 patients (mostly with CAD) with prior ventricular arrhythmia or high-risk syncope. Ventricular arrhythmia was induced in 115 patients, who were randomized to treatment with metoprolol or serial AAD testing; metoprolol was used in non-inducible patients. Again, the recurrence rate of arrhythmia was significantly lower in the non-inducible patients than in inducible patients treated with metoprolol ($p < 0.01$). Among the patients randomized to AAD testing, rate of arrhythmia recurrence and overall mortality were higher in those subjects in whom arrhythmia could not be suppressed.

The results of the large Multicenter Unsustained Tachycardia Trial (MUSTT) [19] fully confirmed the role PVS in risk stratification. This study enrolled 2,202 patients with significant CAD (mostly prior MI), left ventricular ejection fraction (LVEF) <40 % and non-sustained VT. These patients underwent PVS and if VT was induced (as was the case in 34.8 % of participants), they were randomized to AAD treatment guided by repeat PVS or no AAD treatment. Implantable cardioverter defibrillator (ICD) could be used if VT remained inducible despite AAD treatment. The patients with no VT inducible at baseline were not randomized, but were followed in a registry. This design allowed to compare the overall mortality as well as cardiac arrest rate off treatment between patients with and without inducible VT. The results did demonstrate that the former group did have higher risk of arrhythmic

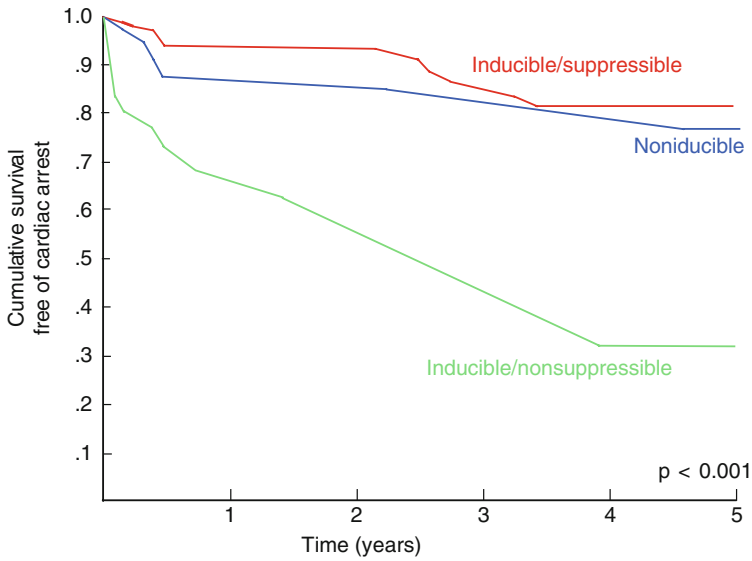

Figure 17–2. Proportion of patients free of death and cardiac arrest in reference [17]. The event rate was significantly higher in patients with inducible VT which could not be suppressed with AAD treatment than in suppressible and noninducible subjects (From Wilber et al. [17]. Reprinted with permission from Massachusetts Medical Society)

events (36 % vs. 24 % over 5 years, p = 0.005) [20]. This difference could not be explained by baseline characteristics of the two populations.

One of the unresolved issues in PVS is the prognostic significance of VF or polymorphic VT. In the MUSTT study, induction of SMVT with 3 extrastimuli was considered a positive result, while VF, VT with CL <220 ms, or polymorphic VT was considered relevant only if induced with 1 or 2 extrastimuli [4]. However, the prognostic significance of polymorphic VT induction has not been analyzed separately. Some light has been shed on this question by the retrospective analysis of Multicenter Automatic Defibrillator Implantation Trial II (MADIT-2) results [21]. This trial randomized 1,232 patients with prior MI and LVEF <30 % to ICD implantation or standard medical treatment. Most of the 742 patients randomized to ICD implantation underwent PVS using protocol similar to MUSTT.[1] Interestingly, the increased rate of arrhythmic events (as determined by appropriate ICD treatment) in the inducible patients did not reach statistical significance, but this difference became significant (odds ratio 1.56, p < 0.02) if only patients with SMVT during the PVS were classified as "positive". This suggests limited prognostic significance of VF induction in this patient group, in accordance with older data [18, 22–24]. However, dissenting opinion appears in the literature [25] and current guidelines support ICD implantation in patient with inducible VF [26]. Induction of ventricular flutter (rapid monomorphic ventricular rhythm) does appear to have prognostic significance [27, 28].

Another area of controversy concerns the optimal timing of PVS with respect to AMI. While PVS performed prior to hospital discharge does appear to carry prognostic significance [22, 29], the inducibility rate decreases significantly between 2 and 20 weeks post MI [30] and the predictive value of VT induction with respect to future arrhythmic events is better for the late study [31]. Although early (prior to discharge) PVS may be able to risk-stratify patients after MI with respect to SCD to some degree [32], the clinical role for this strategy appears limited, since the benefits of early ICD implantation with respect to SCD are balanced by the increased incidence of non-sudden death [33, 34].

Results of Treatment with AADs

The data summarized above confirmed that VT induction in the setting of MI scar is indeed associated with increased arrhythmic and total mortality. They also showed that suppression of VT inducibility with an AAD is associated with better prognosis. However, the natural conclusion

[1]The induction of polymorphic VT with 3 extrastimuli counted as positive result, though VF still had to be induced with 1 or 2 extrastimuli to count as a positive result.

that this justifies AAD selection based suppression of VT induction during PVS turned out to be incorrect. The first serious doubts about AAD effectiveness in the post MI setting were raised by the unexpected result of the Cardiac Arrhythmia Suppression Trial (CAST) [35] and Cardiac Arrhythmia Suppression Trial II (CAST-II) [36] studies. While administration of the class I antiarrhythmics in these trials was not based on result of PVS, it was nevertheless concerning that these agents, often effective in suppression of VT inducibility, turned out to markedly increase mortality in patients with prior MI.

Two studies published in early 1990s weakened the case for AAD selection based on PVS result. The Electrophysiologic Study versus Electrocardiographic Monitoring Trial (ESVEM) [37] was designed to compare serial PVS and serial Holter monitoring for selection of AAD therapy. This trial enrolled patients with prior documented or probable ventricular arrhythmia. Out of the 242 patients randomized for PVS-based approach, "effective" treatment (with respect to VT inducibility suppression) was found in 108 (45 %). Nevertheless, the rate of arrhythmic death in this group was 10 % over 1 year, hardly an acceptable success rate. The issue was examined more directly in the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (CASCADE) trial [38], which randomized 228 patients with prior cardiac arrest to treatment based on a combination of PVS-guided AAD testing and Holter monitoring versus empirical amiodarone treatment. The patients treated with amiodarone had significantly higher arrhythmia-free survival than patients with PVS-based therapy (78 % vs. 52 % at 2 years; $p < 0.001$).

The question of efficacy of antiarrhythmic treatment based on PVS result was finally settled by the MUSTT study [19, 20] described above: the patients assigned to PVS-guided treatment indeed had a slightly lower incidence of arrhythmic and overall mortality than patients randomized to no antiarrhythmic treatment. However, this was solely due to dramatically lower mortality (both arrhythmic and total) in patients treated with ICD implantation – the mortality in patients assigned to "effective" AADs was actually somewhat higher than in patients receiving no antiarrhythmic treatment (Fig. 17.3).

It is thus well established, though somewhat paradoxical, that the prognosis is indeed better in patients in whom an antiarrhythmic drug suppressing VT induction is found, but that treatment with the same drug does not decrease mortality and is probably harmful. The mechanistic explanation for this finding is uncertain, but it is possible that any protective effect which AADs used in the MUSTT, CASCADE and ESVEM trials may have had on the ventricular arrhythmia induced during PVS may be outweighed by their proarrhythmic effects. Many of these patients were treated with class I agents, which may be particularly harmful in the setting of myocardial ischemia, because they can facilitate phase-2 reentry [39]. One way or the other, the implications for management of high-risk patients are straightforward in the current era of wide ICD availability.

Current Role of PVS in Risk Stratification After MI

Although PVS is not useful in AAD selection, inducible VT remains a well validated prognostic factor in CAD patients. Along with LVEF and ventricular ectopy, it remains a widely used clinical tool. Specifically, it is currently employed to guide the decision regarding ICD implantation in the following patients:

(a) patients with remote MI, LVEF 30–35 % and non-sustained VT. If SMVT is induced, then ICD implantation is recommended based on results of Multicenter Automatic Defibrillator Implantation Trial (MADIT) study [40]. For similar patients with LVEF <30 %, ICD implantation would usually be recommended without the need for PVS, based on MADIT-2 trial [41]. Similarly, PVS would be often not considered necessary for patients with stable congestive heart failure (CHF) despite adequate treatment, based on the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [42]. Nevertheless, the survival benefit associated with ICD implantation is

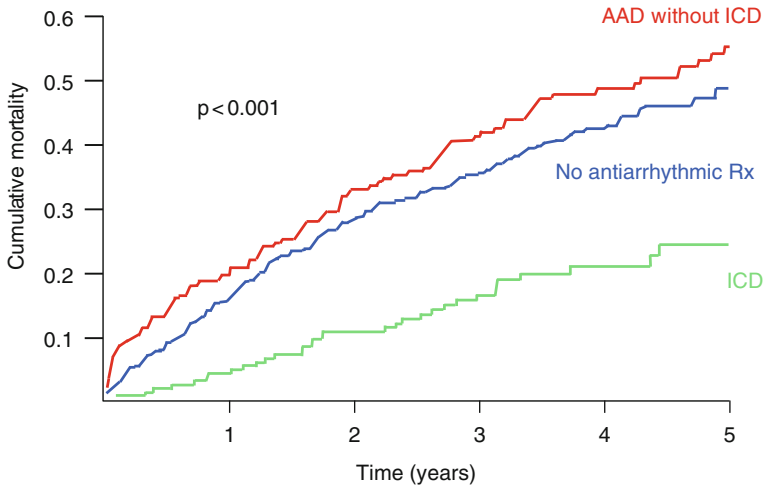

Figure 17–3. Mortality rates in the MUSTT study were markedly lower in patients who received ICD treatment, while patients treated with AAD selected on the basis of PVS result did not decrease mortality compared with no treatment (From Buxton et al. [19]. Reprinted with permission Massachusetts Medical Society)

substantially higher in the MADIT patients (~12 %/year) than in the MADIT-2 or SCD-HeFT populations (~3 % and 1.5 %/year, respectively).

(b) patients with significant CAD, LVEF 30–40 % and non-sustained VT. Based on MUSTT trial, ICD implantation would be usually indicated in patients with inducible SMVT. As described above, positive PVS increases mortality by about 50 % in untreated patients. Again, implantation of ICD in MUSTT trial was associated with substantial survival benefit, similar to MADIT patients.

(c) Patients with prior MI and unexplained syncope. Regardless of LVEF, most physicians would advise ICD placement in patients with SMVT induced by PVS, though this is not based on a result of a randomized trial [26]. For patients with LVEF <40 % or bundle branch block, utility of PVS is supported by published data [43, 44].

Valvular and Congenital Heart Disease

Little systematic information has been published on the role of PVS in patients with valvular heart disease. Due to relatively low risk of SCD after successful valve replacement [45], these patients rarely undergo PVS unless they present with ventricular arrhythmia. Martinez-Rubio et al. [46] retrospectively reported PVS results in 97 patients with valvular disease presenting with VT, VF or syncope. Although the reproducibility of clinical arrhythmia during PVS was relatively poor (32/58 patients presenting with VT), SMVT inducibility was associated with a significantly increased risk of future SCD, VT or VF ($p < 0.002$). Similar to CAD, the risk of arrhythmia recurrence remained high despite use of AADs which suppressed VT inducibility on serial testing.

Ventricular arrhythmias and SCD remain a significant problem in patients who have undergone otherwise successful surgical correction of congenital heart disease. The role of PVS in this population is best characterized in patients after correction of tetralogy of Fallot (TOF). These patients frequently develop SMVT due to reentry around right ventriculotomy scar and are also prone to SCD. The degree of risk correlates with certain clinical parameters, including QRS duration, pulmonary regurgitation and age [47]. A retrospective multicenter study examined the predictive value of PVS in patients several years after TOF repair [48]. Sustained VT (monomorphic or polymorphic) was induced in 87 out of 252 (34.5 %) patients and its presence was a major predictor of future ventricular arrhythmia or SCD (relative risk 5.8, $p < 0.0001$); this relationship remained strong even after correcting for QRS duration and other established clinical risk factors. However, the question of which patients after TOF repair need PVS remains to

be settled; in the absence of noninvasive risk factors, the risk of SCD is relatively low in TOF patients even after positive PVS. It has been suggested that PVS might be useful in TOF patients at intermediate SCD risk [49]. In a retrospective study of a mixed population with congenital heart disease (130 patients, 33 % with TOF), VT induction during PVS also carried a significant risk of clinical VT or SCD; however, the sensitivity was less than perfect [50].

Idiopathic Dilated Cardiomyopathy

Patients with idiopathic dilated cardiomyopathy (DCM) are at risk for SCD [42] and may develop SMVT due to reentry, which can be reproduced during PVS and sometimes successfully treated with radiofrequency ablation (RFA) [51–53] – the specific case of bundle-branch reentry VT is a prominent example [54]. Despite this, results of several smaller studies suggest that role of PVS in DCM is very limited. The rate of SMVT inducibility in patients without sustained VT documented clinically appears to be quite low, on the order of 10–20 % [55–57]. More importantly, negative result of PVS does not necessarily imply benign prognosis with respect to SCD [58, 59]. Treatment with AAD suppressing VT inducibility does not guarantee low risk of future arrhythmia [60, 61]. Whether inducible VT is even associated with worse prognosis in DCM patients remains contentious [62]. In a large population of DCM patients with documented cardiac arrest or sustained VT, no sustained arrhythmia was inducible with PVS in 50 % of subjects; only 19 % had inducible SMVT [63]. It is possible that most instances of SCD in DCM do not involve stable reentry around anatomical obstacle; limited clinical and experimental evidence supports this [64, 65].

Hypertrophic Cardiomyopathy

Sudden death in hypertrophic cardiomyopathy (HCM) is often related to ventricular arrhythmia and several clinical and noninvasive risk factors have been identified in this population [66, 67]. PVS can induce VT in approximately one third of patients with high-risk clinical characteristics [68]; majority of these VTs are polymorphic, while SMVT can be elicited by PVS in <10 % of inducible HCM patients [68–70]. In one study, VT inducibility correlated with high-risk clinical characteristics, and in a kindred with mutation in α-tropomyosin gene, it was associated with high degree of LV hypertrophy [71]. Fananapazir et al. [72] reported that VT induction (their protocol included LV stimulation in addition to 2 RV sites) was strongly associated with future cardiac arrest or clinical VT (14/82 vs. 3/148, $p < 0.002$); prior cardiac arrest was the only other independent predictor of arrhythmic events in their population of 230 HCM patients. Nevertheless, PVS is rarely performed today for risk stratification of HCM patients; instead, LV thickness, non-sustained VT during Holter monitoring and historical information are used widely [73].

Other Conditions Associated with VT Due to Reentry

Replacement of large areas of myocardium with scar or another non-excitable tissue can occasionally form a substrate for reentry VT in several uncommon cardiac conditions, including arrhythmogenic right ventricular dysplasia (ARVD), idiopathic LV aneurysms [74], chagasic cardiomyopathy or cardiac sarcoidosis, among else. In these conditions, which may resemble scaring after prior MI rather than the interstitial fibrosis or myocardial disarray often associated with DCM or HCM, PVS can be useful for identification of patients at risk for VT.

In ARVD, replacement of RV (and, less commonly, LV) myocardium with fatty or fibrous tissue can give rise to SMVT or, occasionally, primary VF. Several authors reported reproduction of VT (usually due to circuit in the RV), and its treatment with RFA [75–77], but the actual value of PVS for risk stratification remains disputed. Corrado et al. [78] reported 132 high-risk ARVD patients (10 % had prior cardiac arrest and 62 % sustained VT) who underwent PVS and ICD implantation. There was no significant difference in the rate of appropriate ICD therapy in patients with inducible vs. non-inducible VT, although multiple clinical factors and LVEF were associated with appropriate treatment for rapid VT/VF. At this moment, there is little data to support PVS as a risk-stratification method in asymptomatic ARVD patients [79].

Chronic Chagas' disease frequently produces myocardial scarring and reentry VT, which can be occasionally targeted with RFA. Induction of VT by PVS in these patients correlates with presence of clinical sustained VT [80]. In most patients, the VT circuit was located in inferolateral LV. In a prospective study of 78 patients with cardiac Chagas' disease, SMVT was induced in 32 % and predicted subsequent arrhythmias as well as cardiac death [81].

Cardiac involvement in sarcoidosis may result in atrioventricular (AV) conduction disturbance or VT. The latter most commonly arises from LV and may be occasionally associated with LV aneurysm [82–84]. In the absence of large studies, the relevant literature consists of case reports or small series [85, 86]. Reentry mechanism of VT related to sarcoidosis has been demonstrated in many cases [86–88], but its induction during PVS may not be a reliable indicator of arrhythmic risk, since the substrate can change depending on the disease activity [85, 89]. On the other hand, in a large study of patients with cardiac sarcoidosis diagnosed by imaging, but without cardiac symptoms, negative result of PVS identified patients at a very low risk of SCD [90].

Primary Electrical Disease

While ventricular tachyarrhythmias in primary electrical disease (congenital long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, short QT syndrome and idiopathic VF) do not seem to involve reentry around an anatomical obstacle, attempts have been made to use PVS for risk stratification.

Bhandari et al. [91] performed PVS in 15 high-risk patients with long QT syndrome, which included LV stimulation in 9 subjects; no sustained VT or VF was induced in any of them, although non-sustained VT of 6 or more beats was seen in 40 %. The induction of non-sustained VT did not carry prognostic significance.

Sustained polymorphic VT or VF can be induced with 3 extrastimuli in many patients with Brugada syndrome – the rate of VF induction is significantly higher than in healthy control subjects (14/21 vs. 0/25), and the RV ERP is shorter [92]. VF induction is relatively reproducible in a given patient [92], but the prognostic significance of this phenomenon remains hotly debated. Brugada et al. [93] reported a large, prospective, multicenter study of 408 patients with asymptomatic Brugada syndrome who underwent PVS. Ventricular fibrillation was induced in ~40 %, and its inducibility was the strongest predictor of future SCD or resuscitated VF (relative risk 8.33, $p < 0.001$). The same authors reported that in a population consisting of both symptomatic and asymptomatic patients, inducible VF predicted future arrhythmic events and was more common in symptomatic than asymptomatic patients [94, 95]. However, this has been disputed by other groups: Priori et al. [96] studied 200 patients with Brugada syndrome, of whom 86 underwent PVS; VF or polymorphic VT was induced in 66 %. Although both prior syncope and spontaneous Brugada pattern on surface ECG predicted future cardiac arrest, there was no difference in the rate of cardiac arrest among inducible and non-inducible patients. Similar result was published by Eckardt et al. [97], who studied 212 patients with both symptomatic and asymptomatic patients with Brugada syndrome, of whom 186 underwent PVS; VF was induced in 50 %. While PVS was more often positive in symptomatic patients (63 % vs. 39 %, $p < 0.001$), the rate of future arrhythmias was extremely low in asymptomatic patients (1 out of 123, with mean follow-up of 34 months), and the PVS results was not helpful in risk-stratification. In a smaller study, Kanda et al. [98] performed PVS in 34 patients with Brugada syndrome; VF was induced in 22 of them. The inducible patients had more pronounced intraventricular conduction disturbance and higher incidence of late potentials on signal-averaged ECG, but a similar rate of cardiac events as non-inducible patients.

The reason for the difference between the result reported by Brugada et al. and the other groups remains uncertain. It is possible that the prognostic significance of PVS result has been missed in the negative studies because of their smaller size. On the other hand, the rate of arrhythmic events in initially asymptomatic patients reported by Brugada et al. is an order of magnitude higher than in one of the negative studies [99] and it is conceivable that there is a real difference between the patients in different registries. The results of a recent meta-analysis do not support role of PVS in risk stratification of patients with Brugada syndrome [100].

Limitations and Complications of Programmed Ventricular Stimulation

The current role of PVS in management of arrhythmic risk in CAD patients is more circumscribed than envisaged in 1980s. This is in part due to recognition of the limitations of the substrate/trigger concept. The abnormalities predisposing CAD patients to SCD may be more dynamic than implied by the concept of a stable scar allowing for reentry. The arrhythmia risk is modified by ischemia, medications, autonomic and hemodynamic factors. For example, hospitalization for heart failure or for coronary events was a strong risk factor for appropriate ICD discharge in MADIT-2 population [101]. These "non-anatomic" variables probably play an even more dominant role in cardiac diseases characterized by absence of large scars and functional reentry.

Despite more than 30 years of research, questions remain about certain aspects of PVS methodology and interpretation, such as the implications of induced VF, ventricular flutter or polymorphic VT. Even in a population with mostly stable CAD, the power of PVS to risk-stratify patients is modest (50 % relative increase of arrhythmic risk in MUSTT). PVS should be indicated and interpreted while respecting the Bayesian principle. The absolute level of risk associated with inducible VT is highest in patients with elevated pre-test risk, as determined by decreased LVEF, ventricular ectopy, non-sustained VT or CHF. On the other hand, ICD implantation without PVS is preferred in patients at highest risk, whose probability of arrhythmic events remains high even after negative PVS [102]. With the increased availability and implantation safety of ICDs, this population has expanded considerably over the last decade.

The diagnostic information obtained by PVS needs to be weighed against the risks of the procedure. The complications include bleeding, vascular injury, venous thrombosis and cardiac perforation, among else. The limited published data suggest that PVS is a quite safe procedure: for example, in a large series from a single institution, the complication rate was 1.1 % in 2,524 electrophysiologic studies without RFA [103]. The risk was somewhat higher in elderly than in young patients (2.2 % vs. 0.5 %) and systemic disease was identified as another predictor of complications. However, some authors have reported higher diagnostic yield in the elderly population [104, 105]. In general, most of the reported complications have been minor.

Risk Stratification in Patients with WPW Syndrome

Patients with antegrade conduction through an accessory pathway have a low but finite risk of SCD due to VF induced by pre-excited atrial fibrillation. About half of these patients never had prior symptoms [106]. While a possibility of SCD preventable by RFA in a patient who is often young and otherwise healthy remains disturbing, available data suggest that this is a very rare event – in two population-based studies of WPW patients, two [107] and zero [108] cases of SCD were reported over 1,338 and 740 years of follow-up, respectively, suggesting annual mortality on the order of 0.1 %. None of the death occurred in patients asymptomatic at diagnosis, who accounted for about half of both populations. While RFA would be typically performed in most symptomatic patients, the appropriate management of truly asymptomatic patients is still debated. Several attempts to risk-stratify WPW patients using invasive EP study (as well as noninvasive markers) have been reported.

Three retrospective reports compared properties of the accessory pathway between patients with prior VF and other WPW patients [109–111]. The shortest preexcited RR interval during induced AF appeared to be the best discriminator (180 ms vs. 240 ms, $p < 0.0001$, in the paper by Klein et al. [111]). Patients with shortest RR interval during of >260 ms are at very low risk [110], but this cutoff has poor positive predictive value. There is a correlation between this value and suppression of accessory pathway conduction by IV procainamide (which can be assessed noninvasively) [109, 110, 112–114]. However, in at least one report, 10 mg/kg of IV procainamide suppressed antegrade pathway conduction in

some patients with history of VF, falsely indicating low risk [110]. Similar considerations apply to loss of preexcitation during sinus tachycardia induced by exercise [113, 115].

In summary, the current role of invasive electrophysiologic study for SCD risk assessment in WPW patients is limited. More than anything else, this is related to the current high success rate and low complication rate of RFA. Nearly all adult symptomatic patients are offered RFA regardless of SCD risk. For the truly asymptomatic patient, the ratio of risk and benefit of RFA is still uncertain, but both are likely of small magnitude.

HV Interval and Infrahisian Block as Risk Factors for Complete Heart Block and Sudden Death

Prolongation of HV interval is an indicator of His-Purkinje system disease. Scheinman has reported that among patients with bundle-branch block and symptoms of possible arrhythmias, HV interval was significantly longer in those patients in whom heart block was documented as cause of their symptoms [116]. In a subsequent prospective study of 121 patients with conduction disturbance on surface ECG and fairly frequent history of syncope (36 %), HV interval >70 ms was associated with higher rate of progression to second or third degree heart block (21 % over 18 months) compared to patients with HV <70 ms (1.3 %, $p < 0.0001$). Rate of sudden death, total mortality and heart failure were also higher in the former group [117]. On the other hand, McAnulty et al. [118] reported a low incidence of new complete heart block (~1 %/year) in a large prospective study of 554 patients with bifascicular block. There was no significant difference in this respect between the patients with and without HV prolongation. In this study, syncope was a better predictor of development of complete heart block than HV interval. Age and heart failure, but not HV interval, were associated with total mortality. In another large, prospective study of patients with bifascicular block (517 patients with mean follow-up of 3.4 years), 39 % of patients had HV >55 ms. These subjects had significantly higher incidence of AV block during follow-up than patients with normal HV (28 vs. 12 % over 7 years, $p < 0.001$) [119]. Again, total mortality and sudden death rate were both higher in patients with HV prolongation. However, this may not be related to increased rate of bradycardic arrest due to AV block, since these patients also had higher rate of heart failure, angina and structural heart disease. It is likely that to a degree, HV interval may be a marker of heart disease severity.

Non-functional infrahisian block during atrial pacing occurs less frequently than HV interval prolongation (~3 % of patients with bifascicular block), although some patients with this phenomenon have normal HV [118, 120]. It appears to be associated with high risk of future AV block, especially in symptomatic patients (approximately 50 % over 5 years) [120, 121].

Some patients with normal HV interval may in fact have conduction system disease, as manifested by subsequently documented high-grade infrahisian AV block. In some of them, abnormal HV conduction may be elicited by administration of a sodium-channel blocker (typically procainamide at dose of 10 mg/kg IV). Infrahisian AV block or marked HV interval prolongation may develop and is considered an abnormal response [122, 123]. However, little outcome data is available on these patients. This phenomenon occurs rarely (~3 %) in patients with normal HV interval [124].

Currently, EP study would be rarely indicated for the sole reason of HV interval measurement, given the relatively low positive predictive value of HV interval prolongation for high-grade AV block. In patients with bundle-branch block and syncope, the negative predictive value is also less than ideal [125]. However, marked HV interval prolongation or infrahisian block during atrial pacing may well justify pacemaker placement in a patient with syncope if no other abnormality is found [26]. Also, HV interval measurement may be of value in some patients with hereditary neuromuscular diseases with high pretest probability of conduction system disease [126].

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18
Provocative (Drug) Testing in Inherited Arrhythmias

Wataru Shimizu and Michael J. Ackerman

Abstract

Molecular genetic studies have established a link between a number of heritable channelopathies, including congenital long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), and mutations in genes encoding for ion channels or other membrane components, therefore, have become a golden standard for diagnosing these channelopathies. Clinical diagnosis by standard 12-lead electrocardiography (ECG) at baseline misses some patients, who are genetically affected by these channelopathies (so called concealed form). Therefore, there is a strong need to devise clinical tools to improve the sensitivity of clinical tests to establish the diagnosis of these heritable channelopathies. Provocative testing with catecholamines and pharmacologic testing with sodium channel blockers are critical diagnostic tests in the evaluation of these heritable channelopathies and enable to unmask LQTS, BrS, and CPVT in their concealed state.

Keywords

Arrhythmia • Diagnosis • Genes • Long-QT syndrome • QT interval • Torsade de Pointes • Catecholamines • Brugada syndrome • ST segment • Sodium channel blocker

W. Shimizu, MD, PhD (✉)
Division of Arrhythmia and Electrophysiology,
Department of Cardiovascular Medicine,
National Cerebral and Cardiovascular Center,
5-7-1 Fujishiro-dai, Suita,
Osaka 565-8565, Japan
e-mail: wshimizu@hsp.ncvc.go.jp

Division of Cardiology,
Department of Internal Medicine,
Nippon Medical School, 1-1-5 Sendagi,
Bunkyo-ku, Tokyo 113-8603, Japan
e-mail: wshimizu@nms.ac.jp

M.J. Ackerman, MD, PhD, FACC
Department of Medicine, Division of Cardiovascular Diseases, Department of Pediatric and Adolescent Medicine, Division of Pediatric Cardiology,
Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic,
Rochester, MN, USA
e-mail: ackerman.michael@mayo.edu,
haglund.carla@mayo.edu

Heritable channelopathies that include congenital long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) affect at least 1 in 2,000 persons, may present with syncope or sudden cardiac death, and often elude detection by standard 12-lead electrocardiography (ECG). In LQTS, an estimated 40 % of genetically affected subjects have "concealed" LQTS with a normal or borderline heart rate corrected QT interval (QTc) at rest. A significant proportion of patients with BrS have concealed BrS with no evidence of a type 1 Brugada electrocardiographic pattern at rest. Every patient with CPVT has a normal resting ECG. Provocative testing with catecholamines and pharmacologic testing with sodium channel blockers are critical diagnostic tests in the

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evaluation of these channelopathies and can help unmask LQTS, BrS, and CPVT in their concealed state. The role of these provocative tests in the evaluation of inherited arrhythmia syndromes will be reviewed in this chapter.

Congenital Long QT Syndrome

Congenital LQTS is characterized by QT prolongation in the electrocardiogram (ECG) and its trademark dysrhythmia of polymorphic ventricular tachycardia known as Torsade de Pointes (TdP) [1]. The clinical diagnosis of LQTS is based mainly on the resting QTc, cardiac events such as syncope, aborted cardiac arrest and sudden cardiac death, and a family history of apparent LQTS [2]. However, the electrocardiographic diagnosis at baseline misses some patients affected by congenital LQTS (so called concealed LQTS) as evidenced by syncopal events occurring among family members with a "normal" QT interval [3]. Since 1995, when the first two genes responsible for LQTS were identified, molecular genetic studies have revealed a total of 13 genetic subtypes of congenital LQTS caused predominantly by cardiac channel mutations or mutations involving key beta or auxiliary subunits [4–8]. Among the 13 genetic subtypes, LQT1, LQT2 and LQT3 constitute the vast majority of genotyped LQTS and approximately 75 % of all LQTS [9]. With these molecular illuminations, this entity of concealed or low penetrant LQTS has been proved genetically. Vincent et al. reported that 5 (6 %) of 82 mutation carriers from 3 LQT1 families had a normal QT interval [10]. Priori et al. conducted molecular screening in nine families with apparently sporadic cases of LQTS, demonstrating a very low penetrance (38 %, 9/24 patients) [11]. Swan and co-workers reported that the sensitivity and specificity for identifying genotype-positive patients were 53 and 100 %, respectively, in an LQT1 family with a specific *KCNQ1* mutation (D188N) [12]. A larger study of genotyped LQTS by Priori et al. showed that the percentage of genetically affected patients with a normal QTc was significantly higher in the LQT1 (36 %) than in the LQT2 (19 %) or the LQT3 (10 %) syndromes [13]. Overall, these findings indicated the need for novel tools to unveil concealed mutation carriers of LQTS, especially those with type 1 LQTS (LQT1). The identification of patients with concealed LQTS affords the opportunity to initiate potentially life-saving pharmacotherapies and health style modifications.

Some patients with congenital LQTS suffer from cardiac events such as syncope and/or sudden cardiac death during physical exercise or mental stress. Therefore, provocative testing using catecholamine infusion or exercise has long been used to unmask concealed forms of congenital LQTS, before genetic testing became available [14].

The Epinephrine QT Stress Test in LQTS

Infusion of isoproterenol, a β-adrenergic agonist, or epinephrine, an α + β adrenergic agonist, was reported as a useful provocative test in LQTS more than two decades ago [14]. The heart rate increases to >120 beats/min with isoproterenol, especially by the use of bolus injection, which often makes difficult to measure the QT interval precisely due to an overlap of the next P wave on the terminal portion of T wave. Prior to the discovery of the distinct genetic subtypes of LQTS, the responses to either epinephrine or isoproterenol were extremely heterogeneous, deemed impossible to interpret, and epinephrine QT stress testing once disappeared from the diagnostic work-up of LQTS. However, the heterogenous response is now understood to stem from the underlying genetic heterogeneity and the gene-specific responses to epinephrine can be exploited to expose different types of LQTS in its otherwise concealed state, particularly type 1 LQTS (LQT1). Although isoproterenol is still used occasionally, epinephrine infusion, a strategy pioneered independently by Ackerman [15] and Shimizu [16], has been a standard test and is reviewed in more detail below. In contrast to provocation studies using catecholamines, Viskin and colleagues have shown that sudden heart rate oscillations precipitated by intravenous administration of adenosine may expose some patients with concealed LQTS although genotype-specific responses have not been demonstrated [17]. Compared to controls, patients with LQTS exhibited an exaggerated increase in the QT interval during adenosine-induced bradycardia.

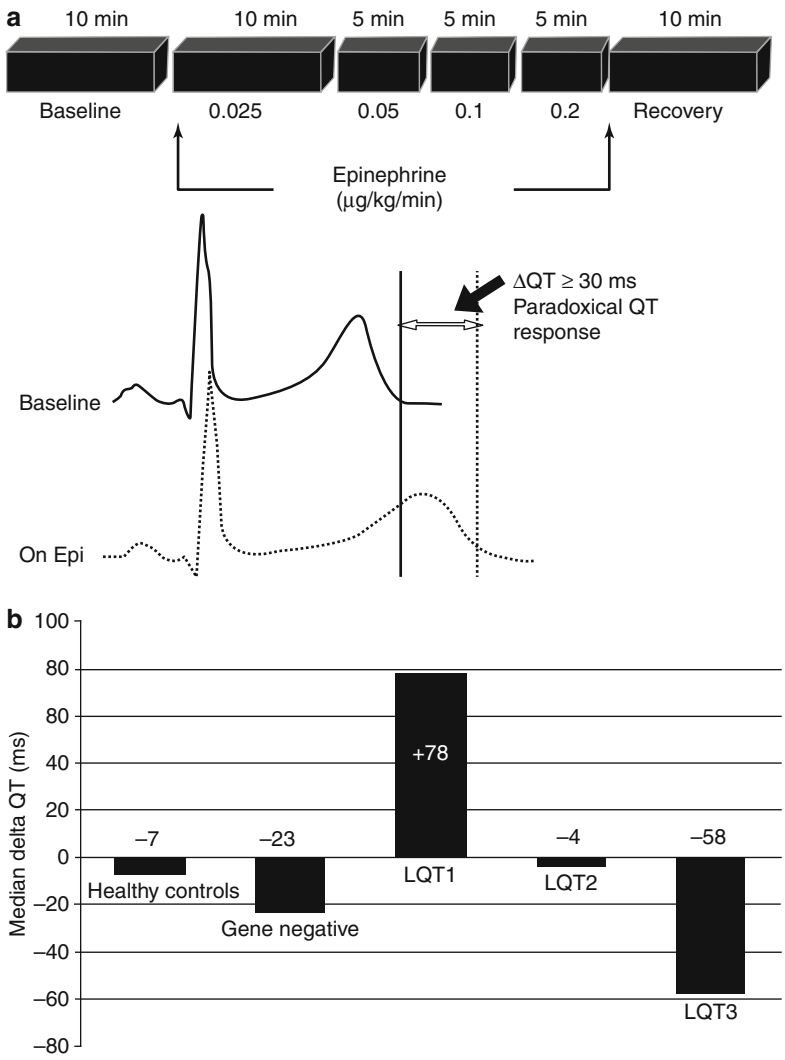

Figure 18–1. Epinephrine QT stress testing in LQTS (Ackerman/Mayo Clinic Protocol). (**a**). Schematic of the continuous epinephrine infusion protocol used to unmask, concealed type 1 long QT syndrome (LQT1). With this protocol, the paradoxical response is defined as an increase in the absolute QT interval by ≥30 ms during infusion of low dose epinephrine (≤0.1 μg/kg/min). (**b**). Summary of the low dose epinephrine-absolute QT response performed in over 800 subjects at Mayo Clinic

The two major protocols developed for epinephrine QT stress testing include the escalating-dose protocol by Ackerman's group (Ackerman/Mayo Clinic protocol) [15], and the bolus injection followed by brief continuous infusion by Shimizu's group (Shimizu protocol) [16]. Both protocols are extremely useful and safe, and overall are well tolerated. Each protocol has some advantages and disadvantages with respect to the other.

Incremental, Escalating Epinephrine Infusion (Ackerman Protocol)

Ackerman and co-workers have used a 25-min incremental, escalating infusion protocol (0.025–0.2 μg/kg/min) in the LQT1, LQT2, LQT3 patients and genotyped-negative patients (Fig. 18.1a) [15, 18, 19]. With epinephrine infusion at low-dose of ≤0.1 μg/kg/min, the median change of the QT interval was 78 ms in LQT1, -4 ms in LQT2, -58 ms in LQT3, and -23 ms in the genotype-negative patients (Fig. 18.1b). With this protocol, paradoxical QT prolongation, defined as a 30-ms increase in the QT (not QTc) interval during low-dose epinephrine infusion, specific in the LQT1 patients (92 %), but not in the LQT2 (13 %), the LQT3 (0 %), and the genotype-negative patients (18 %). The paradoxical QT prolongation had a sensitivity of 92.5 %, specificity of 86 %, positive predictive value of 76 %, and negative predictive value of

ΔQT	LQT1	Non-LQT1	
ΔQT ≥30 ms	37	12	Positive predictive value = 76 %
ΔQT <30 ms	3	73	Negative predictive value = 96 %
	Sensitivity = 92.5 %	Specificity = 86 %	

Table 18–1. Validity of the epinephrine QT stress test (Ackerman/Mayo Clinic Protocol) at a QT ≥30 ms

Δ, the change (delta) in the QT interval (epinephrine minus baseline)

96 % for LQT1 vs. non-LQT1 status (Table 18.1), and provides a presumptive, pre-genetic clinical diagnosis of type 1 LQTS (LQT1).

Major advantages of this escalating infusion protocol are better patient tolerance and a lower incidence of false-positive responses. On the other hand, this protocol seems less effective in exposing patients with LQT2 compared to the bolus protocol by Shimizu et al. described below. However, this disadvantage is reported to be partially overcome by focusing on the change of T wave morphology during low-dose of epinephrine infusion. Khositseth et al. reported that epinephrine-induced notched T wave was more indicative of LQT2 status [19].

Bolus Injection Followed by Brief Continuous Infusion (Shimizu Protocol)

The bolus protocol by Shimizu and co-workers was developed on the basis of a differential response of action potential duration (APD) and QT interval to sympathetic stimulation with isoproterenol between the experimental LQT1, LQT2 and LQT3 models employing arterially-perfused canine left ventricular wedge preparations [20]. Persistent prolongation of APD and QT interval at steady state conditions of isoproterenol infusion was reported in the LQT1 model. Under normal conditions, β-adrenergic stimulation is expected to increase net outward repolarizing current, due to larger increase of outward currents, including Ca^{2+}-activated slow component of the delayed rectifier potassium current (I_{Ks}) and Ca^{2+}-activated chloride current ($I_{Cl(Ca)}$), than that of an inward current, Na^+/Ca^{2+} exchange current ($I_{Na\text{-}Ca}$), resulting in an abbreviation of APD and QT interval. A defect in I_{Ks}/Kv7.1 as seen in LQT1 could account for failure of β-adrenergic stimulation to abbreviate APD and QT interval, resulting in a persistent and paradoxical QT prolongation under sympathetic stimulation. In the LQT2 model, isoproterenol infusion was reported to initially prolong but then abbreviate APD and QT interval probably due to an initial augmentation of $I_{Na\text{-}Ca}$ and a subsequent stimulation of I_{Ks}. In contrast to the LQT1 and LQT2 models, isoproterenol infusion constantly abbreviated APD and QT interval as a result of a stimulation of I_{Ks} in the LQT3 model, because an inward late I_{Na} was augmented in this genotype. Therefore, the bolus protocol of epinephrine testing was expected not only to unmask concealed patients with LQTS but also to presumptively diagnose the three most common subtypes: LQT1, LQT2, and LQT3, by monitoring the temporal course of the QTc to epinephrine at peak effect following bolus injection and at steady-state effect during continuous infusion.

Clinical data using bolus protocol suggested that sympathetic stimulation produces genotype-specific responses of the QTc in patients with LQT1, LQT2 and LQT3 (Fig. 18.2) [21, 22]. Epinephrine remarkably prolonged the QTc at peak effect when the heart rate is maximally increased (1–2 min after the bolus injection), and the QTc remained prolonged during steady-state epinephrine effect (3–5 min) in patients with LQT1 [21, 22]. As an aside, this steady-state effect likely correlates with the paradoxical prolongation of the absolute QT interval seen with the Ackerman protocol. The QTc was also prolonged at peak epinephrine effect (during bolus) in patients with LQT2, but returned to close to the baseline levels at steady state epinephrine effect [22]. In contrast, the QTc was less prolonged at peak epinephrine effect in the LQT3 patients than in the LQT1 or LQT2 patients, and was abbreviated below the baseline levels at steady state epinephrine effect [22]. The responses of the corrected Tpeak-Tend interval

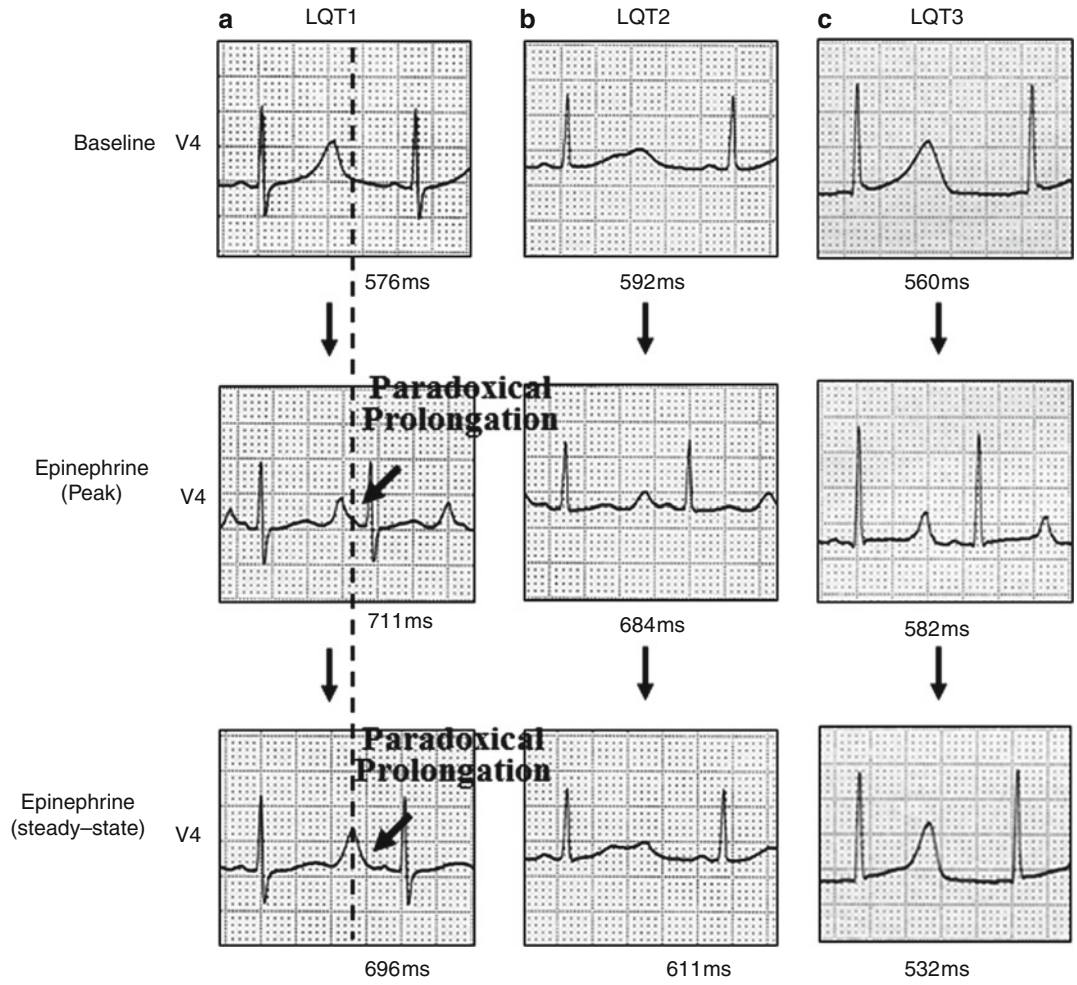

Figure 18–2. Differential temporal course of the heart rate corrected QT interval (QTc) to epinephrine QT stress testing in LQT1, 2, and 3 (Shimizu Protocol). V4 lead ECG under baseline conditions, at peak and steady state epinephrine effects in LQT1 (**a**), LQT2 (**b**), and LQT3 (**c**) patients using the Shimizu bolus and infusion protocol. The corrected QT interval (QTc) was prominently prolonged from 576 to 711 ms at peak epinephrine effect, and remained prolonged at steady state (696 ms) in the patient with LQT1. It is noteworthy that paradoxical QT prolongation was seen both at peak and steady state epinephrine effects (*arrows*). In the patient with LQT2, the QTc was also dramatically prolonged from 592 to 684 ms at peak, but returned to the baseline level at steady state (611 ms). It was much less prolonged (560–582 ms) at peak in the LQT3 patient than in either the LQT1 or LQT2 patient, and returned below the baseline level at steady state (532 ms)

reflecting transmural dispersion of repolarization (TDR) approximately paralleled those of the QT interval [23], supporting the cellular basis for genotype-specific triggers for cardiac events.

By using the steady state epinephrine effect, Shimizu et al. reported the improvement of clinical electrocardiographic diagnosis (sensitivity) from 68 to 87 % in the 31 patients with LQT1 and from 83 to 91 % in the 23 patients with LQT2, but not in the six patients with LQT3 (from 83 to 83 %) [22]. The bolus protocol of epinephrine effectively predicts the underlying genotype of the LQT1, LQT2 and LQT3 (Fig. 18.3) [22]. The prolongation of QTc ≥ **35 ms** at steady state epinephrine effect could differentiate LQT1 from LQT2, LQT3 or control patients with a predictive accuracy ≥90 %. The prolongation of QTc ≥80 ms at peak epinephrine effect could differentiate LQT2 from LQT3 or control patients with predictive accuracy of 100 %.

Whether utilizing the Ackerman protocol or the Shimizu protocol, the responses to epinephrine

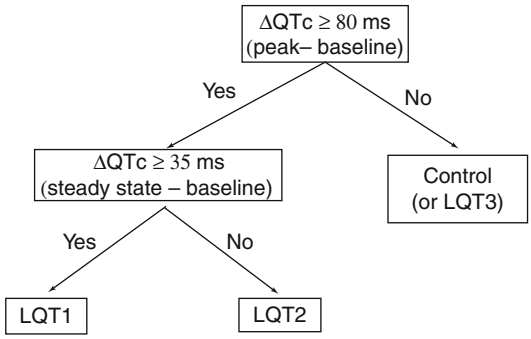

Figure 18–3. Schema illustrating a flow chart to predict genotype with the bolus epinephrine QT stress test (Shimizu Protocol)

should be viewed as diagnostic only, not prognostic. Induction of torsade de pointes (TdP) or ventricular fibrillation is extremely uncommon. In over 1,000 studies conducted using the Ackerman protocol and the Shimizu protocol respectively, we have observed only two episodes of TdP (10 beats and 20 beats) and one episode of macroscopic T wave alternans. In addition, these gene-specific responses are attenuated by beta blockers. If a patient displays, epinephrine-induced bradycardia rather than the expected increase in heart rate, then the study should be terminated, a diagnostic interpretation should not be rendered, and a period of monitored beta blocker washout should be considered.

Importantly, the diagnostic profiles gleaned from one protocol should **NOT** be applied to the other protocol. For example, using the Ackerman protocol, we have observed healthy volunteers display a QTc of 600 ms (ΔQTc = 140 ms) during epinephrine infusion due to a negligible change in the absolute QT interval but a brisk chronotropic response. This response could be viewed as either a LQT1 (steady state) or LQT2 (peak) response if one erroneously applied the Shimizu algorithm (Fig. 18.3) in the setting of the Ackerman continuous infusion protocol (Fig. 18.1a). Here, it is critical to remember that the key determinant is epinephrine-mediated changes in the **QT interval** for the Ackerman protocol and epinephrine-mediated changes in the **QTc** for the Shimizu protocol. Finally, a caveat regarding epinephrine-accentuated U waves is in order as erroneous inclusion of such U waves during epinephrine infusion underlies some of the false positives.

Since molecular diagnosis is still unavailable for many patients throughout the world, unmasking concealed LQTS by the epinephrine QT stress test can direct proper counseling and facilitate the use of β-blockers and the avoidance of QT-prolonging drugs. Furthermore, a presumptive, pre-genetic diagnosis of either LQT1, LQT2, or LQT3 based upon the response to epinephrine can guide gene-specific treatment strategies. Clur and co-workers recently evaluated the role of epinephrine test (using Shimizu protocol) in the diagnosis and management of children suspected of having congenital LQTS, who showed a borderline baseline QTc (441 ± 28 ms) and non-diagnostic Schwartz score. They reported that the epinephrine test cannot be used to diagnose genotype-positive LQTS, but suggested that it can be a tool to guide clinical decision making in a pediatric cohort with a suspicious LQTS phenotype [24]. Finally, since 25 % of LQTS remains genetically elusive, the identification of patients with LQTS and a LQT1-like response to epinephrine for example, may lead to the identification of novel LQTS-causing susceptibility genes.

Brugada Syndrome

BrS is characterized by coved-type ST-segment elevation in the right precordial electrocardiographic leads (V1 – V3) and an episode of ventricular fibrillation (VF) in the absence of structural heart disease [25]. However, the ST segment elevation is dynamic and often concealed, and is reported to be accentuated just before and after episodes of ventricular fibrillation (VF) [26]. A variety of antiarrhythmic drugs and autonomic agents have been reported to provoke typical ST-segment elevation [27]. Experimental studies have suggested that an intrinsically prominent transient outward current (I_{to}/Kv4.3)-mediated action potential (AP) notch and a subsequent loss of AP dome in the epicardium, but not in the endocardium of the right ventricular outflow tract, give rise to a transmural voltage gradient, resulting in a typical ST-segment elevation in leads V1–V3 [28]. Because the maintenance of the AP dome is determined by the balance of currents active at

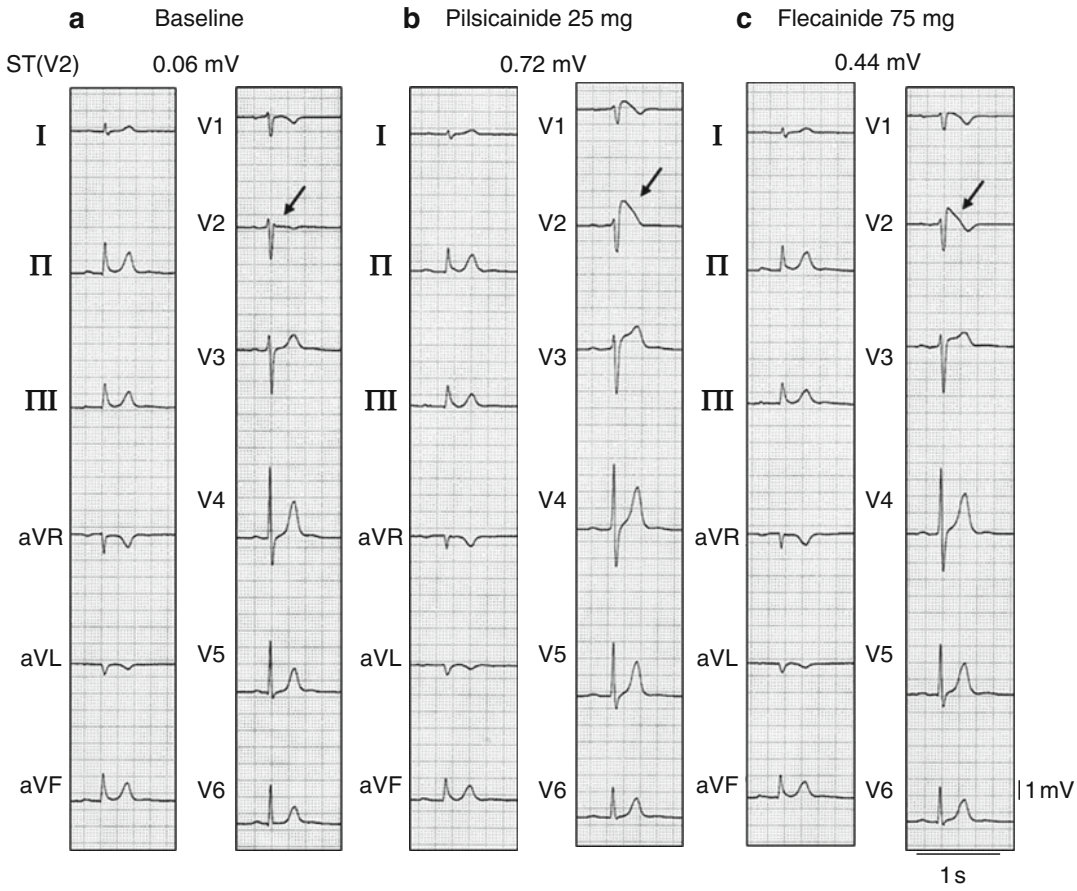

Figure 18–4. Effects of class IC sodium channel blockers on ST-segment in a patient with concealed Brugada syndrome. At baseline condition (**a**, *arrow*), no significant ST-segment elevation in leads V1–V3 was observed. Both pilsicainide (**b**, *arrow*) and flecainide (**c**, *arrow*) induced type 1 coved ST-segment elevation, however, smaller dose of pilsicainide injection (25 mg) produced more prominent ST-segment elevation than that by flecainide injection (75 mg) in lead V2 (0.72 vs. 0.44 mV)

the end of phase 1 of the AP (principally I_{to} and L-type calcium current [$I_{Ca\text{-}L}$]), any interventions that increase outward currents (e.g. I_{to}, I_{Ks}, I_{Kr}) or decrease inward currents (e.g. $I_{Ca\text{-}L}$, fast I_{Na}) at the end of phase 1 of the AP can accentuate ST-segment elevation, thereby producing a Brugada phenotype.

Provocative BrS Testing with Sodium Channel Blockers

Among the interventions above, sodium channel blockers effectively amplify or unmask ST-segment elevation, and are used as a provocative testing in patients with concealed BrS showing transient or no spontaneous ST-segment elevation [29, 30]. Among the sodium channel blockers, the class IC drugs (flecainide, 2 mg/kg in 10 min, i.v.; pilsicainide 1 mg/kg in 10 min, i.v.) produce the most pronounced ST-segment elevation due to strong use-dependent blocking of fast INa secondary to their slow dissociation from the sodium channels [29]. Pilsicainide, a pure class IC drug developed in Japan, seems to induce ST-segment elevation more than flecainide, which is widely used throughout the world (Fig. 18.4). Induction of ventricular arrhythmias by pilsicainide may be more common than anticipated [31]. Accordingly, caution should be exercised when using pilsicainide in BrS drug challenge testing because of the increased potential for false positive responses.

Class IA antiarrhythmic drugs (ajmaline, procainamide, disopyramide, cibenzoline, etc.), which exhibit less use-dependent block of fast INa due to faster dissociation of the drug, are expected to show a weaker ST-segment elevation than class IC drugs (Figs. 18.5a, b) [27, 29, 30]. Ajmaline (1 mg/kg, in 5 min, i.v.) has been used frequently, and reported to be safer with malignant ventricular arrhythmias in only 1.3 % of the patients tested [32]. Wolpert et al. reported that ajmaline induced or enhanced type 1 ST-segment elevation more frequently than flecainide because ajmaline is a purer sodium channel blocker with less concomitant inhibition of Ito than flecainide [33]. Disopyramide (2 mg/kg in 10 min, i.v.) and procainamide (10 mg/kg, in 10 min, i.v.) show weaker accentuation of the ST-segment elevation due to their smaller effect on fast INa and mild to moderate inhibition of Ito (Fig. 18.5c) [27, 29, 30]. Class IB drugs (mexiletine, lidocaine, etc.) dissociate from the sodium channel rapidly and therefore have little or no effect on fast INa at moderate and slow heart rates, and thus are unable to cause ST-segment elevation (Fig. 18.5d) [29]. The recommended dosage of each sodium channel blocker is listed in Table 18.2 [34].

Practice of Sodium Channel Blocker Testing to Unmask Type 1 Brugada ECG Pattern

The definition of a positive provocative testing is a development of the diagnostic type 1 Brugada ECG pattern (an increase in the absolute J wave amplitude of >0.2 mV with or without right bundle branch block in at least one of the V1–V3 leads) when there is a negative ECG or only a type 2 (saddle back) or type 3 pattern at baseline. The test does not add any diagnostic value in patients with spontaneous and constant type 1 Brugada ECG pattern. The test should be monitored with a continuous 12-lead electrocardiographic recording (a speed of 10 mm/s can be used to monitor throughout the test period, interposed with recordings at 25 or 50 mm/s), and cardiopulmonary resuscitation facilities and isoproterenol infusion should be at hand. The end point of the test is when (1) the diagnostic type 1 Brugada ECG pattern develops; (2) ST-segment in type 2 ECG increases by ≥ 0.2 mV; (3) ventricular or other arrhythmias develop; or (4) QRS widens to ≥130 % of baseline. Particular caution should be exercised in patients with a preexisting atrial and/or ventricular conduction disturbance (e.g. suspected cases of progressive cardiac conduction defect) or in the presence of wide QRS, wide P waves or prolonged PR intervals (infra-nodal conduction disease) so as to avoid the risk of precipitating complete AV block.

Clinical Significance of Sodium Channel Blocker Provocative Testing for BrS

Two studies evaluated sensitivity and specificity of provocative testing with sodium channel blockers and the presence or absence of *SCN5A* mutation [35, 36]. Hong et al. reported that the sensitivity, specificity, and positive and negative predictive values of the ajmaline test were 80, 94, 93, and 83 %, respectively [35]. Meregalli et al. also reported similar values with flecainide test [36]. Most of recent meta-analysis and multicenter studies suggested that a type 1 Brugada ECG pattern induced only by sodium channel blocker test identified subjects at lower risk compared to those patients with a spontaneous type 1 ECG pattern [37–39], although exception exist [40]. Moreover, Evain et al. reported that subjects with baseline type 2 or 3 Brugada ECG pattern and a negative sodium channel blocker test showed better prognosis than those with a positive test [41]. More recently, Zorzi et al. suggested that a positive sodium channel blocker test was associated with a significantly higher cardiac event rate in only symptomatic Brugada patients (cardiac arrest or syncope) but not in asymptomatic individuals, indicating sodium channel blocker test does not provide additional prognostic and therapeutic value in asymptomatic individuals with baseline type 2 or 3 Brugada ECG patterns [42].

Catecholaminergic Polymorphic Ventricular Tachycardia

Unlike LQTS and BrS where the cardinal feature is often evident on the resting 12-lead ECG, this diagnostic test is always normal in patients with CPVT

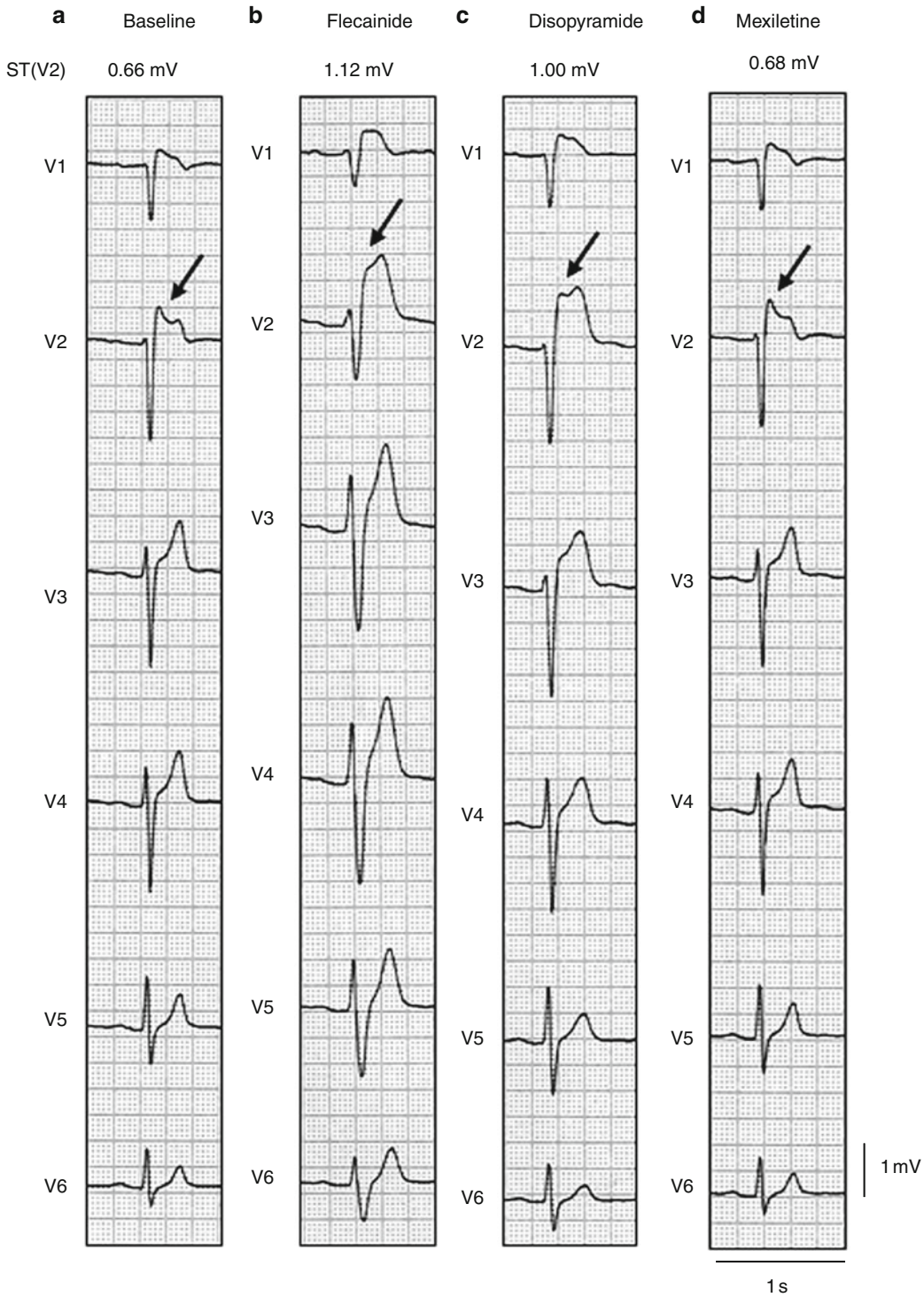

Figure 18–5. Effects of different sodium channel blockers on ST-segment elevation in a patient with Brugada syndrome. Six precordial leads electrocardiograms at baseline condition (**a**), after 100 mg flecainide injection (class IC drug) (**b**), after 100 mg disopyramide injection (class IA drug) (**c**), and after 125 mg mexiletine injection (class IB drug) are shown. At baseline conditions (a, *arrow*), Type 2 saddle-back ST-segment elevation was seen in lead V2 (0.66 mV). Flecainide more remarkablly accentuated the ST-segment elevation (1.12 mV) than disopyramide (1.00 mV) (b, c, *arrows*), while mexiletine had no effect on the ST-segment elevation (0.68 mV) (**d**, *arrow*)

Table 18–2. Drugs used to unmask the type 1 Brugada ECG pattern

Flecainide	2 mg/kg/10 min, i.v. (400 mg, p.o.)
Pilsicainide	1 mg/kg/10 min, i.v.
Ajmaline	1 mg/kg/5 min, i.v.
Disopyramide	2 mg/kg in 10 min, i.v.
Procainamide	10 mg/kg/10 min, i.v.

excepting the often noted sinus bradycardia. Phenotypically, CPVT mimics LQTS, particularly LQT1, with exercise-induced syncope, seizures, or sudden death but in the setting of a structurally normal heart and an essentially normal 12-lead ECG [43, 44]. Approximately two-thirds of CPVT stems from mutations in the *RYR2*-encoded ryanodine receptor/calcium release channel (CPVT1). One possible clue for CPVT1 may be the presence of marked bradycardia [45]. However, the most specific, but not sensitive, signature of CPVT's presence is exercise-induced or catecholamine-induced bi-directional ventricular tachycardia [46]. Presently, it is not clear whether or not catecholamine provocation testing is additive to standard exercise stress testing or whether isoproterenol (more commonly used for CPVT) is superior to epinephrine.

Practically speaking, when faced with a patient presenting with exercise-induced syncope or exercise-induced aborted cardiac arrest and a normal ECG (QTc = 430 ms for example), the differential diagnosis includes both concealed LQT1 and CPVT. As such, we advocate using the epinephrine QT stress test (either the previously discussed Ackerman or Shimizu protocol). Remember that significant epinephrine-induced ventricular ectopy is extremely uncommon in LQTS and occasional premature ventricular contractions (PVCs) and even couplets are not informative. If there is paradoxical QT lengthening, then concealed LQT1 is the presumptive clinical diagnosis. On the other hand, if there is epinephrine-induced bi-directional ventricular tachycardia, then CPVT is likely. Suspicion for CPVT should be raised and CPVT-directed genetic testing initiated for lesser degrees of epinephrine-induced ventricular ectopy such as epinephrine-induced non-sustained ventricular tachycardia, TdP in the absence of paradoxical QT lengthening, and possibly even PVCs in bigeminy during epinephrine infusion. One caveat to remember is that bi-directional ventricular tachycardia can also be seen in *KCNJ2*-mediated Andersen Tawil syndrome [47].

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19
Novel Predictors of Sudden Cardiac Death

Sumeet S. Chugh, Rasmus Havmöller, Carmen Teodorescu,
Adriana Huertas-Vazquez, Audrey Uy-Evanado, and Kyndaron Reinier

Abstract

Despite recent advances in resuscitation science, survival from sudden cardiac arrest (SCA) remains low, and sudden cardiac death (SCD) remains a public health problem of significant proportions. In the United States, estimates of the annual incidence of SCD range from 250,000 to 300,000. Currently, severe left ventricular (LV) dysfunction measured by the LV ejection fraction is the best available predictor of SCD risk and the major indication for primary prevention with the implantable cardioverter-defibrillator (ICD). However, there are major inadequacies associated with using LV ejection fraction for prediction of risk and there is a significant scope for enhancement of risk stratification. This chapter will discuss the utility and limitations of severe LV systolic dysfunction as a risk predictor of SCD, other predictors in the process of being evaluated and finally, the promise that new genomic predictors may also contribute to the process of SCD risk stratification.

Keywords

Death, sudden cardiac • Prediction • Prevention • Risk stratification • Epidemiology • Ejection fraction

S.S. Chugh, MD (✉)
The Heart Institute,
Cedars-Sinai Medical Center, 8700 Beverly Blvd,
Saperstein 2S48, Los Angeles, CA 90048, USA
e-mail: chughs@cshs.org

R. Havmöller, MD, PhD
Cedars-Sinai Heart Institute,
8700 Beverly Blvd. Davis, Suite 1059,
Los Angeles, 1059, CA, USA

Department of Cardiology, Karolinska University Hospital, Odengatan 37, 11351 Stockholm, Sweden
e-mail: rasmushavmoller@hotmail.com

C. Teodorescu, MD, PhD • A. Uy-Evanado, MD
K. Reinier, PhD, MPH
Cedars-Sinai Heart Institute,
8700 Beverly Blvd. Davis, Suite 1059,
Los Angeles 1059, CA, USA
e-mail: carmen.teodorescu@cshs.org;
audrey.evanado@cshs.org

A. Huertas-Vazquez, PhD
Cedars-Sinai Heart Institute,
8700 Beverly Blvd. Davis, Suite 1059,
Los Angeles 1059, CA, USA
e-mail: adriana.huertasvazquez@cshs.org

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Introduction

Despite recent advances in resuscitation science, survival from sudden cardiac arrest (SCA) remains low, and sudden cardiac death (SCD) remains a public health problem of significant proportions. Estimates of the annual incidence of SCD in the United States (US) range from 250,000 to 300,000 [1–3]. Currently, severe left ventricular (LV) dysfunction is the best available predictor of SCD risk and is the major indication for primary prevention with the implantable cardioverter-defibrillator (ICD) [4–7]. Based on this indication, it is estimated that there will be at least 100,000 potential ICD recipients per year among the US Medicare population alone, which is likely to translate into $3–4 billion per year for implantation and follow-up of ICDs [8, 9]. However, using severe LV dysfunction as the criterion for a prophylactic ICD, it takes approximately 15–20 ICD recipients to save one life during an intermediate follow-up period, indicating that there is a significant scope for enhancement of risk stratification [4,7,10]. Therefore, there is a need to extend beyond the LV ejection fraction (LVEF), and to identify novel predictors of SCD. This chapter will discuss the utility and limitations of severe LV systolic dysfunction as a risk predictor of SCD, other predictors in the process of being evaluated and finally, the promise that new genomic predictors may also contribute to the process of SCD risk stratification. Wherever possible, predictors of SCD will be discussed in the context of the overall population, as opposed to population sub-groups that can have variable risk.

Left Ventricular Dysfunction and Sudden Cardiac Death in the General Population

Severe LV dysfunction was identified as an important prognosticating factor for SCD almost three decades ago [11], leading to its use as the major criterion for the design and conduct of the prospective randomized ICD trials [4–7, 12]. Severe LV dysfunction clearly predicts risk of SCD, but its effectiveness as a determinant of risk, particularly in the context of primary prevention, has recently been debated because of two observations. Firstly, among recipients of primary prevention ICDs, appropriate ICD therapies may be delivered in less than 30 % of ICD recipients over an intermediate (4–5 years) follow-up. This has led to an active discussion regarding cost-effectiveness of the ICD when the LVEF is employed for risk stratification [13, 14]. Secondly, it had been hypothesized that patients with severely decreased LV dysfunction who present to health care providers as a high risk group (as a result of symptoms or following survival from cardiac arrest) may comprise a small proportion of overall SCD cases [15]. Others and we have observed this hypothesis to indeed be true in the general population [16–18]. In a population-based analysis from the Oregon Sudden Unexpected Death Study (Oregon SUDS), severe LV dysfunction was a significant predictor, but was found to affect only a third of all SCD cases in the community. In fact, we observed that at least 65 % of overall SCD cases would have not met criteria for prophylactic ICDs by the current guidelines [18]. Almost half of all SCD cases had normal LV function and the remaining 20 % had either mildly or moderately decreased (LVEF >0.35 and <0.50) LV systolic function. Similar observations have been made in a community-based study in Maastricht, the Netherlands [16, 17]. Among 200 cases of SCD with an assessment of LV function available, 101 (51 %) had normal LVEF, defined as >0.50, and 38 (19 %) had severely reduced LVEF, defined as ≤0.30. Despite the fact that the Netherlands study was limited to cases 20–75 years old while Oregon SUDS included all ages, the findings are very similar in both studies. While severe LV dysfunction remains a contributor to risk stratification, the above findings underscore the significant need to extend beyond the ejection fraction and identify novel predictors that could be used independently as well as in combination with the LVEF.

Phenotypes That Merit Consideration as Predictors

In addition to severe LV dysfunction, current predictors that are incorporated in stratification of risk for SCD, are limited to a small subset of

relatively rare conditions such as hypertrophic obstructive cardiomyopathy and the long QT and Brugada syndromes [15, 19]. Therefore, in the general population, determinants of SCD risk may presently be undefined for the majority of cases. This lack of information regarding SCD risk markers in the general population is a significant and critical gap in our knowledge of SCD [20]. However, there are potential predictors that have been discussed in the literature and are currently either areas of active investigation, or definitely warrant being investigated.

Left Ventricular Hypertrophy

The presence of left ventricular hypertrophy (LVH) is a strong independent risk factor for future cardiac events and all-cause mortality. A recent meta-analysis of 20 studies (48,545 participants) highlighted the strong relationship between LVH and overall adverse outcome, emphasizing the clinical importance of detecting this entity [21]. The adjusted risk of future cardiovascular morbidity associated with baseline LVH ranged from 1.5 to 3.5, with a weighted mean risk ratio of 2.3 for all studies combined. The adjusted risk of all-cause mortality associated with baseline LVH ranged from 1.5 to 8.0, with a weighted mean risk ratio of 2.5 for all studies combined. With the exception of one study in dialysis patients, LVH consistently predicted high risk, independently of examined covariates, and irrespective of race, presence or absence of hypertension or coronary disease, or between clinical and epidemiologic samples [21]. Studies at the bench would also suggest that LVH constitutes a significant substrate for genesis of ventricular arrhythmias. Prolonged action potential duration is a salient feature of LVH, independent of cause [22–25]. This may lead to the phenomena of early after-depolarizations and triggered activity as well as increased dispersion of repolarization that can sustain torsades de pointes ventricular arrhythmia [26–29]. In addition the myocardial fibrosis and myofibrillar disarray observed in LVH predispose to discontinuities in conduction by disrupting intercellular coupling [30–32]. This remodeling of the interstitium in LVH also affects distribution of gap junctions and properties of ion channel excitation and recovery; also leading to inhomogeneities of sympathetic nervous system innervation and altered mechanical and electrical loading properties [31, 33–35]. Some have postulated that subjects with LVH are in a pro-thrombotic state and therefore at increased risk for acute coronary thrombosis and SCD [36, 37]. Finally, there is evidence to suggest that a subgroup of patients with LVH will eventually develop severe LV dysfunction. There is a lack of clinical investigations that have examined the possibility of an independent association between LVH and SCD. The overall risk of SCD appears to be increased in subjects with LVH, independent of etiology of LVH. An analysis from the Framingham Heart Study observed an independent association between LVH and SCD, among patients who had risk factors for coronary artery disease (CAD) [38]. This study examined 60 SCDs that occurred among 3,661 subjects after up to 14 years of follow up. It was found that LVH (determined by echocardiography) increased the risk of SCA independent of CAD risk factors with a hazard ratio (HR) of 2.16. In this study, there was limited information regarding the mode of death and whether patients had actually developed significant CAD. However, with a minimum estimated prevalence of LVH ranging between 20 and 50 % among patients with CAD [39–41], patients with LVH may represent a large subgroup of the population at risk for SCA. Recent postmortem evaluations of patients with SCD and CAD have revealed stable plaque morphology without evidence of acute coronary syndromes, suggesting that a primary electrical event and not coronary ischemia may have been the terminal event leading to SCD [42, 43]. Given that the majority of fatal arrhythmias are ventricular tachyarrhythmias [44], a causal link with LVH can be readily postulated. Therefore, LVH may have significant potential to extend risk stratification for SCD beyond LVEF. In fact, recently published data from Ores-SUDS showed that the echocardiographically derived variables severe LV systolic dysfunction (defined as LVEF ≤35 %) and LVH (defined as increased LV mass indexed to body surface area) were independently associated with an almost two-fold increase of risk of SCD [45]. Moreover, a subject with both risk factors had almost four-fold risk

of SCD [45]. The findings of additive risk suggest, at least to some extent, the existence of independent pathophysiological pathways linking SCD with LV systolic dysfunction and LVH respectively.

Electrocardiographic Markers of Sudden Cardiac Death Risk

Abnormalities of ventricular repolarization on the ECG including prolongation of the QT interval, QRS duration and T peak to T end interval, have been associated with SCD. The link between the prolonged corrected QT interval (QTc) and increased risk of fatal arrhythmogenesis is well established by the detailed investigation of the rare monogenic, long QT syndromes that constitute a human model for this causative association [46–49]. However, the Rotterdam study reported that QTc was independently associated with SCD even in a cohort of unrelated individuals [50]. In a cohort of 6,693 patients followed for 2 years, patients without evidence of cardiac dysfunction and QTc >440 ms had a 2.3-fold higher risk of SCD compared to those with QTc <440 ms. This association was independent of age, gender, history of myocardial infarction (MI), heart rate, and drug use. A more recent analysis from the same cohort reported that prolonged QTc was an independent risk factor for SCD in older adults followed for 6.7 years [51, 52]. Similar observations were reported in a population-based study of non-related SCD victims with CAD in the general population [53]. Idiopathic abnormal QTc prolongation (i.e. in the absence of diabetes and QT-prolonging drugs) was associated with five-fold increased odds of SCD.

Likewise, prolongation of the QRS duration has been found to be associated with SCD. In a study of patients undergoing aggressive antihypertensive therapy, prolonged QRS duration predicted SCD, even after controlling for left bundle branch block, other known risk factors for SCD, and LVH [54]. Among patients with CAD in a community-based setting, prolonged QRS duration (as with QTc/JTc and severe LV systolic dysfunction) also had independent contributions to risk of SCD [55]. This abnormality might reflect damaged areas of the myocardium that could distort the normal spread of electrical forces, and thus predispose to ventricular arrhythmias. The fact that prolonged QRS duration (a marker of disturbed depolarization) and prolonged JTc (a marker of disturbed repolarization) were not only independent contributors to the risk of SCD but also showed minimal (3 %) overlap in this population is interesting and underlines the complex nature of the pathways of SCD and the multifactorial approach that is likely to be needed to find effective ways of predicting risk of SCD.

A novel ECG variable that has been shown to be associated with SCD is the interval between the peak of the T-wave and the end of the T-wave (TpTe). A prolonged TpTe is thought to reflect either increased transmural dispersion of ventricular repolarization or total (regional) dispersion of the repolarization. Early studies indicated its potential as a predictor of ventricular arrhythmogenesis and findings from Oregon SUDS further showed its independent association with SCD with particular utility when the QTc was normal or not measurable due to prolonged QRS duration [56]. The potential of TpTe as a stratifier of risk among unrelated individuals in the general population, clearly merits further evaluation.

And lastly, two other manifestations of abnormal repolarization merit mention, but their role for SCD risk stratification in the general population is not clear yet. The association between a short QT-interval and fatal arrhythmias has been identified in several kindreds as the short QT syndrome. There is a growing body of evidence that early repolarization, previously considered a benign ECG finding, may be associated with increased risk of idiopathic ventricular fibrillation. Short QT syndrome and the early repolarization syndrome, including their associations with SCD, are discussed in greater detail in the corresponding chapters of this book.

Diabetes Mellitus

There are a relatively small number of studies in which the independent role of diabetes mellitus (DM) in enhancing risk of SCD has been investigated. However, the results are intriguing as

well as consistent. The "Paris Prospective Study I" conducted a longitudinal follow-up of >6,000 middle-aged, healthy male Parisian civil servants, over 23 years. A distinction was made between the 120 SCDs and 192 deaths from acute MI that occurred over this time period. In a multivariate analysis, DM independently conferred the highest risk for SCD (Relative Risk [RR] 2.2) compared to all other variables (age, body mass index, tobacco use, parental history of MI or SCD, heart rate, systolic blood pressure, cholesterol and triglyceride levels) [57, 58]. Similar findings were reported from the US Nurses' Study and the Physicians' Health Study populations [59, 60] as well as a retrospective clinical database analysis from a health cooperative in Seattle [61]. In a recent analysis of two prospective post-MI studies, diabetic patients had a higher incidence and risk of SCD compared to non-diabetic patients (adjusted HR 2.5) [62]. Furthermore, LV systolic dysfunction had an additive effect. The highest incidence of SCD was observed in diabetics with LV systolic dysfunction (LVEF ≤35 %) and the lowest incidence was observed in non-diabetic patients with relatively preserved systolic function (LVEF >35 %). The incidence of SCD among diabetic patients with preserved LVEF was similar to that of non-diabetic patients with LV dysfunction. While these findings clearly implicate DM as an important factor in pathogenesis of SCD, the relationship has not been evaluated in prospective, community-wide studies of SCD. In addition, little is known about the specific ways in which DM-related mechanisms contribute to the pathogenesis of SCD. However, several mechanisms have been postulated. It is widely accepted that DM increases risk of CAD, a condition that is commonly found in association with SCD. However, there may be DM-specific accelerated forms of atherosclerosis with enhanced thrombogenicity [63]. Evidence is accumulating for the existence of a distinct form of cardiac dysfunction that has been termed "diabetic cardiomyopathy" [64, 65]. Presence of diabetes complications may influence the risk of SCD. Compared to subjects with no diabetes, patients with diabetes and microvascular disease (retinopathy or proteinuria) had higher risk of SCD (Odds Ratio [OR] 2.7) than diabetic patients without microvascular disease (OR 1.7) or patients with borderline diabetes (OR 1.2) [61]. In addition, poor glycemic control was associated with SCD in 1,255 diabetic hemodialysis patients from the German Diabetes and Dialysis Study [66]. With each 1 % increase in HbA1c the risk of SCD increased by 18 %, cardiovascular events and mortality increased by 8 %. An intriguing and universal finding among diabetics is their propensity to have a greater prevalence of abnormal prolongation of the QT interval from the ECG [67]. Earlier clinical studies have also reported a good correlation between prolonged QTc and overall cardiac mortality in diabetics [68, 69]. Recently, it was shown that DM is a determinant of QTc prolongation and of SCD in patients with CAD [53]. However, in patients with dilated cardiomyopathy, DM did not affect ventricular repolarization as measured by QT variability [70]. Several studies have found a significant association between diabetic autonomic dysfunction and prolongation of the QTc [71–74]. Given the recently confirmed status of prolonged QTc as a marker of SCD risk in a large, community-based cohort [53], this parameter warrants further attention as a risk marker of SCD among diabetics.

Plasma Biomarkers as Risk Predictors of Sudden Cardiac Death

Troponins and blood lipids are examples of important cardiac biomarkers. The definition of a biomarker varies, but commonly a cardiac biomarker is considered as a substance that can be measured in blood or plasma, and that helps in the clinical decision making. Besides being practical and affordable, the usefulness of a potential biomarker should have been evaluated scientifically, ideally in prospective studies, with good sensitivity, specificity, and predictive values [75]. The number of studies on biomarkers and SCD are currently limited, but growing in number, mainly targeting markers involved in the vulnerable plaque pathway (C-reactive protein [CRP], LDL-cholesterol), indicatinghemodynamiccompromise(N-terminal pro B-type natriuretic peptide [NT-proBNP]), or possessing suggested pro- or antiarrhythmic properties (free fatty acids, magnesium).

There is conflicting data regarding CRP, an acute phase reactant and inflammatory marker. Findings from the Physicians' Health Study [76] showed that CRP levels remained an independent risk factor for SCD (adjusted RR 2.65). In keeping with this, Blangy et al. reported an association between CRP levels and ventricular tachycardias in an ischemic group of ICD-recipients [77]. However, one must bear in mind that this might be of limited relevance to SCD cases without established CAD. In contrast, a study performed in a large cohort of presumably healthy women (Nurses' Health Study) did not show any significant correlation between SCD and high-sensitive CRP [78]. A similar negative finding was observed by Empana et al. [79] in a large cohort of European men that was followed for over 10 years.

The association between elevated NT-proBNP levels and risk of SCD has been investigated in two larger studies. Korngold et al. reported a moderately increased RR per 1 standard deviation (SD) increment of 1.49 [78]. A slightly stronger association was reported by Patton and co-workers in an elderly population (adjusted HR 2.5) [80].

Free fatty acids have been assigned both positive and negative cardiac affects. Jouven and co-workers found that elevated levels of free fatty acids remained an independent risk factor for SCD (but interestingly not for fatal MI) in a large French population of presumable healthy men, also after adjusting for co-founding factors (RR 1.70) [81]. In contrast, levels of long-chain n–3 fatty acids were inversely related to the risk of SCD in men without known cardiovascular disease (men with levels in the highest quartile had an 81 % lower risk of sudden death compared to the lowest quartile) [82]. Taken together, these findings are also in keeping with data from a case–control study of 95 cases of SCD [83], nested in the Cardiovascular Health Study (CHS), where elevated levels of *trans*-18:2 fatty acids were associated with higher risk of SCD (OR 2.34) and higher *trans*-18:1 with lower risk (OR 0.18). Even though the role of LDL-cholesterol in predicting CAD is well established, the association with SCD is less clear. Indeed, the only larger case–control study that has investigated this association (nested in the Physicians' Health Study) could not verify an association between plasma lipid levels and SCD [76].

The proposed antiarrhythmic properties of magnesium are controversial. However, two recent studies have reported an inverse risk of SCD with increased magnesium levels [84, 85] (40 % risk reduction when comparing extreme quartiles and 41 % risk reduction per 1 standard deviation increment of magnesium levels respectively).

The association between diabetes mellitus and SCD has been reviewed above. Consistent with this finding, Jouven and co-workers reported that a 1 standard deviation increase in glucose levels was associated with a slightly elevated risk for SCD (adjusted OR 1.20) [61].

Other interesting biomarkers that have been associated with risk for SCD although in cohorts of limited generalizability or with relatively few events, in single studies, and/or where data are conflicting include markers of hemostasis [79, 86], cystatin C [87], interleukin 6 [79], and renin [88].

In summary, there are promising results but no biomarker has yet stood the test of multiple prospective, case–control studies. Moreover, the issue of causality is still unexplored in most cases of biomarkers. Future studies should focus on presumably healthy study populations to ensure that the biomarker is useful in SCD risk stratification among the general population.

Genetic Contribution to Sudden Cardiac Death and the Discovery of Novel Genetic Variants

Several initial studies provided evidence that genetic factors influence susceptibility to SCD. Friedlander et al. [89] analyzed the potential association with SCA in a cohort of men and women attended by first responders in King County, Washington (235 cases, 374 controls). The second study, conducted in Paris [58] analyzed deaths in a cohort of 7,746 asymptomatic middle aged males followed for a mean of 23 years, using retrospective autopsy and clinical data analyses to classify cardiac deaths as either SCD or fatal MI. Multivariate analyses indicated that the occurrence of SCD in a parent resulted in a 1.6–1.8 fold increase in SCD

susceptibility despite controlling for conventional CAD risk factors. In a very limited number of cases in the Parisian study, where there was a history of both maternal and paternal SCD events (n = 19), the relative risk in offspring was almost nine-fold, indicating an additive genetic model. Familial incidence of SCD in the Parisian study segregated independently of familial incidence of death due to acute MI. Subsequently, a study conducted in Finland [90] reported that individuals with a family history of SCD had an increased risk of dying suddenly during an acute coronary event (OR = 1.6). Together, these studies strongly supported a significant genetic contribution to SCD.

Two main approaches have been conducted for the identification of genes associated with SCD: the candidate gene approach and genome-wide association studies (GWAS). The first approach focuses on the investigation of genes involved in pathways known to influence the disease etiology. For example, candidate genes for SCD could be genes encoding for cardiac potassium and sodium ion channel subunits. Several genes encoding to ion channel subunits have been associated with primary arrhythmogenic disorders such as long and short QT syndromes, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia [91–94]. However, one must bear in mind that these syndromes only account for a minority (<5 %) of all SCDs [95]. Recent studies have demonstrated that susceptibility genes previously associated with primary arrhythmogenic disorders are also associated with SCD risk at the population level [96, 97]. Data from the Harvard cohorts showed that two common intronic DNA variants in KCNQ1 and SCN5A are associated with increased risk of SCD at the population level (rs228322, OR = 1.36, and rs1172052, OR = 1.30). A second study from the Oregon SUDS cohort [97] showed that DNA variants in CASQ2 (rs3010396) and GPD1L (rs9862154) are associated with increased risk of SCD. Taken together with the fact that mutations in CASQ2 and GPD1L have previously been associated with monogenic forms of arrhythmias [93, 94, 98], these findings suggest a possible genetic overlap between rare and complex forms of SCD. Another well known gene associated with SCD susceptibility is the nitric oxide synthase 1 adaptor protein gene (NOS1AP). DNA variants in NOS1AP have previously been found to be associated with QT interval in the general population [99]. Kao and colleagues investigated the contribution of NOS1AP in SCD [100]. In this study, 19 tag single-nucleotide polymorphisms (SNPs) in 19,295 Caucasians and African-Americans (SCD events in Caucasians n = 334, African Americans n = 164) from the Atherosclerosis Risk in Communities Study (ARIC) and the CHS were investigated. Two SNPs were significantly associated with increased risk of SCD in Caucasians (rs16847548 and rs125667209). However, a second report from the Rotterdam study did not find evidence for association with SNPs rs16847548 and rs125667209 [101]. Interestingly, when the data was pooled with the ARIC and CHS studies and the case definition in the Rotterdam study was restricted to witnessed SCD, the association with these two NOS1AP SNPs did become significant. In addition, a SNP in NOS1AP in high LD with rs125667209 (rs12084280) was significantly associated with SCD in a case–control study nested in the Oregon SUDS [97]. In a population-based prospective cohort, Sotoodehnia and colleagues demonstrated that Gln27Glu polymorphism in the β-2 adrenergic receptors (B2AR) was associated with increased risk of SCD [102]. Gln27 homozygous had a 58 % higher SCD risk compared with Glu27 carriers. This finding was replicated in 155 SCD cases and 144 controls from the Cardiac Arrest Blood Study (CABS). B2AR receptors mediate the catecholamine-induced activation of adenylate cyclase through the action of G proteins. Beta adrenergic receptors are key modulators of myocardial contractility, heart rate and peripheral vascular resistance [103]. Despite of the identification of candidate genes associated with SCD, a number of contradictory findings have been reported, and in several cases it has proved difficult to reproduce initial results due to modest effect sizes, genetic or phenotypic heterogeneity, and small sample sizes which make the studies underpowered to detect true association of modest effects. None of the candidate genes identified so far account for a major genetic component in SCD.

The second approach, GWAS, is a hypothesis-free approach that allows for the discovery of novel genes associated with the disease across the genome.

The first GWAS for SCD in the community was conducted in the Oregon SUDS among 424 SCD cases and 226 control subjects with CAD but without history of SCD [104]. Although genome-wide significance was not achieved in the discovery population, a follow up in samples from the ARIC and CHS studies showed that the GPC5 gene was associated with lower risk of SCD (HR 0.85). Glypicans are heparan sulfate proteoglycans that are bound to the external surface of the plasma membrane by a glycosylphosphatidylinositol linkage [105]. GPC5 is one of the six members of the glypican family. Interestingly, GPC5 and GPC6 genes show homology with GPC3 and GPC4, genes involved in the Simpson-Golabi-Behmel syndrome, a rare genetic disorder known to cause heart defects [106]. A recent large-scale collaborative genome-wide association meta-analysis of SCD investigated SNPs association in 1,238 SCD cases and more than 20,000 controls of European ancestry [107]. This study identified the BAZ2B locus, located in chromosome 2q24, to be significantly associated with SCD. BAZ2B belongs to a family of ubiquitously expressed bromodomain containing proteins. Proteins of the BAZ family are characterized by a carboxy-terminal bromodomain adjacent to a PHD finger and a WACZ motif [108]. The biological function of BAZ2 is unknown but it has been suggested that BAZ2B plays an important role in chromatin remodeling and transcription [109]. Further investigation is warranted to elucidate the biological role of BAZ2B in the pathogenesis of SCD.

Although the identification of genes associated with SCD is challenging, large GWAS consortia have facilitated the identification of novel genetic loci associated with SCD. Many of the SNPs identified map to introns or to intergenic regions, with no apparent functionality. Further efforts are warranted to understand the biological function of these genes in the context of SCD. Next generation sequencing technologies, epigenetic studies, animal models, and gene expression will provide new insights into the biological role of genes associated with SCD.

Societal Predictors and Socioeconomic Status

While socioeconomic factors are likely to have significant effects on incidence of SCD [110–112], until recently this association had not been evaluated in prospective, population-based manner. In addition, most studies of primary cardiac arrest limit evaluation to those subjects that undergo resuscitation. As a result, the 40–50 % of overall SCA cases that are unwitnessed or do not undergo attempted resuscitation may not be included in most existing analyses. In the ongoing Oregon SUDS [113], a 2-year prospective evaluation of the potential relationship between socioeconomic status and occurrence of SCA was performed, evaluating both address of residence as well as specific geographic location of cardiac arrest [114]. Analysis was conducted for both witnessed and unwitnessed SCA cases. In this investigation of all cases of SCA in a large urban and suburban US county (population 670,000), incidence of SCA based on address of residence was 30–80 % higher among residents of neighborhoods in the lowest socioeconomic status quartile compared to neighborhoods in the highest socioeconomic status quartile. The gradient of socioeconomic status was significantly steeper for patients under age 65 years compared to those over 65 years. Identical, as well as significant effects were observed based on geographic location of SCD. These findings were recently replicated in a population-based registry study that analyzed more than 9,000 SCA cases from seven North American metropolitan areas [115]. It was found that the incidence of SCA was significantly higher in residential areas of lowest versus highest socioeconomic status. The incidence rate was nearly doubled and again the association was strongest among patients younger than 65 years. Given that automated external defibrillators (AEDs) are likely to have a significant beneficial impact on survival from out-of-hospital SCA [116, 117], these findings would suggest that for the placement of AEDs in the community, neighborhood socioeconomic status should be taken into consideration. In the long term, there are likely to be multiple factors that result in the observed

association between socioeconomic status and SCD, and these merit further evaluation. Risk factors for CAD such as lack of physical activity, smoking, hyperlipidemia, hypertension, obesity, and DM are more common among individuals with lower socioeconomic status [112, 118, 119]. A study conducted in the United Kingdom found that incidence of out-of-hospital SCA was significantly higher in areas of socioeconomic deprivation, but the same was not true for overall CAD [120]. A contributory role of psychosocial factors as direct triggers of ventricular arrhythmias and consequent SCA has also been postulated [111].

Summary and Conclusions

Predictors of SCD are likely to be diverse and multi-factorial. While LVEF is a predictor of SCD, the majority of individuals in the general population that suffer SCD, do not appear to have severe LV systolic dysfunction. As a consequence, there is a significant need to extend beyond the LVEF and identify novel predictors of SCD. This review has discussed several clinical predictors that appear to have promise, but will require more detailed evaluation, particularly in large population-based investigations. The availability of potential genetic predictors is imminent, but these will also require validation in multiple populations before they can find utility in day to day clinical risk stratification. For risk stratification of SCD to be comprehensive, factors as diverse as genomics and socioeconomic status may have to be taken in consideration.

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20
Genetic Testing

David J. Tester and Michael J. Ackerman

Abstract

Within the field of molecular cardiac electrophysiology, the previous two decades of research have elucidated the fundamental genetic substrates underlying many arrhythmogenic disorders associated with sudden cardiac death including long QT syndrome (LQTS), Andersen-Tawil syndrome, Timothy syndrome, short QT syndrome (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada Syndrome (BrS), familial AV block, early repolarization syndrome, and atrial fibrillation. In addition, the molecular underpinnings for structural cardiomyopathies vulnerable to sudden arrhythmic death: dilated cardiomyopathy, hypertrophic cardiomyopathy, left ventricular noncompaction syndrome, and arrhythmogenic right ventricular cardiomyopathy, are understood now in greater detail. Gene testing for several of these heritable channelopathies and cardiomyopathies are currently available through specialized clinical and/or research based laboratories.

The purpose of this chapter is to equip the reader with a basic understanding of molecular genetics and genetic testing in the setting of cardiac electrophysiologic disorders. First, the chapter will present a primer on fundamental molecular genetics including the organization of the human genome, transfer of genetic information, different modes of inheritance, and types of mutations in human genetic disease. Next, techniques utilized in genetic testing will be illustrated. And finally, this chapter will address the important issues of genetic testing, including clinical versus research based testing, benefits of genetic testing, limitations to genetic testing, interpretation of the genetic test, role of genetic counselors, and ethical, legal and societal implications.

Keywords

Cardiomyopathies • Channelopathies • Genes • Genetic Testing • Mutation

D.J. Tester, BS
Cardiovascular Diseases Division,
Department of Medicine, Mayo Clinic,
505 Guggenheim, 200 First St SW, Rochester,
MN 55905, USA
e-mail: tester.david@mayo.edu

M.J. Ackerman, MD, PhD, FACC (✉)
Department of Medicine, Division of Cardiovascular Diseases, Department of Pediatric and Adolescent Medicine, Division of Pediatric Cardiology,
Department of Molecular Pharmacology and Experimental Therapeutics,
Mayo Clinic, Rochester, MN, USA
e-mail: ackerman.michael@mayo.edu,
haglund.carla@mayo.edu

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Through advances in molecular medicine, the previous several decades of research have elucidated the fundamental genetic substrates underlying over 4,000 genetic disorders, most of which are rare. Currently, genetic tests (www.genetest.org) for over 2,000 diseases are available clinically and are offered by more than 600 diagnostic laboratories worldwide. In addition, numerous genetic tests are available on a research basis.

Genetic disease is more common then once believed. In fact, genetic abnormalities are a major cause of illness and death. It is estimated that by 25 years of age, 80 per 1,000 live births (8 %) will suffer from a genetically based disorder [1]. This genetic load is accounted for by multifactorial disorders (4.64 %), congenital anomalies with a genetic etiology (2.66 %), single gene disorders (0.36 %), chromosome abnormalities (0.18 %), and disorders of unknown genetic etiology (0.12 %). However, these values may represent an underestimate of the true prevalence of genetic involvement in disease. Many disorders once thought to be non-genetic are now understood to be multifactorial diseases with contributions from various genetic and environmental factors. Disorders of mild genetic conditions may go unrecognized. Disorders of low penetrance and variable expressivity may go undiagnosed in asymptomatic yet genetically affected individuals.

Within the field of molecular cardiac electrophysiology, the previous two decades of research have elucidated the fundamental genetic substrates underlying many arrhythmogenic disorders associated with sudden cardiac death including long QT syndrome (LQTS), Andersen-Tawil syndrome, Timothy syndrome, short QT syndrome (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada Syndrome (BrS), familial AV block, early repolarization syndrome, and atrial fibrillation. In addition, the molecular underpinnings for structural cardiomyopathies vulnerable to sudden arrhythmic death: dilated cardiomyopathy, hypertrophic cardiomyopathy, left ventricular noncompaction syndrome, and arrhythmogenic right ventricular cardiomyopathy, are understood now in greater detail. Gene testing for several of these heritable channelopathies and cardiomyopathies are currently available through specialized clinical and/or research based laboratories.

The purpose of this chapter is to equip the reader with a basic understanding of molecular genetics and genetic testing in the setting of cardiac electrophysiologic disorders. First, we will present a primer on fundamental molecular genetics including the organization of the human genome, transfer of genetic information, different modes of inheritance, and types of mutations in human genetic disease. Next, we will explore techniques utilized in genetic testing. And finally, we will tackle the important issues of genetic testing, including clinical versus research based testing, benefits of genetic testing, limitations to genetic testing, interpretation of the genetic test, role of genetic counselors, and ethical, legal and societal implications.

Primer on Molecular Genetics

General Organization and Structure of the Human Genome

Through a multinational effort, the Human Genome Project was completed in 2003 ushering in the molecular millennium providing the architectural blueprints of virtually every gene in the human genome. The human genome represents the total genetic information or DNA content in human cells and is distributed amongst 46 chromosomes: 22 autosomal pairs and two sex (X and Y) chromosomes [2, 3]. Each chromosome contains tightly packaged linear double stranded DNA. The 24 unique chromosomes are distinguished by chromosome banding techniques (karyotype analysis) and are classified largely according to their size. The organization of the genomic DNA is rather complex. Much of the genome is made up of single-copy DNA with precise DNA sequences represented only once per genome. The remaining portion of the genome consists of several classes of repetitive DNA, including DNA whose sequences are repeated either perfectly or with some variation. The human genome contains 2.9 billion base pairs of genetic information containing the molecular blueprints for ~25,000 genes whose highly coordinated expression

renders us human. In contrast, the genome of the *Drosophila melanogaster* fruit fly consists of 120 million base pairs and 13,600 genes. Though the human genome contains less than twice as many genes as the fruit fly, the genes are more complex and create a larger number of protein products through alternate splicing of the coding sequences within the genes. Now, let's examine the basic structure of the DNA molecule and the basic hereditary element called the gene.

Basic Structure of DNA and the Basic Hereditary Element, the Gene

In 1953, Drs. Watson and Crick described the basic structure of the molecular essence of life: the deoxyribonucleic acid or DNA molecule. DNA is a polymeric nucleic acid macromolecule comprised of "building blocks" called deoxyribonucleotides of which there are four types: adenine (A), guanine (G), thymine (T) or cytosine (C) [2, 3]. The DNA molecule is essentially nucleotides that are polymerized into long polynucleotide chains. DNA is a double stranded molecule made up of two anti-parallel complementary strands that are held together by noncovalent (loosely held) hydrogen bonds between complimentary bases where A and T always form complementary base pairs and G and C always pair (Fig. 20.1). DNA in its native state forms a double helix which resembles a right handed spiral staircase. DNA segments that store genetic information in the form of a genetic code are called genes (Fig. 20.2).

Approximately 30 % of the genome is spanned by genes, however less than 2 % of the genomic DNA is actually made up of protein encoding segments within genes called exons. In between the exons are intervening DNA sequences called introns which are not a part of the genetic code. Usually upstream (20–100 bp) from the first exon is a regulatory element called the promoter which controls transcription of the hereditary message as defined by the gene sequence.

Transfer of Genetic Information

Inherited genetic information is transferred to a finished product (protein) through a two step process often referred to as the central dogma of

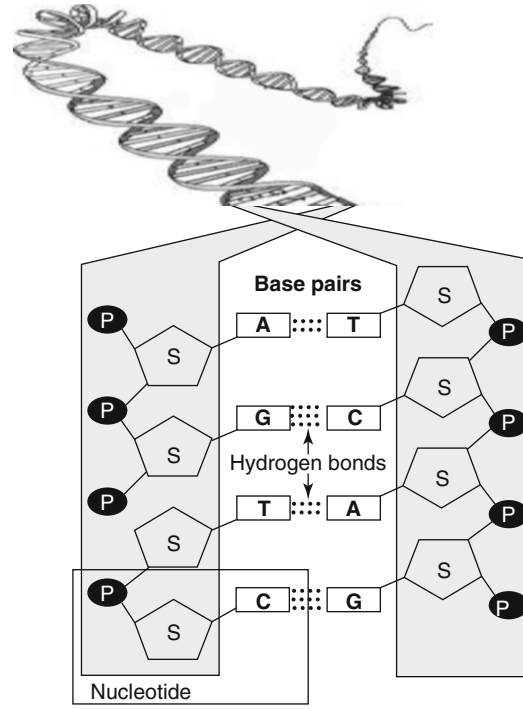

Figure 20–1. Structure of DNA. Depicted is the general organization of DNA, illustrating complimentary base pairing via hydrogen bonds between cytosine (*C*) and guanine (*G*) and between adenine (*A*) and thymine (*T*). As defined by the *box*, a single nucleotide consist of a phosphate (*P*) group, deoxyribose sugar (*S*), and a base (A, C, G, or T) (Modified from Tester and Ackerman [4])

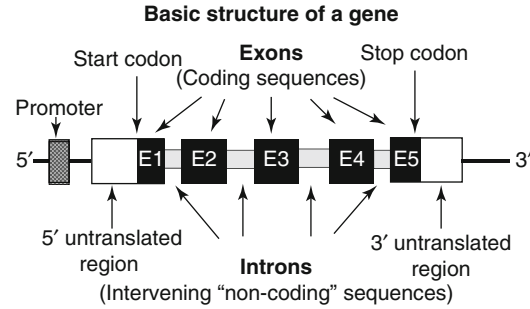

Figure 20–2. Basic structure of a gene. Shown here is the basic structure of a gene consisting of DNA segments (exons) that encode for a protein product. Between the exons are intervening sequences called introns. At the 5′ end of the gene is a regulatory element called the promoter which initiates transcription. At the 5′ and 3′ ends are "untranslated" regions that are considered apart of the first and last exons respectively. These sequences are not apart of the genetic code, but may contain additional regulatory elements. To begin translation of the genetic message, as encoded by the gene, is a start codon and to terminate the message a stop codon (Modified from Tester and Ackerman [4])

molecular biology. This passage of genetic information begins with **transcription**, which is the process by which the genetic code is transcribed in the form of messenger RNA, which begins with the dissociation of the double stranded DNA molecule and formation of a newly synthesized complementary RNA (ribonucleic acid) molecule. This primary RNA molecule undergoes RNA splicing to remove the non-coding intronic regions from the transcript. Within the intron and exon boundaries are highly conserved splicing recognition sequences that allow the RNA splicing machinery to know precisely were to cleave the sequence in order to remove the non-coding regions (introns) and bring the coding sequences (exons) together. If these sites are disrupted, certain consequences like splicing errors can occur.

Next, **translation** involves the decoding of the mRNA-encrypted message and assembly of the intended polypeptide (protein) that will serve a biological function. Polypeptides are polymers of linear repeating units called amino acids. The assembly of a polypeptide or protein is governed by a triplet genetic code, or codon (three consecutive bases) of which there are 64 types that encode for 20 unique amino acids. One codon, ATG, encodes for the amino acid methionine and is always the first codon (start codon) to start the message. Each codon in the linear mRNA is decoded sequentially to give a specific sequence of amino acids that are covalently linked through peptide bonds and ultimately constitute a protein. Three codons, TAA, TAG, and TGA, are stop codons that terminate the linearization of the peptide and signal a release of the finish product. The genetic code is redundant in that more than one codon can encode for the same amino acid. For example, often when varying the nucleotide at the third position (wobble position) in a codon, the message does not become altered.

Each of the 20 amino acids has a unique side chain that provides for its characteristic properties. Some amino acids are considered nonpolar and hydrophobic (water fearing), while others are polar and hydrophilic (water loving). Some amino acids are negatively charged and have acidic properties while others are positively charged and have basic properties. It is the unique sequence in which these amino acids occur within a protein that dictates its structural and functional properties. One can imagine that if an amino acid in a protein is substituted for an amino acid with different properties, this could alter the overall function of that protein and provide a pathogenic substrate for disease.

The standard nomenclature for numbering nucleotides and codons within a gene begins with the A of the start codon (ATG) representing nucleotide 1 and ATG as codon 1. Generally only consecutive nucleotides constituting the coding region of the gene are numbered. Intronic nucleotides are numbered relative to either the first or last nucleotide in the exon preceding or following the intron. For example, the LQT1-associated *KCNQ1* splice error mutation M159sp (exon 2, nucleotide substitution: 477 +5 G>A), results from a G to A substitution in the intron, 5 nucleotides following exon 2, where nucleotide 477 is the last nucleotide in exon 2. This substitution results in a splicing error following the last codon of the exon (codon 159 encoding methionine, M) [5].

Genetics of Disease: Modes of Inheritance

Inherited variation in the genome is the basis of human and medical genetics. Reciprocal forms of genetic information at a specific locus (location) along the genome are called alleles [3]. An allele can correspond to a segment of DNA or even a single nucleotide. The normal version of genetic information is often considered the "wild-type" or "normal" allele. A large majority of the human genome represents a single version of genetic information. The DNA from one individual is mostly made up of the same exact nucleotide sequence as another individual. However, there are numerous small sections of sequence or even single nucleotides that vary from one individual to another. These normal variations at distinct loci in the DNA sequence are called polymorphisms.

Some polymorphisms are quite common and others represent rare forms of the genetic information. In medical genetics, a disease-causing mutation refers to a variation in DNA sequence that embodies an abnormal allele and is not

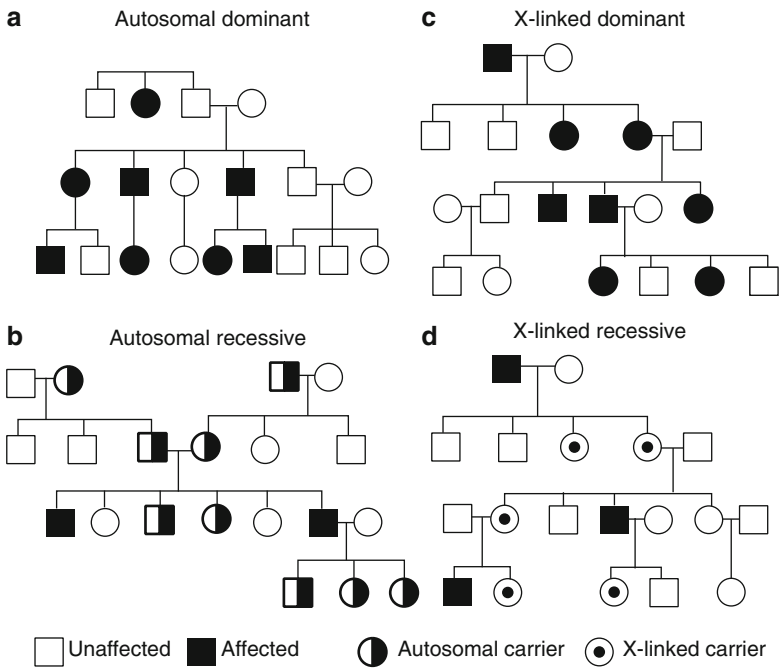

Figure 20–3. Modes of inheritance in human genetic disorders. Illustrated are pedigrees exemplifying four different modes of inheritance, (**a**) autosomal dominant, (**b**) autosomal recessive, (**c**) X-linked dominant, and (**d**) X-linked recessive (Modified from Tester and Ackerman [4])

found in the normal population but subsists only in the disease population. If an individual has a pair of identical alleles, one paternal (from father) and one maternal (from mother), that person is said to be homozygous for that allele. When the alleles are different, then that person is said to be heterozygous for that specific allele. The terms genotype and phenotype are used to refer to an individual's genetic or DNA sequence composition at a particular loci or at a combined body of loci (genotype) and to an individual's observed clinical expression of disease (phenotype) in terms of a morphological, biochemical, or molecular trait, respectively.

Genetic disorders are characterized by their patterns of transmission within families (Fig. 20.3). There are four basic modes of inheritance: autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive [3]. These patterns of inheritance are based largely on two factors: (1) what type of chromosome (autosome or X-chromosome) the gene locus is located on and, (2) whether the phenotype is expressed only when both chromosomes of a pair carry an abnormal allele (recessive) or if the phenotype can be expressed even when just one chromosome harbors the mutant allele (dominant).

Many seemingly monogenic genetic disorders are often found to be genetically heterogeneous once completely analyzed. Genetically heterogeneous disorders are those disorders that have a related clinical phenotype but arise from multiple different genotypes. Genetic heterogeneity may be a consequence of different mutations at the same locus (gene) or as a result of mutations at different loci (genes) or both.

In many genetic disorders, the abnormal phenotype can be clearly differentiated form the normal one. However, in some disorders, the abnormal phenotype is completely absent in individuals hosting the disease-causing mutation while other individuals show extremely variable expression of phenotype in terms of clinical severity, age at onset, and response to therapy. Penetrance is the likelihood that a gene will have any expression at all, and when the frequency of phenotypic expression is less than 100 %, the gene is said to show reduced or incomplete penetrance (Fig. 20.4). Expressivity refers to the level of expression of the phenotype, and when the manifestations of the phenotype in individuals who have the same genotype are diverse, the phenotype is said to exhibit variable expressivity (Fig. 20.4). Reduced penetrance and variable expressivity create a significant

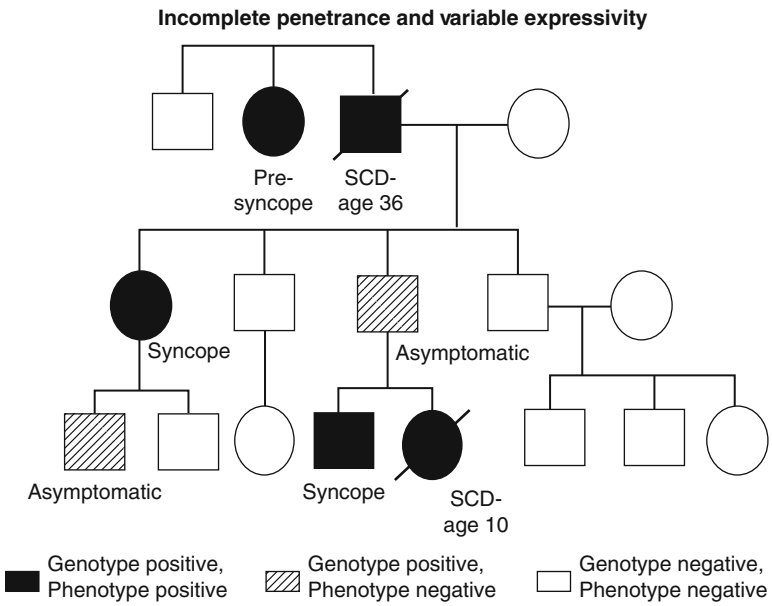

Figure 20–4. Incomplete penetrance and variable expressivity in autosomal dominant genetic disorders. Depicted is a pedigree demonstrating an autosomal dominant disorder with incomplete or reduced penetrance (mutation positive asymptomatic individuals) and variable expressivity (expression of the disorder ranging from symptom free to sudden cardiac death (*SCD*) at a young age) (Modified from Tester and Ackerman [4])

challenge for the appropriate diagnosis, pedigree interpretation, and risk stratification for the disorder.

Genetic disorders are often subcategorized into three major groups: chromosome disorders, single gene disorders, and multifactorial disorders.

Types of Mutations in Human Genetic Disease

Like many genomes, the DNA of the human genome is fairly stable but not immutable. Instead, it is susceptible to an assortment of different types of germline (heritable) and somatic anomalies (i.e. mutations). In general, mutations can be classified into three categories: genome mutations, chromosome mutations, and gene mutations (Fig. 20.5) [3]. Genome mutations entail the abnormal segregation of chromosomes during cell division. Trisomy 21 (Down syndrome) would be an example of this type of mutation where the abnormal cells contain three copies of chromosome 21 instead of two copies found in a normal cell (Fig. 20.5a). Using the "encyclopedia" analogy, trisomy 21 would be similar to having an extra volume whereas Turner's syndrome (XO) with its omitted Y chromosome would be equivalent to a missing volume. Next, chromosome mutations involve the structural breakage and rearrangement of chromosomes during cell division.

In addition, major portions of a particular chromosome may be missing (deleted) or inserted (Fig. 20.5b). Patients with chromosome 22 microdeletion syndrome for example have variable size deletions involving the long arm of one of the #22 chromosomes (22q11.2). Such a genetic perturbation would be analogous to a specific volume of the encyclopedia having several chapters torn from the book.

Finally, gene mutations involve the alterations at the nucleotide level and disrupt the normal function of a single gene product (Fig. 20.5c). Such single gene mutations are classified into three essential categories: nucleotide substitutions, deletions, and insertions. Single nucleotide substitutions are most common and may represent a transition or a transversion. Transitions are substitutions of a purine (A or G) for a purine or a pyrimidine (C or T) for a pyrimidine. Transversions are substitutions of a purine for a pyrimidine or vice versa.

If a single nucleotide substitution occurs in the coding region (exon), the consequence may be either a synonymous (silent) mutation whereby a different codon still specifies the same amino acid or a non-synonymous mutation whereby the altered codon dictates a different amino acid or terminates further protein assembly (i.e. introduces a premature stop codon) (Fig. 20.6a–d). The term "missense" mutation is

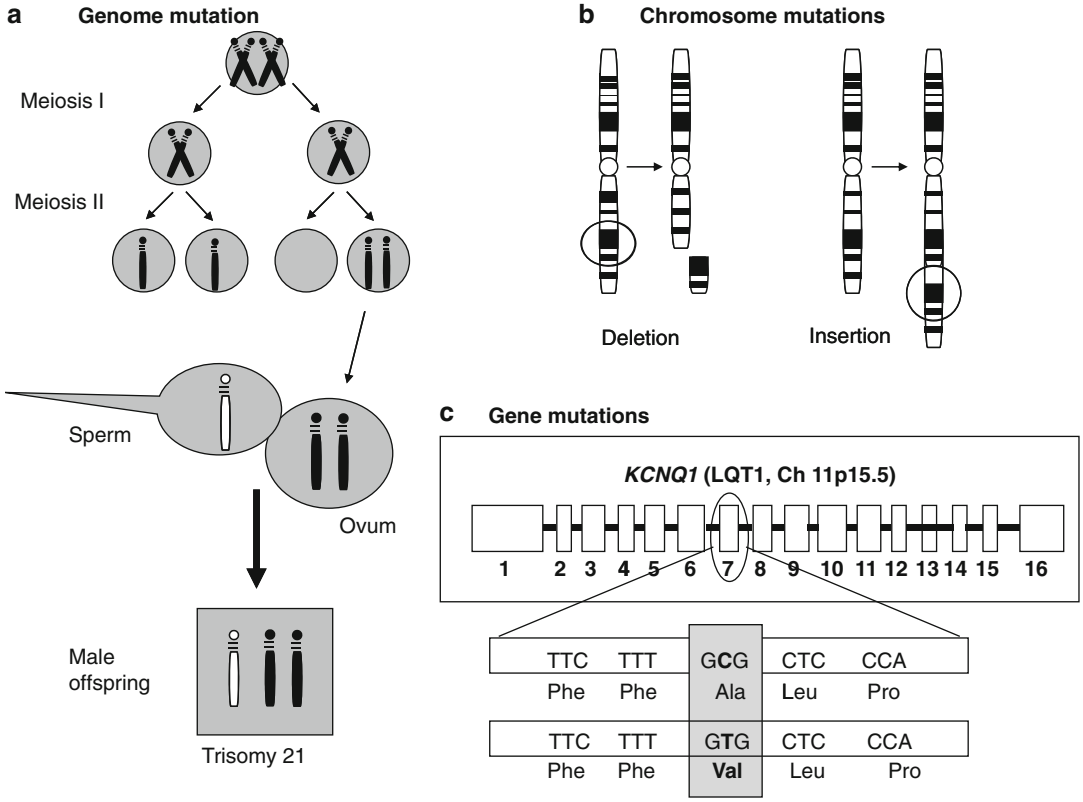

Figure 20–5. Three major classifications of mutations in genetic disorders. There are three major categories of mutations in human genetic disease, (**a**) Genome mutations are those which involve the abnormal segregation of chromosomes during cell division, (**b**) Chromosome mutations, are mutations where major portions of chromosomes may be deleted or duplicated, and (**c**) Gene mutations involve changes at the nucleotide level and disrupt the normal function of a single gene product (Modified from Tester and Ackerman [4])

also used to indicate a single nucleotide substitution that changes one of the protein's amino acids (Fig. 20.6c). Importantly, a missense mutation may or may not result in a functionally perturbed protein. The functional consequence of a missense mutation depends on the differences in biochemical properties between the amino acids that are being exchanged and/or the location in the protein at which the exchange occurs. Again, turning to the "encyclopedia" analogy, the substitution of a single letter (for example "set" and "sex") alters the intended meaning of a sentence. A "nonsense" mutation refers to a non-synonymous mutation resulting in an exchange of an amino acid for a stop codon (Fig. 20.6d). This type of mutation, results in a truncated (shortened) gene product at the location of the new stop codon. Again, depending on where in the protein a nonsense mutation occurs, the functional effects could range from no appreciable difference to functional lethality (i.e. a non-functioning protein).

Base substitutions occurring in the intron (non-coding) can result in an altered gene product as well (Fig. 20.7). The normal process by which intronic sequences are cleaved from newly transcribed RNA to give a mature messenger RNA product is reliant on specific nucleotide sequences located at the intron/exon (acceptor site) and exon/intron (donor site) boundaries. Base substitutions within these highly conserved regions can result in inappropriate splicing of the immature RNA. In some cases, entire exons can be deleted or entire introns may be included in the mature messenger RNA.

Gene mutations may also involve deletions and insertions. As their names indicate, deletions are subtractions of nucleotides from the normal

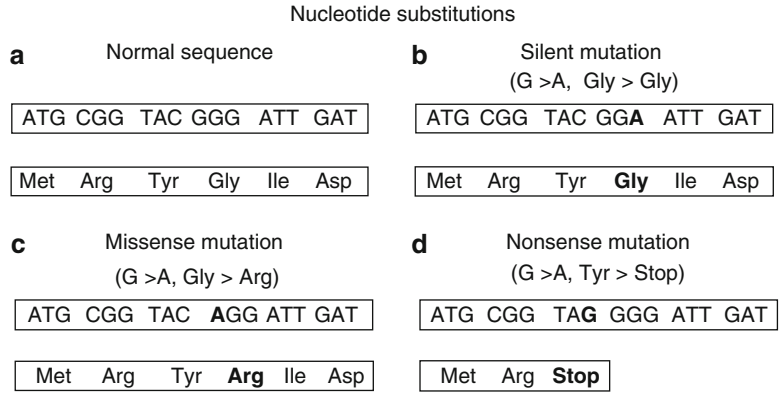

Figure 20–6. Nucleotide substitutions. Illustrated are examples of nucleotide substitutions where (**a**) represents both the normal DNA and amino acid sequences. (**b**) Shown here is a synonymous (silent) mutation. Comparing the sequence to the normal sequence (**a**) we see that the G>A nucleotide substitution results in GGA codon which encodes for the same amino acid (glycine, Gly) as the reciprical codon (GGG) in the normal sequence. (**c**) Shown here is a non-synonymous (missense) mutation. Here a G>A nucleotide substitution results in a codon (AGG) which encodes for a different amino acid than the normal codon (GGG). Here the normal amino acid glycine (Gly) is replaced by a new amino acid arginine (Arg). (**d**) Depicted here is a non-synonymous (nonsense) mutation. Here a C to a G nucleotide substitution alters the normal codon (TAC), which encodes for the amino acid tyrosine (Tyr), to give a new codon (TAG) which encodes for a STOP. This mutation leads a truncated protein

DNA sequence and insertions are additions of nucleotides to the normal sequence. Both deletions and insertions can be as small as a single nucleotide or as large as several hundreds of nucleotides in length. Most of these exonic insertions and deletions alter the "reading frame" of translation at the point of the deletion/insertion and give rise to a new sequence of amino acids in the finished product, a so-called "frame-shift" mutation (Fig. 20.8a). Many frame-shift mutations result not only in an altered amino acid sequence from the point of the insertion or deletion, but also often result in a different product length from the normal gene product. Frame shifts often create a new stop codon, which give rise to either a shorter or longer gene product depending on the location of the new stop codon. In-frame deletions and insertions can occur when the number of nucleotides affected is in a multiple of three (Fig. 20.8b). Perhaps, the most common pathogenic in-frame mutation known occurs in cystic fibrosis. Here, a three base-pair deletion in the *CFTR* gene, that results in an altered gene product missing a single amino acid (phenylalanine at amino acid position 508), accounts for nearly 70 % of cystic fibrosis.

Importantly, not all nucleotide alterations (mutations) create a new gene product that cause or modify a clinical disease state. A DNA sequence variation/change that may (non-synonymous) or may not (synonymous) alter the encoded protein is called a common polymorphism if present in at least 1 % of the normal population. Although not pathogenic or disease causing, non-synonymous single nucleotide polymorphisms can indeed be functional polymorphisms and exert a significant effect on how endogenous and exogenous triggers are handled. Functional polymorphisms are sought to explain the human variation observed with therapeutic and side effect profiles of pharmaceutical agents ("Pharmacogenomics") or to rationalize the heterogeneous expression of disease in families harboring the same, presumptive disease-causing mutation (i.e. "modifier genes").

Techniques Used in Genetic Testing at the Single Gene Level

Biological Material Used for Genetic Testing

In general, for either the research based or clinical genetic tests, 5–15 cc of blood obtained from venipuncture placed in EDTA-containing tubes ("purple top") is requested

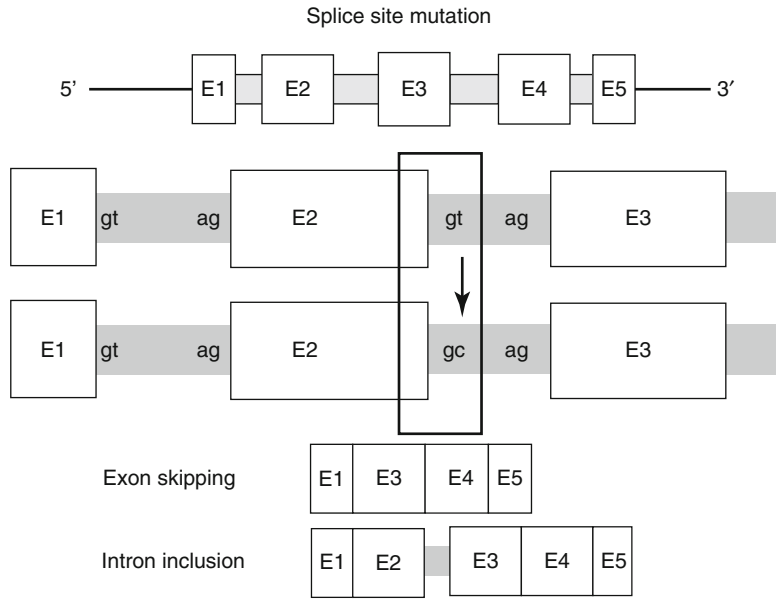

Figure 20–7. Splice site mutations. Depicted here is a schematic representation of a 5 exon gene (E1–E5). Exons are represented by *white boxes*. Intronic sequences are illustrated in gray. Within the intron and exon boundaries, are highly conserved splicing recognition sites as shown in the *black box*. These particular sequences allow the RNA splicing machinery to know precisely were to cleave the sequence in order to remove the non-coding (introns) regions and bring the coding (exons) sequences together. If we have a DNA alteration (T to C) occurring within the splice recognition sequence as shown here, this can result in either exon skipping where in this example exon 2 has been deleted, or intron inclusion where intron 2 is now included in the transcript

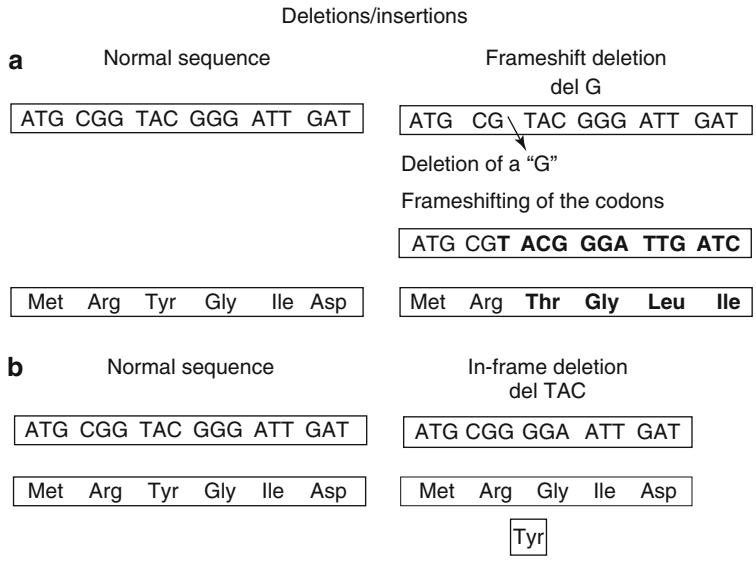

Figure 20–8. Deletion mutation. (**a**) Illustrated is a frameshift mutation. With the deletion of a single nucleotide, in this case a G in the second codon, a shift of the reading frame occurs. Note how the sequence of amino acids has been altered from this point forward. Although not illustrated here, frameshift mutations whether by a result of a deletion or insertion of nucleotides, often lead to a premature stop codon and thus a truncated protein. (**b**) Illustrated here is an in-frame deletion mutation. Here we see that the deletion of three nucleotides (TAC) has lead to the deletion of a single amino acid (tyrosine, Tyr) in the protein. The remaining amino acid sequence is left unaltered. Three nucleotide insertions (not shown) can have a similar affect whereby an amino acid is inserted into the protein product

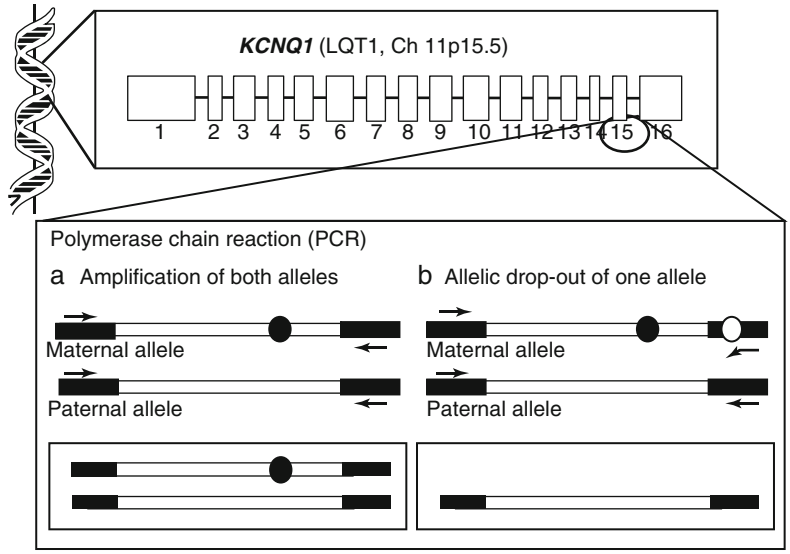

Figure 20–9. Allelic drop-out: a possible mechanism explaining false negative results. In order to understand how allelic drop-out can cause false negative results, we first need to explore the general design of how PCR is performed for mutation analysis using genomic DNA. By focusing on LQTS associated exon 15 of *KCNQ1*, we can see how a PCR reaction is first designed in order to amplify both the maternal and parental alleles. By designing a forward and reverse primer complementary to flanking intronic DNA sequences, PCR products containing the desired exon can be produced. (**a**) If a mutation exists on one of the alleles as depicted here with a black circle, then PCR amplification of this sample would generate products containing the mutation that could be easily detected by most mutation detection platforms, such as DHPLC. (**b**) However, if a single nucleotide polymorphism or SNP (*white circle*) localized to the same allele as the mutation (*black circle*) and within the sequence complementary to the 3′ end of the primer such that the primer annealing is disrupted, then amplification of that allele would not occur and the mutation would be missed. This in essence defines allelic drop-out (Modified from Tester et al. [7]. With permission from Springer-Verlag)

as the source of genomic DNA for genetic testing. Alternatively, DNA isolated from a buccal (mouth cheek) swab can also be adequate particularly for confirmatory testing of family relatives. However, such sampling may not yield a sufficient amount of DNA for comprehensive mutational analysis. Umbilical cord blood may be acquired at the time of birth for newborn screening. In cases of autopsy negative sudden unexplained death, a cardiac channel molecular autopsy can be completed on EDTA-blood if isolated [6]. Alternatively, genomic DNA can be extracted from a piece of frozen tissue. The tissue requested is typically left ventricle myocardium although any organ (liver, spleen, thymus) with a high nucleus to cytoplasm ratio will suffice. Both research based and clinical genetic testing require a signed and dated informed consent accompany the samples to be tested.

Polymerase Chain Reaction

The identification of gene mutations typically involves the polymerase chain reaction (PCR) technique used to amplify many copies of a specific region of DNA sequence within the gene of interest. Generally, 20–25 base pair (bp) forward and reverse oligonucleotide primers are designed to be complementary to reciprocal intronic DNA sequences flanking the exon (amino acid encoding) of interest in order to produce PCR products (200–400 bp in length) containing the desired exon to be analyzed. When analyzing large exons, overlapping PCR products may need to be designed. It is critical that primers be designed properly in this mutation detection process as false negatives secondary to poor primer design and possible allelic drop-out can occur (Fig. 20.9). For example in LQTS, the differential amplification of a single allele due to the prevention of primer annealing during polymerase chain reaction (PCR), (termed allelic dropout), was reported recently as a mechanism underlying false negative genetic test results [8].

Briefly, a genomic DNA sample isolated from blood or tissue is pooled with both the forward and reverse amplification primer specific for the

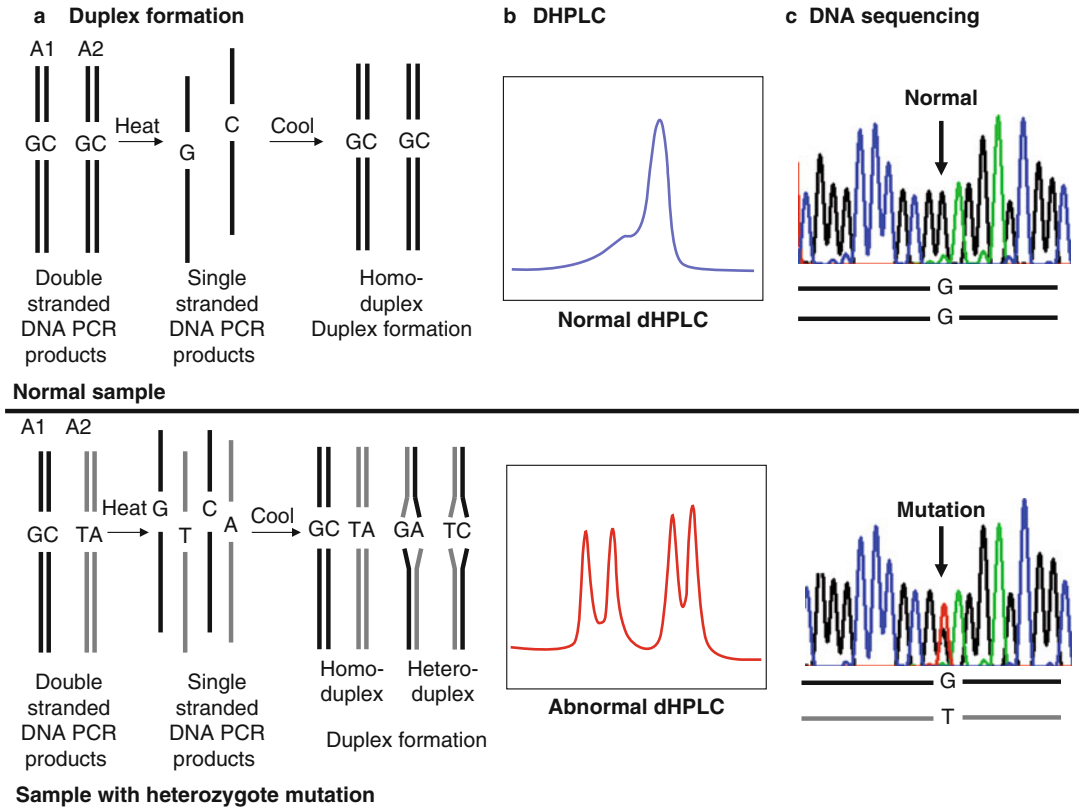

Figure 20–10. Mutation detection process of PCR, DHPLC, and DNA sequencing. Mutation detection by DHPLC relies on (**a**) heteroduplex (mismatch) and homoduplex (perfect match) formation by heating and cooling of both DNA alleles (A1 and A2) and then separating such types by ion-exchange chromatography resulting in (**b**) DHPLC elution profiles that vary from normal profiles. (**c**) DNA sequencing is then used to resolve the underlying heterozygote DNA change (Modified from Tester [7]. With permission from Springer-Verlag)

region of desired amplification (usually an entire exon) along with a reaction mixture containing dinucleotides (dATP, dCTP, dGTP, and dTTP) or "DNA building blocks" and a DNA polymerase. The reaction mixture is subjected to cycling (typically 30–40 cycles) of specific temperatures designed to: denature (95 °C) double stranded DNA, allow for primer annealing (typically at 55–62 °C), and to extend (72 °C) the new synthesized DNA strand. A well optimized PCR reaction will yield millions of copies of only the specific sequence of interest. These PCR products can be used in numerous downstream molecular techniques.

Intermediate Mutation Detection – Denaturing High Performance Liquid Chromatography (DHPLC)

PCR amplification is often followed by the use of an intermediate mutation detection platform such as single stranded conformational polymorphism (SSCP) or denaturing high performance liquid chromatography (DHPLC). These methods are used to inform the investigator of the presence or absence of a DNA sequence change in the samples examined. DHPLC is one of the most sensitive and accurate technologies for the discovery of an unknown gene mutation [9, 10]. DHPLC is based on the creation and separation of double stranded DNA fragments containing a mismatch in the base pairing between the "wild-type" and "mutant" DNA strands, known as heteroduplex DNA. In general, PCR products are subjected to denaturing (heating) and re-annealing (cooling) in order to create heteroduplex (mismatch) and homoduplex (perfect match) molecular species (Fig. 20.10a). If a sample harbors a heterozygous mutation, then heteroduplex and homoduplex fragments will be produced following denaturing and re-annealing. If a sample is "wild-type" or homozygous, then

only homoduplex fragments will be produced. The crude PCR products are injected on to a solid phase column that is heated to a specific temperature (individually optimized for each specific PCR product) that allows for partial denaturing of the DNA sequence of interest. A linear acetonitrile gradient based on the size of the PCR product is applied to the column to flush the DNA strands and propel the PCR products through a UV detector resulting in a chromatogram showing the sample's elution profile. This elution profile is highly reproducible under optimal conditions. Since heteroduplex species are less thermodynamically stable than homoduplexes, these double stranded complexes will begin to unravel at the elevated temperature and elute from the column prior to their homoduplex or "wild-type" counter parts, thus producing an elution profile that is unique from the "wild-type" profile, and allowing for detection of mutation hosting samples. Specifically, PCR products containing heterozygote mutations result in the presence of profiles with "shouldering" or additional "peaks" as when compare to "wild-type" samples (Fig. 20.10b).

Direct DNA Sequencing

While intermediate mutation detection platforms alert the investigator of which samples contain mutations, direct DNA sequencing must be used to decipher the precise underlying DNA change(s). Usually, PCR products to be sequenced are purified from the unincorporated amplification primers and dinucleotides (dNTP) using either an enzymatic or filter column based method. Pure PCR products are then subjected to sequencing using a single oligonucleotide primer (typically the same forward amplification primer used in the original PCR reaction) and a sequencing reaction mixture containing a sequencing DNA polymerase, dinucleotides (dNTP) and dye-labeled dideoxynucleotides (ddATP-green, ddCTP-blue, ddGTP-black, and ddTTP-red). This composite of sequencing reaction components and PCR product templates are cycled through a series of temperatures similar to that seen in a typical PCR reaction. Resulting sequencing products are then separated according to size by gel-based or capillary-based electrophoresis and a sequencing chromatogram is created (Fig. 20.10c).

Review and comparison of the resulting sequence chromatograms and the published "wild-type" DNA and amino acid sequence for the gene/protein of interest will allow for the elucidation of whether the underlying DNA change is protein altering and potentially pathogenic or a non-pathogenic normal variant. It is imperative that extreme caution be exercised with respect to the assignment of a variant as a pathogenic mutation. Ethnic matched controls must be performed. To illustrate this need, we performed the first comprehensive determination of the spectrum and prevalence of non-synonymous single nucleotide polymorphisms (i.e. amino acid substitutions) in the 5 LQTS-associated cardiac ion channel genes in approximately 800 healthy control subjects from four distinct ethnic groups [11, 12]. Approximately 2–5 % of healthy individuals were found to host a rare amino acid altering variant. Some of these variants observed in the normal population may represent sub-clinical disease modifiers or simply benign background noise.

In this three step approach: (1) PCR amplification, (2) DHPLC heterozygote analysis or alternative mutation detection intermediate step, and (3) DNA sequencing, only samples believed to contain a DNA alteration are further analyzed by DNA sequencing. While most research laboratories incorporate this three step approach, for most commercially available genetic test, the use of an intermediate mutation detection platform such as DHPLC is bypassed for direct DNA sequencing or next generation sequencing of all samples examined. While this direct approach to mutational analysis is presently more expensive, its sensitivity, specificity, and rapidity for mutation detection are superior to research-based mutation detection platforms. Recent advances in DNA sequencing methodologies and technical instrumentation have quickly grown DNA sequencing capacity and genetic information output. For example, through the use of "next-generation" sequencing, massively parallel sequencing, and oligonucleotide hybridization-chip based technologies, the molecular examination of a patient's complete assortment of specific disease associated protein-coding

sequences in a single or a few reactions with remarkable cost-effectiveness [13, 14] is now available to research laboratories. The research cost to sequencing a person's whole exome (i.e. the open reading frames for all 25,000+ genes) is about $3,000–$4,000. At the current rate, it is likely that specific gene panel genetic testing for specific heritable diseases will become extinct by 2020, being supplanted by comprehensive human whole genome testing.

Collectively these techniques offer outstanding precision and accuracy to detect (i) single nucleotide substitutions that produce missense, nonsense, and splice site mutations and (ii) small insertions or deletions. Yet, large whole gene, multiple exon, or single exon deletions or duplications escape detection by this approach. Techniques like multiple ligation probe analysis (MLPA) and high resolution comparative genomic hybridization (HR-CGH) enable the identification of such large gene rearrangements [15–17], often referred to as a copy number variant (CNV).

Genetic Testing in Electrical Diseases of the Heart and Sudden Cardiac Death

The study of cardiac channelopathies, also referred to as the electrical cardiomyopathies, embodies a relatively new discipline among heart rhythm specialists and allied professionals. In 1995, the discipline of cardiac channelopathies originated with the discovery that defective cardiac channels were at the heart of congenital long QT syndrome (LQTS) [18, 19]. Besides LQTS, the channelopathies include short QT syndrome (SQTS), Brugada syndrome (BrS), Andersen Tawil syndrome (ATS), Timothy syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), progressive cardiac conduction disease, familial atrial fibrillation, idiopathic ventricular fibrillation, and some cases of autopsy negative sudden unexplained death during infancy, childhood, adolescence and beyond. From 1995 to 2004, genetic testing for these cardiac channelopathies was performed in select research laboratories world wide. Such genetic testing has been conducted principally for the purpose of discovery and genotype-phenotype correlations (to advance the science), and has provided for an important tool for an improved diagnosis, risk stratification, and management of patients. Now, genetic testing for these disorders is viewed as a standard test that is clinically available and provides disease-specific diagnostic, prognostic, and therapeutic impact.

The fundamental pathogenic mechanisms responsible for these disorders have been elucidated at least in part and marked genetic and clinical heterogeneity is a common theme with multiple genes and allelic variants responsible for the underlying mechanisms discovered (http://www.fsm.it/cardmoc/). Phenotype-genotype correlations have exposed the distinguishing features of each genetic variant. Consequently, each channelopathy consists of multiple genetic forms that manifest with specific clinical characteristics. For example, LQTS is no longer thought of as a single disorder, but rather a family of multiple related disorders with a common feature of prolonged QT interval on a 12-lead surface electrocardiogram (ECG), yet have distinct characteristics in terms of severity, prognosis, risk stratification, and response to treatment depending on the underlying genetic cause [20].

Notably, the cardiac channelopathies necessitate a comprehensive approach that is not predicated *apriori* on a specific set of mutations. This stems from the fact that many families affected by a channelopathy have their own, private mutation not to be identified in another unrelated family. Until saturation of all possible disease-causing mutations is accomplished, conversion to diagnostic gene chips annotated with specific mutations will not be possible and a sequencing based approach as described above will be required.

Genetic Testing in a Clinical Versus Research Setting

Research studies are those in which patient samples are collected based on study design and inclusion or exclusion criteria. Research-based genetic tests are performed mostly for discovery

purposes and the advancement of science with direct benefit to the "research subject" as a secondary feature whereas commercial, clinical, fee-based genetic testing is a patient-centric test ordered by a referring physician based on his or her clinical index of suspicion and clinical objective to establish or refute a contemplated diagnosis, acquire further risk stratifying information, and guide clinical decision making [21]. An investigator's research program usually covers the cost of research testing. Research laboratories may be granted permission to inform a study participant of their genetic test result, in accordance with their institutional review board (IRB). Notably, research-derived test results are given primarily to the research subject rather than to his or her health care provider. When applicable, research laboratories usually quote research subjects 6–24 months as an "expected" time frame to learn of a positive result from examination of established disease-susceptibility genes and of course, an indefinite and indeterminate time frame when research testing is strictly focused on novel discovery. For some cases, several years may pass after submission of a blood sample, before the research participants become direct beneficiaries of the testing results. In some research environments, participants may never learn of either a positive or negative genetic test result. Genetic testing in the research setting often rely on in-house developed assays rather than on commercially available kits approved by the Food and Drug Administration (FDA) [22] and genetic tests are often available before analytical and clinical validity are reputable. Furthermore, quality control systems and "good laboratory practices" are not under the same strict guidelines and regulations of a clinical diagnostic test. Since quality control mechanisms are generally not in place in the research environment, mutation detection misses may be more likely to occur. Clinically definite cases reported as "negative" following research –laboratory based analysis may benefit from repeat testing in the clinical genetic testing environment.

In contrast, a clinical genetic test is a fee based test performed with the intent to inform both the health care provider and patient of the test result with a definite diagnostic, prognostic, and/or therapeutic end result in mind [21]. The clinical genetic test charge is typically based on the intricacy of the test and is usually proportional to the amount of genetic material being analyzed. In the United States, a clinical laboratory must be Clinical Laboratory Improvement Amendments (CLIA) approved and regulated by the Centers for Medicaid and Medicare Services (CMS) [23]. To be CLIA-approved, the genetic testing laboratory must meet quality control and proficiency testing standards in the accordance with "good laboratory practices". On-site inspections are performed to assure appropriate personnel qualifications, clinical testing procedures, and quality control measures and documentation.

A clinically available genetic test is usually a high throughput, automated, direct DNA sequencing based assay executed with two- to four-fold redundancy to maximize diagnostic accuracy. In contrast to the research laboratory setting, the clinical laboratory is typically a highly ordered environment with personnel in specifically designated roles to ensure highest efficiency and quality control measures of the genetic test. Results (both positive and negative) from the clinical genetic test are typically conveyed to the ordering physician in a written report within about 4–8 weeks for index case testing and 2–4 weeks for mutation specific confirmatory testing for family members.

Benefits of Genetic Testing for These Cardiac Conditions

Genetic testing may offer clear diagnostic, prognostic, and therapeutic implications for some disorders [24–26]. Genetic testing may (1) provide diagnostic value for symptomatic individuals by identifying the precise molecular basis for the disorder, (2) institute an authoritative molecular diagnosis or disease prediction when the clinical evaluation for the disorder is uncertain, (3) confirm or exclude the presence of a disease-causing mutation in pre-symptomatic relatives with a family history of the genetic disorder, and (4) assist in personalize treatment recommendations and management of a patient's specific disorder by characterization of the exact genotype [21, 27, 28].

Current Limitations in Genetic Testing for Arrhythmia Syndromes

Clinical genetic testing is increasingly becoming available for all of the heritable arrhythmia syndromes. Notably, the expected yield from genetic testing is disease-specific ranging from 25 to 30 % for BrS genetic testing to a 75 % yield for LQTS genetic testing. In the case of LQTS, approximately 25 % of families with strong clinical probability of LQTS will have a negative genetic test result. Therefore, it is vital to recognize that a negative test result can not fully exclude the diagnosis as a stand alone test. However, in cases where the clinical index of suspicion is intermediate at best, a negative test result may be used as another piece of impartial evidence that has failed to establish the diagnosis. Patients with a strong, unequivocal clinical phenotype for their respective disorder who have a "negative" genetic test ought to be informed of continued research efforts and directed towards research centers specializing in the study of their specific disorder. Continued genetic interrogation on a research basis of well phenotypically characterized patient cohorts will allow for new gene discovery and continued enhancement, expansion, and refinement of genetic testing in clinical practice.

Who Should Undergo Genetic Testing for Cardiac Channelopathies?

In 2011, two consensus documents, the Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) Expert Consensus Statement [29] and the Canadian Cardiovascular Society (CCS) /Canadian Heart Rhythm Society (CHRS) joint position paper [30] were published on the use of genetic testing in the clinical evaluation of cardiac channelopathies and cardiomyopathies. All patients or family members for whom a clinical diagnosis of a channelopathy is suspected should undergo genetic testing from either a commercially available test or via research laboratories depending on the suspected diagnosis. From a clinical test perspective, any patient and his or her first degree relatives with a suspected clinical diagnosis of LQTS or CPVT should be offered clinical genetic testing. LQTS and/or CPVT clinical genetic testing may also be warranted for patients with unexplained, exertional syncope who do not meet full diagnostic criteria for LQTS or CPVT. LQTS genetic testing for patients with drug-induced QT prolongation/torsade de pointes may also be warranted. Patients suspected of having BrS could undergo clinical genetic testing as long as it is recognized that the yield from the currently available test is approximately 20 %. In addition surviving relatives of an individual suffering a sudden unexplained death even in the setting of a negative family history of cardiac events may benefit from genetic testing. In CPVT and LQTS for example, the sudden death of relative may be the sentinel event in these potentially lethal familial disorders [6].

Interpretation of Genetic Testing Results

The patient and family suspected of having a cardiac channelopathy should be evaluated and managed by a heart rhythm specialist with specific expertise in this discipline. Because of issues associated with incomplete penetrance and variable expressivity, the results of the genetic test must be interpreted cautiously and incorporated into the overall diagnostic evaluation for these disorders. The assignment of a specific variant as a true pathogenic disease-causing mutation will require vigilant scrutiny, even when a genetic variant has been published previously as a putative pathogenic mutation. Without a doubt, genetic tests are fundamentally probabilistic tests rather than absolute binary (yes or no) deterministic ones.

If the cardiologist or cardiac channelologist lacks expertise with regard to the pathogenetic basis of these disorders, it may be beneficial to have a master's trained, board-certified genetic counselor as part of the team to be involved in the communication process with the patient concerning the implications of genetic testing and genetic test results. A genetic counselor may be invaluable in (1) collecting a family history comprising at least three-four generations, (2) providing information as to the clinical manifestation of the disorder, mode of inheritance, and implications in family planning, (3) explaining the benefits, limitations, risk, availability, costs,

and potential outcomes of genetic testing, and (4) discussing the possible psychosocial impact of these potentially lethal disorders with the patient and their family [31, 32]. However, given the multitude of genotype-phenotype considerations specific to these disorders, it seems reasonable to expect that the cardiologist/channelologist should be the primary physician responsible for directing the patient's care.

Family Matters – Ethical, Legal, and Societal Implications

Patients should be well informed on the implications of genetic testing and in no way should be coerced into providing a DNA sample for analysis. Full disclosure should be given as to the intent of either the research or clinical genetic test, the results of the analysis, and who will have access to the results. Genetic information should be considered private and personal information with the potential for mishandling [33, 34]. Disclosure of confidential information to third parties, such as insurance companies or employers can have consequences to the patient in the form of genetic discrimination. However, in May 2009, the Genetic Information Nondiscrimination Act (GINA) was signed into federal law preventing employers and health insurers from denying employment or insurance to a healthy individual based on genetic test results [35]. Notwithstanding this long-awaited advance, the law neglected to extend discriminatory protection over either life insurance or disability insurance.

Genetic testing is both a family and individual experience [36]. Although genetic testing is performed on genetic material isolated from an individual, the individual's decision to undergo genetic testing and the individual's test results may have profound implications for other family members, especially in those disorders associated with sudden cardiac death. Under current guidelines, only the index case or legal guardian, if the index case is a minor, may be informed of their genetic test results, and the decision/responsibility to inform unsuspecting relatives of the potential for genetic predisposition for sudden cardiac death, lies solely on the informed patient. To what degree moral or even legal obligation should be placed on the informed family member to be responsible for disclosing potentially life saving genetic information to uninformed and unaware relatives who maybe at risk for a potentially lethal cardiac event is debatable. For example, should an individual with a family history for sudden cardiac death be held accountable, if he/she has been informed of the identification of their family's LQTS mutation yet fails to inform a family member who subsequently experiences sudden cardiac death?

With the increase in availability of genetic testing, a wider distribution of the potential benefits such as certainty of diagnosis, increased psychological well-being, and greater awareness of prophylactic treatment and risk stratification may be achieved. However, it may also contribute to an increase in risks associated with genetic testing including depression, anxiety, guilt, stigmatization, discrimination, family conflict, and unnecessary or inappropriate use of risk-reducing strategies [36].

Conclusions

Advances in molecular medicine and genetic testing are propelling the field of cardiac electrophysiology rapidly into the post-genomic era of medicine. As novel genes are discovered, the compendium of available genetic tests will surely increase. To be sure, it is our hope that through the discovery of new underlying mechanisms of disease and further refinement of our existing knowledge of these genetic disorders, we can in the words of Dr. Charles W. Mayo, "heal the sick and advance the science".

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Part III
Risk Stratification of Sudden Cardiac Death in Acquired Clinical Conditions

Michael J. Ackerman, Brian D. Powell, Arthur A.M. Wilde, Win-Kuang Shen, and Ihor Gussak

M.J. Ackerman, MD, PhD, FACC
Department of Medicine, Division of Cardiovascular Diseases, Department of Pediatric and Adolescent Medicine, Division of Pediatric Cardiology,
Department of Molecular Pharmacology and Experimental Therapeutics,
Mayo Clinic, Rochester, MN, USA
e-mail: ackerman.michael@mayo.edu, haglund.carla@mayo.edu

B.D. Powell, MD
Division of Cardiovascular Diseases,
Sanger Heart & Vascular Institute,
Charlotte, NC, USA

A.A.M. Wilde, MD, PhD, FESC, FAHA
Department of Cardiology, Heart Center
Academic Medical Center, University of Amsterdam,
Meibergdreef 9, 1105 AZ,
Amsterdam, The Netherlands

W.-K. Shen, MD
Division of Cardiovascular Diseases,
Department of Medicine, Mayo Clinic College of Medicine, Mayo Clinic Arizona, Phoenix, AZ, USA
e-mail: wshen@mayo.edu

I. Gussak, MD, PhD, FACC
Ono Pharmaceutical USA,
Lawrenceville, NJ, USA

Department of Internal Medicine,
University of Medicine and Dentistry of New Jersey,
Robert Wood Johnson Medical School,
New Brunswick, NJ, USA
e-mail: igussak@hotmail.com

21
Introduction to Part Five: Screening for Risk of Sudden Cardiac Death

John B. Kostis

Abstract

Sudden cardiac death a clinical catastrophe that appears unpredictable in individual cases occurs in many clinical subsets described in this section of the book. The difficulty in identifying patients at increased risk derives from the reciprocal relationship between the risk in different patient subsets and the size of the subset. Screening methods must be evaluated from the points of view of sensitivity, specificity, positive and negative predictive values in the relevant subsets as well as from the point of view of cost effectiveness. Receiver operator characteristic curves may be used to compare screening methodologies and in deciding what decision criterion (cut-off) to be used.

Keywords

Receiver operator characteristic curves • Prediction • Risk stratification

The chapters included in this section address the issue of sudden cardiac death, primarily sudden arrhythmic death, from ten different perspectives varying from sudden cardiac death in infancy to clinical trials of sudden cardiac death prevention. Sudden cardiac death affects persons with cardiovascular disease most commonly cardiovascular disease such as coronary heart disease, heart failure and cardiomyopathies. However, sudden cardiac death may also occur unexpectedly in apparently healthy individuals. It terminates the life of the patient and degrades the quality of life of family and friends.

J.B. Kostis, MD
UMDNJ-Robert Wood Johnson Medical School,
Cardiovascular Institute,
125 Paterson Street, CAB-5200,
New Brunswick, NJ 08901, USA
e-mail: kostis@umdnj.edu

Identifying patients at increased risk for sudden cardiac death is difficult because of the reciprocal relationship between the risk in different patient subsets and the size of the subset. The size of the subset is an important determinant of the number of individuals who will be affected by this unforeseen clinical event. The reason for this is that the size of the population at low risk is much higher than the sizes of populations at high risk. Thus, although the risk of sudden cardiac death is higher among persons with severe cardiac disease especially in the presence of left ventricular dysfunction or among survivors of sudden cardiac death, there are many more sudden cardiac deaths among populations at low risk than among those at very high risk (Fig. 21.1).

Many screening strategies have been proposed with varying degree of success in optimizing their sensitivity and specificity and

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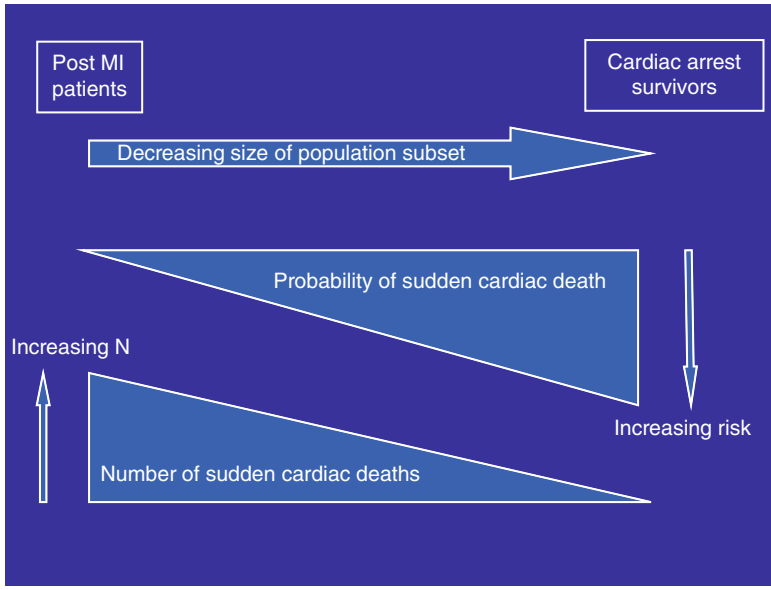

Figure 21–1. The inverse relationship between the probability of sudden cardiac death in a given subset of the population and the number of sudden cardiac deaths in that subset

many have been described in other chapters of this tome. Screening methods must be evaluated not only from the point of sensitivity and specificity and positive and negative predictive values in a given population but also from the point of view of cost effectiveness in terms of financial expense of screening, cost, adverse effects and clinical utility of potential preventive interventions, follow-up costs and inconvenience, labeling, insurability and emotional distress. Cost effectiveness studies "measuring" the dollar cost for a death prevented or for a given increase in quality adjusted life years have been reported. Most have limitations imposed by the perspective of the analysis, e.g. costs to patients, to the insurance companies, to society at large, opportunity cost of employed patients and especially in assuming utilities that have not been explicitly agreed upon by the society at large. Also, the findings of these analyses pertain to populations with similar characteristics to persons participating in clinical trials that pertain primarily to efficacy rather than effectiveness in the community. This caveat is not always stated in presentations and publications. The nature of the preventive strategy will affect this calculus. Efficacy and adverse effect profile are more important in anti-arrhythmic drug therapy while complications and financial issues are more relevant for device therapy.

Screening methods with 100 % sensitivity and 100 % specificity in predicting sudden cardiac death are not currently available. The interplay of sensitivity and specificity of the various screening strategies displayed as receiver operator characteristic curves can be used in deciding which diagnostic method and what decision criterion (cutoff) of the relevant variable to employ (Fig. 21.2). When the diagnostic screening technique is of low cost and has low rate of adverse effects, a cut-off of high sensitivity and, necessarily, low specificity can be used. This will result in identifying (and potentially treating) a large number of individuals at low risk of suffering sudden cardiac death. Treating such patients could be acceptable since the intervention is inexpensive and safe. On the other hand, most individuals destined to develop sudden cardiac death will be detected and treated due to the high sensitivity of the test. Alternatively, when the intervention is expensive and carries significant risk and adverse effects, a cut-off criterion of high specificity can be used. The high specificity will assure that only a small number of persons who will not develop sudden cardiac death will sustain the risk and

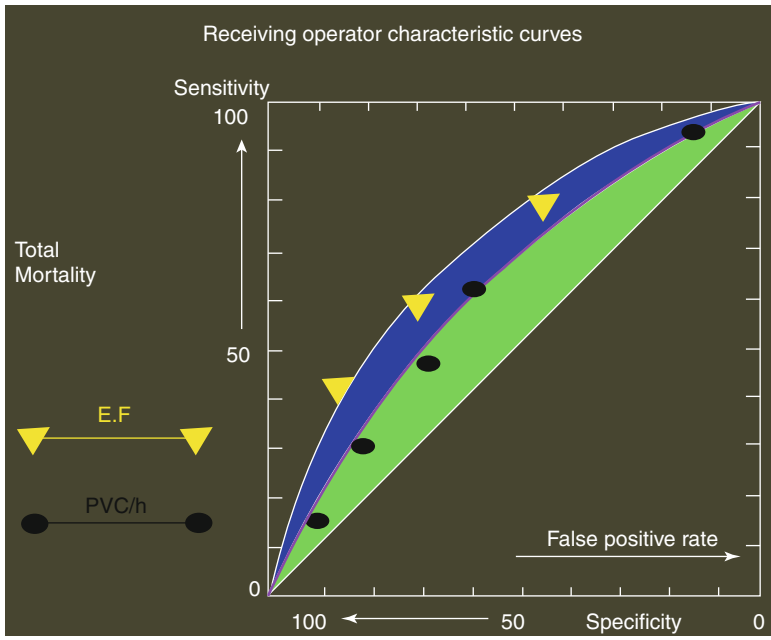

Figure 21–2. Receiver operator characteristic curves of ventricular ectopic activity (PVC/h) and ejection fraction (*EF*) in survivors of acute myocardial infarction. The EF carries more prognostic information

expense of the intervention. The price of this strategy is that the low sensitivity of the test will leave a significant proportion of those destined to develop sudden cardiac death uncovered. The relationship of sensitivity to specificity, expressed as a receiver operator characteristic curve (ROC), allows the choice of an appropriate decision criterion as discussed above, as well as the comparison of the utility of different screening methods. Figure 21.2 indicates that, among survivors of acute myocardial infarction, the value of the ejection fraction is a better predictor of sudden cardiac death than ambulatory electrocardiography. The combination of both increases specificity but degrades sensitivity.

The specific screening strategies that may be used in stratifying individuals for the risk of sudden cardiac death are determined in great part by the clinical suspicion in the individual person. In other words, initial stratification and categorization of patients for risk of sudden cardiac death and the selection of the relevant screening strategy is done on general clinical grounds. The authors of the ten chapters included in part V of this volume describe the state of the art in risk stratification and prevention of sudden cardiac death in different patient subsets. Most strategies are based on clinical factors including family history, the pathological substrate for serious arrhythmias such as myocardial hypertrophy, ventricular dilatation, fibrosis, myofiber disarray, coronary calcium score; the electrophysiological milieu including the channelopathies, the dynamics of QT interval, T-wave alternans, etc.; and on the presence triggering factors including the autonomic nervous system, ischemia, exercise, transient arrhythmias, etc. A plethora of procedures has been used for each of the factors mentioned above. Also, a combination of variables has been proposed including, in the case of coronary artery disease, low ejection fraction, ventricular ectopic activity, late potentials and heart rate variability. It must be kept in mind, however, that requiring that two or more tests be positive to classify an individual to a high risk category increases the specificity of the decision criterion (i.e. decreases the number of those not destined to have a cardiac arrest), at the expense of decreasing the sensitivity i.e. the number of individuals who will sustain sudden cardiac death who are not going to be identified by the combination of tests. In such situations,

the additive costs described above must be considered.

Estimation of the marginal improvement of the ROC curves can be used to compare the improvement in diagnostic efficacy to the additional cost and complexity of testing. Use of genetic screening whose price has decreased markedly may be very useful in identifying patient subsets with channelopathies and hereditary abnormalities of the contractile proteins where the risk may be high and may justify an intervention especially the presence of positive family history.

22
Risk Stratification for Sudden Death in Patients with Coronary Artery Disease

Emerson H. Liu, Lilian P. Joventino, and Alfred E. Buxton

Abstract

Approximately one-half of all deaths in patients with coronary artery disease occur suddenly and unexpectedly. The majority of these events appear to result from ventricular tachycardia or fibrillation. Although acute ischemia or infarction may precipitate such events, data suggest that a large proportion of these are not due to acute ischemic events. Rather, primary electrical phenomena that are a consequence of previous myocardial infarctions, such as intramyocardial reentry or other mechanisms, cause most of these events. These events usually occur without any apparent precipitating factor. While we have effective treatment for survivors of cardiac arrest, a minority of arrest victims survive the acute event. Thus, there is a need to identify patients at risk for these events before they occur, in order to institute prophylactic therapy.

Multiple tests to identify persons at risk for sudden death have been developed. No single test has been identified that has adequate sensitivity and specificity, when used by itself, because no test identifies patients at risk for all the various mechanisms that can cause sudden death. Increasing evidence suggests that the presence of multiple risk factors in an individual identifies persons at increased risk, while patients with only single risk factors, regardless of the specific factor, are at relatively low risk. However, at this time, the optimal combination of risk factors is not known. Also unknown is the optimal time for initial and repeat testing. Because of the progressive nature of coronary artery disease, tests will have to be repeated at intervals in patients with initial negative tests. Clinical trials are needed to define the best timing and combinations of tests.

E.H. Liu, MD
Cardiovascular Division, Medicine Department,
Beth Israel Deaconess Medical Center,
Harvard Medical School, West – Baker 4, 185 Pilgrim Road, Boston, MA 02215, USA
e-mail: ehliu@bidmc.harvard.edu

L.P. Joventino, MD
Department of Cardiology,
Wentworth-Douglass Hospital, Dover, NH, USA
e-mail: ljoventi@bidmc.harvard.edu,
lpjoventino@yahoo.com

A.E. Buxton, MD (✉)
Clinical Electrophysiology Laboratory,
Cardiovascular Division, Department of Medicine,
Beth Israel Deaconess Medical Center,
Harvard Medical School, West – Baker 4, 185 Pilgrim Road, Boston, MA 02215, USA
e-mail: abuxton@bidmc.harvard.edu

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Keywords
Sudden death • Cardiac arrest • Risk stratification • Ventricular tachycardia • Ventricular fibrillation

For many years it has been recognized that some persons with coronary artery disease are at increased risk for sudden cardiac death. This is especially true for survivors of acute myocardial infarction (MI), some of whom remain at considerable mortality risk for years [1]. However, it is important to remember that cardiac arrest may occur as the initial manifestation of coronary disease. In fact, 50 % of all cardiac arrests may occur as the initial manifestation of heart disease [2]. In these cases acute severe ischemia or acute infarction usually appears to be the cause, if the patient survives the event, and undergoes appropriate evaluation. It is also recognized that approximately half of deaths in patients with coronary disease occur suddenly and unexpectedly. Since the advent of telemetric ECG monitoring for patients with acute MI in the 1960s, ventricular tachycardia and fibrillation have been understood to precipitate most cardiac arrests after MI. However, recent studies have provided new insight into mechanisms underlying cardiac arrest in the early post-infarction period, demonstrating that not all such events are due to arrhythmias [3]. These events usually occur without any apparent precipitating factor. While we have effective treatment for survivors of cardiac arrest, a minority (2–30 %) of arrest victims survive the acute event [4–9]. Thus, there is considerable rationale to attempt primary prevention of cardiac arrest if we are to improve the overall survival of patients with coronary disease.

In order to carry out primary prevention of sudden death effectively, several requirements must be satisfied. First, the at-risk population must be identified. Second, we must understand mechanisms responsible for sudden death in the population in question. Third, based on our understanding of these mechanisms, practical tests must be developed that identify sub-populations possessing the substrate to support specific arrhythmia mechanisms. Finally, having identified those patients possessing risk factors, effective treatments, preferably specific for each arrhythmia mechanism, must be developed and applied.

The purpose of this chapter is to review the current status of the third factor – risk stratification tests – in patients with coronary heart disease. Tests to identify persons at risk for sudden death have been developed along several lines, and may be classified in different ways. For example, some tests are relatively non-specific, and identify patients with more advanced disease, thereby placing them at increased risk for non-sudden as well as sudden death. While such tests may be useful in identifying large populations at risk, employment of such tests alone is not likely to be very cost-effective, because by their very nature large numbers of patients will be treated who are not likely to benefit because their mortality risk may be due primarily to non-arrhythmic mechanisms. One example of such a test is measurement of left ventricular ejection fraction (EF), which is an excellent way to identify patients at increased overall mortality risk, but bears no direct relation to arrhythmia mechanisms. Patients with depressed EF are at increased for both sudden and non-sudden death, but the increase in risk of sudden death is proportional to the increased risk for non-sudden death. Thus, a test such as EF may be useful for identifying a high-risk population to enroll in a randomized trial to evaluate efficacy of a treatment, in which a large number of events is desirable. On the other hand, tests associated with risk for sudden death that is increased out of proportion to risk for non-sudden death are more likely to bear a cause and effect relation to mechanisms responsible for sudden death, rather than just an association with increased mortality, and therefore may be more cost-effective. Examples of the latter might include the signal-averaged ECG and programmed electrical stimulation of the ventricles.

Another way to classify risk stratification tests is to recognize that some identify relatively stable substrates that may cause cardiac arrhythmias by reentrant mechanisms. Examples of these would be the signal-averaged ECG, and programmed electrical stimulation performed during electrophysiologic studies. T wave alternans may also identify certain types of underlying electrophysiologic substrates. Other tests have been performed under the presumption that they identify factors that trigger or activate the substrate. Examples of this would be ambulatory ECG monitoring used to recognize frequent ventricular premature depolarizations or episodes of nonsustained ventricular tachycardia. The latter tests have not proven to be very helpful. Recognition that the interaction between presumed arrhythmia triggers and the substrate, or the "condition" of the substrate (its ability to be activated) may be modulated by alterations in autonomic nervous system tone led to development of other tests. The latter include measurement of heart rate variability and baroreflex sensitivity. These tests are thought to measure relative balance between parasympathetic and sympathetic tone. Autonomic nervous system function, specifically sympathetic cardiac innervation may also be evaluated by radionuclide scans such as Iodine-123 metaiodobenzylguanidine (MIBG).

Some general issues in risk stratification are worth considering before discussion of specific tests. It should be recognized that mechanisms of sudden death are dependent upon a variety of factors. These include the anatomic substrate – the presence, type and severity of structural heart disease. Even within the common anatomic substrate of ischemic heart disease mechanisms responsible for sudden death vary, depending on the presence or absence of myocardial infarction, size of infarct, compensatory responses of noninfarcted ventricular myocardium (such as hypertrophy), as well as coronary artery anatomy that may predispose to recurrent ischemia. Functional alterations, such as development of the syndrome of heart failure add other mechanisms that may precipitate cardiac arrest, when superimposed on the anatomic substrate. In addition, the fact that coronary disease is a progressive condition means that mechanisms responsible for sudden death in individuals may well evolve over time. The inescapable conclusion is that no one risk stratification test alone will be appropriate for all patients with coronary artery disease. Rather, one must screen for multiple potential mechanisms of sudden death, and some tests will require repetition at certain time intervals. However, the need to screen for multiple potential mechanisms does not necessarily equate with a need for multiple (expensive) tests. For example, much useful information may be gained from careful history and physical examination, screening for evidence of heart failure or symptomatic ischemia. In addition, measurement of a variety of risk variables may be accomplished by single tests. For example, a single (extended) exercise test might provide information regarding ischemia, the presence of T wave alternans, and spontaneous arrhythmias. A 24-h ambulatory monitor may provide information on spontaneous ventricular arrhythmia, T wave alternans, heart rate variability, and heart rate turbulence. Furthermore, a signal-averaged ECG might be coupled to either of these tests.

The fact that multiple tests have been developed since the 1970s (and continue to be developed) to evaluate risk of sudden death in survivors of MI is testimony to the failure to find one test suitable for all, or even a majority of patients. In addition to the multiplicity of potential mechanisms causing sudden death, we suspect that another source of fault in this area stems from the fact that most (although not all) exploration of this problem has been empiric, focused on identifying clinical factors associated with cardiac arrest or sudden death after MI, rather than having as the major focus attempting to understand mechanisms responsible for cardiac arrest and then developing tests that detect the presence of the substrates to support these mechanisms .

In the remainder of this chapter, we will review the various tests that have been developed, discussing their individual strengths and weaknesses. We will group tests into categories, based on whether they are thought to identify substrates for arrhythmias, triggers, or autonomic dysfunction, recognizing that there is likely to be overlap (i.e., an abnormality in autonomic function might constitute the substrate for some types of arrhythmia),

as well as disagreement. Another cautionary note is warranted at this point. Our focus in this chapter is identification of patients at risk for primary arrhythmic events precipitating cardiac arrest or sudden death. However, the importance of acute myocardial ischemia as a contributing factor to sudden death cannot be ignored. Multivessel, as opposed to single vessel coronary disease, has long been recognized as a marker for patients at increased mortality risk (though not specifically sudden death). Presumably this identifies patients having potential for recurrent ischemic events, in contrast to patients with single vessel disease who may experience a single large MI (that may form substrate for reentrant ventricular tachycardia) but have little potential for recurrent ischemia. Thus, we strongly advocate search for ischemia in MI survivors, and interventions to correct this whenever possible, prior to evaluation for primary electrical events. Indirect evidence to support beneficial effects of coronary revascularization were observed in the Coronary Artery Surgery Study, which demonstrated that the major beneficial effect of coronary bypass surgery on overall survival resulted from reduction in sudden death [10].

In this review, we have been careful to include reports from both the pre-thrombolyticera, as well as from more recent periods that include patients treated with thrombolytic therapy or primary angioplasty. The reason for this is that while reperfusion therapy certainly alters the natural history following acute MI, many patients today do not receive this therapy for a variety of reasons. We suspect that a major explanation for differing outcomes in the current era is the widespread, appropriate use of beta-adrenergic blocking agents and converting enzyme inhibitors or receptor blockers. It is important to realize that it is possible that patients with differing sets of risk factors may respond differently to these agents, and predictive properties of various risk factors may differ in patients who are treated with beta-adrenergic blocking agents [11]. Of note, results from the GISSI trials suggest that clinical variables traditionally associated with increased mortality retain their value in the presence of thrombolytic therapy [12].

Clinical Factors – Value of the History

Physicians often tend to place more weight on variables that require evaluation by specialized tests. However, it is good to keep in mind the value of factors obtained from a careful history. For example, history of previous MI has been repeatedly associated with poorer prognosis [12–14]. It has been recognized since the earliest studies evaluating mortality risk after MI that the presence of congestive heart failure during the initial hospitalization or later is associated with poor long-term prognosis [12, 15, 16]. Inability to perform an exercise test is also associated with poorer prognosis [12, 17]. Other variables available from the history associated poorer outcomes (both sudden and nonsudden death) include abnormal renal function, atrial fibrillation, and advanced age. It is important to recognize the limitation that all clinical variables evaluated to date lack specificity for differentiating patients at risk for sudden versus non-sudden death.

Standard 12 Lead Electrocardiogram

The standard ECG is attractive as a potential risk stratification tool because of its universal availability, low cost and reproducibility. It provides information on ventricular depolarization as well as repolarization. Depolarization abnormalities, such as QRS duration, have been demonstrated to relate to prognosis in both the pre-thrombolytic as well as post-thrombolytic eras [11, 15, 16]. This may be because widened QRS duration may reflect more advanced myocardial disease, and slowed conduction may also lead to dyssynchronous ventricular activation as well as dispersion of ventricular recovery, which may in turn promote ventricular arrhythmias. Autopsy evidence suggests a direct relation between QRS duration and myocardial fibrosis [18]. Studies of patients with recent MI suggested that both right bundle branch block (RBBB) and left bundle branch block (LBBB) are associated with increased risk [16]. However, the data are not uniform. A subgroup analysis from MUSTT involving predominantly patients

with remote MI found significantly increased risk in mortality for patients with LBBB or nonspecific intraventricular conduction delay (IVCD) but not in patients with RBBB [19]. Evidence to support a direct link between QRS duration or type of conduction abnormality and ventricular arrhythmias is limited. When stratified by QRS duration and intraventricular conduction abnormalities, subgroup analysis from the MADIT-II, MUSTT, and SCD-HeFT trials showed survival benefit from ICD therapy in patients with QRS duration >= 120 msec [20–22]. However, none of these trials were designed to address the impact of QRS duration in risk stratifying an ICD population. Also, no studies have shown that conduction abnormalities are specifically related to sudden, as opposed to non-sudden death. A substudy of patients with ICDs enrolled in the PainFREE Rx II trial demonstrated that the QRS duration was correlated with mortality (9 % for QRS ≤120 ms vs. 15 % for QRS >120 ms) but not ventricular tachycardia (VT) or ventricular fibrillation (VF) events [23].

Repolarization abnormalities have been used to prognosticate in two ways. First, the magnitude of ST segment deviation after MI has been related to late mortality, as well as risk for recurrent ischemic events [24, 25]. This relation has been examined primarily in patients with non-Q wave MI. Repolarization abnormalities have also been examined for their relation to primary arrhythmia-mediated sudden death. Most of these analyses have focused on the QT interval or QT dispersion, as measured by the maximal difference in the duration of the QT interval among leads recorded on the standard ECG. Proposed mechanisms to explain an increased mortality due to QT abnormalities include facilitation of premature or triggered action potentials, or spatial or temporal heterogeneity allowing functional reentry. QT abnormalities may also be manifestations of perturbations in autonomic tone. Nevertheless, the clinical utility of these repolarization metrics is presently unclear. While prolonged QT intervals are generally associated with increased risk, the data are conflicting, especially when excluding those with long-QT syndrome [26]. Additionally, only a few studies have specifically examined a coronary disease population, and specifically addressed risk for sudden cardiac death in relation to QTc prolongation [27, 28]. The Rotterdam prospective population based cohort study involving 7983 patient age 55 and older found that an abnormally prolonged QTc interval (>450 ms in men, >470 ms in women) was associated with a threefold increase in adjusted risk of sudden cardiac death [29]; the same Rotterdam study had previously reported adjusted hazard ratios of 1.8 and 1.7 for all-cause mortality and cardiac mortality, respectively, for the highest quartile of the heart-rate corrected QT interval compared to those in the lowest quartile [30]. Also, a meta-analysis of 23 observational studies determined the pooled Relative Risk estimates of the highest versus the lowest categories of QT-interval length to be 1.44 for sudden cardiac death, as compared to 1.35 for total mortality, 1.51 for cardiovascular mortality, and 1.71 for coronary heart disease mortality [31].

Current consensus holds that QT dispersion is not helpful in risk stratification, in part because of methodologic difficulties [32], as well as failure to identify at risk patients adequately [33]. Other studies have examined measures of the repolarization "gradient" (angle between depolarization and repolarization) [34], and duration of various components of the T wave [35]. Novel measures of dispersion of repolarization such as prolongation of the T-peak to T-end have been associated with SCD in the general population [36]. Unfortunately, while theoretically attractive, prospective evaluation of the performance of such measures has been disappointing [33]. The association between QT indices and SCD may further be complicated by incompletely elucidated genetic and racial factors. For example, common variations in NOS1AP (associated with QT interval abnormalities) are associated with increased risk of SCD in patients with CAD [37].

It is well established that myocardial hypertrophy in a variety of settings is linked to increased mortality, both sudden and non-sudden. The standard ECG is certainly not the gold standard for detection of left ventricular hypertrophy (LVH). However, LVH (detected by the ECG) has long been associated with

increased risk for SCD in hypertensive patients, as well as patients with CAD [38–40]. In light of this, it is interesting that a substudy of the MUSTT trial noted a significant relation between mortality after remote MI and LVH detected on the ECG [19]. This analysis assumes even more interest because the risk of sudden death was increased out of proportion to the increase in total mortality observed in patients with LVH. Thus, LVH probably deserves more attention as a contributor to risk of SCD in patients with CAD.

Left Ventricular Ejection Fraction

Since the earliest investigations of mortality after MI, abnormalities of left ventricular function have been associated with risk for sudden and non-sudden death [41]. Ejection fraction has repeatedly been one of the most powerful and consistent risk stratifiers for mortality, in both the pre-thrombolytic as well as the reperfusion era [14, 42, 43], and its widespread application has been facilitated by its accessibility and ease of interpretation. As a result, low EF has been used as a major determinant for inclusion in clinical trials of post-infarction patients evaluating newer therapies such as implantable cardioverter/defibrillators [44–46]. An analysis of 20 studies comprising 7294 patients found that a postinfarction EF ≤ 0.30–0.40 had a mean sensitivity of only 59.1 %, a mean specificity of 77.8 %, and conferred a relative risk of 4.3 for major arrhythmic events [47]. However, while a low EF is associated with increased risk for sudden death, there is no evidence that there is any causal relationship between low EF and sudden death (the increase in total mortality parallels the increase in sudden death risk) [48].

Using EF has a number of other practical limitations. Guidelines incorporating low EF as a risk stratification tool are largely based on two pivotal trials – MADIT II used an EF ≤ 0.30 in patients with CAD as the sole inclusion criteria, and SCD-HEFT used an LVEF ≤ 0.35 in patients with nonischemic or ischemic cardiomyopathy with NYHA functional class II or III. The reliance on a single cut-off value for therapeutic decisions (or in the design of clinical trials) may obscure the fact that the risk distribution for SCD is continuous rather than dichotomous. Thus, this approach fails to account for the biologic basis of the process. Most prospective analyses of EF as a continuous variable show that the breakpoint at which mortality risk begins to increase is 0.40 [14]. Death due to arrhythmias in stable heart failure patients enrolled in the Digitalis Investigation group trial, a majority of whom had prior MI, increased linearly for patients with an EF ≤ 0.45 [49].

Secondly, although risk stratification based on EF identifies the highest risk patients, it paradoxically excludes the majority of events that actually occur in the larger but lower risk group of patients with EF > 0.3. This holds true for both post-MI patients, as well as population-based studies of out-of-hospital arrests [50]. Data from the Maastricht Circulatory Arrest Registry show that 56.5 % of SCD victims had an LVEF >0.30, and 20 % had a LVEF >0.50 [51]. Importantly, the proportion of patients surviving acute MI with low EF is declining. A recent multicenter observational study in Japan revealed that 83 % of consecutive patients surviving acute MI in the PCI era had EF > 0.40, and 95 % had EF > 0.30 [52]. Thus, use of EF as a primary, or exclusive risk stratification instrument is compromised by poor sensitivity, which ranges from 50 to 60 % in most studies [47, 53]. That most sudden deaths occur in patients deemed to be at "lower risk" by virtue of their EFs ultimately limits its more general utility. Conversely, a low EF might be a good tool to identify high-risk populations to test efficacy and safety of an intervention.

There are additional potential ambiguities in using a low EF to guide decisions about therapeutic interventions such as ICD implantation. As noted above, the EF alone does not provide insight into how patients are likely to die (sudden versus non-sudden). Also, despite an emphasis on strict EF cut-offs by current guidelines, further examination of the MUSTT Study suggested that multiple variables in addition to LV dysfunction (such as functional class, history of heart failure, inducible VT, NSVT, age and presence of atrial fibrillation) modify risk such that some patients with EF > 0.30 may be at higher risk of sudden death than some patients with EF ≤ 0.30 [21].

Given a need to dichotomize risk categories, however, the timing of EF determinations (either

once or serially) may also be relevant. There is likely considerable variability in measurements depending on temporal biologic fluctuations, such as volume status or autonomic factors, as well as issues with consistency in technique and interpretation. In one study, LV function determined by a single observer even in clinically stable patients demonstrated a 6.4 ± 8.9 % variation over sequential echocardiograms [54]. Utility of EF measured within the first month after MI may be limited by competing causes of mortality [3]. This may account for the lack of prognostic utility for measurements made early after MI [55].

Spontaneous Ventricular Ectopy and Non-sustained Ventricular Tachycardia

Multiple studies in the pre-thrombolytic era have demonstrated an adverse prognostic significance attached to frequent premature ventricular complexes (VPCs, usually defined as >10 VPCs per hour on average over a 24 h period) and non-sustained ventricular tachycardia (NSVT) documented after recent (10 days – 3 months) MI [43, 56–58]. The occurrence of NSVT within 1 month of MI more than doubles the risk of subsequent sudden death. Non-sustained ventricular tachycardia detected 3 months to 1 year post-myocardial infarction is also associated with a significantly higher mortality rate [59, 60]. Furthermore, frequent VPCs documented 1 year after MI have predicted increased mortality over the subsequent 2 years [59]. Interestingly, while frequent ectopy has remained an independent marker of adverse prognosis after acute MI, the prognostic significance of NSVT is more ambiguous in the context of current therapies. With reperfusion and use of beta-blockers, NSVT after MI has not always been demonstrated to predict mortality, particularly after EF is taken into account, since spontaneous NSVT has traditionally had adverse prognostic significance only in patients with EF ≤ 0.40 [43, 61]. Part of the explanation may also relate to the low frequency with which spontaneous NSVT is detected in patients that have received reperfusion therapy [62]. The sensitivity for prediction of arrhythmic events of spontaneous ventricular arrhythmias on Holter monitoring was only 43 % in one comprehensive meta-analysis [47].

The presence of NSVT and frequent VPCs after MI has been associated with mortality, but not specifically to the risk of sudden death. In one large observational study of 2,130 AMI patients, NSVT on 24 h electrocardiographic recordings predicted SCD with a hazard ratio of 2.9, but also predicted non-SCD with a hazard ratio of 2.3 [63]. More recently, in the MERLIN-TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 36) trial, NSVT lasting ≥4 beats was common (25.3 % subjects) and if occurring more than 48 h after admission, related to a significantly increased risk of SCD at 1 year with an adjusted hazard ratio of >2 ($p < 0.001$), independent of EF [64]. The explanation for the positive association between NSVT and SCD in this trial in comparison to other recent trials, may be accounted for by the 1 week of continuous ECG monitoring used in this trial, versus 24–48 h in earlier trials. Interestingly, greater than 90 % of subjects for whom an echocardiogram was available had EF > 0.40, and it may be that NSVT has greater value in predicting risk in patients with less abnormal ventricular function. One limitation to understanding the significance of this finding is the absence of total mortality data in this substudy. Thus, we do not know whether the risk for SCD in patients with NSVT was increased more than the risk for non-SCD. Whether NSVT is causally related to SCD or is instead a marker for other risk factors, such as an arrhythmogenic substrate or autonomic dysregulation, is not clear. Importantly, there has not been demonstrated improvement in clinical outcomes with attempted arrhythmia suppression in any pharmacologic trials, including ranolazine in MERLIN-TIMI 36 as well as encainide and flecainide in CAST (Cardiac Arrhythmia Suppression Trial).

Signal-Averaged Electrocardiography

The signal-averaged electrocardiogram (SAECG) has been used to detect late potentials, which are high frequency, low amplitude signals at the terminal portion of the QRS that correlate with

local areas of slow, delayed activation after MI. Signal averaging is used to reduce noise to allow for high gain amplification and filtering of surface ECG signals. Common measures of abnormal late potentials include (1) a total QRS duration greater than 114 ms, (2) a low amplitude signal less than 40 μV greater than 38 ms in duration, and (3) a root mean squared voltage of the terminal 40 ms of the QRS that is less than 20 μV. Multiple studies have examined the prognostic significance of the SAECG alone and in combination with other tests, such as ambulatory electrocardiographic monitoring and measurement of EF after acute MI [65–69]. A majority of the studies have utilized time domain rather than frequency domain analysis of signals. In these studies, sensitivity has averaged 62 % for prediction of sudden death or spontaneous sustained ventricular tachycardia, during follow-up periods of 6–24 months. Its primary benefit in these reports appears to be the ability to identify patients at low risk for developing arrhythmic events, with reported negative predictive values in the neighborhood of 95 % [47]. The high negative predictive values are partly related to low event rates. Similarly, low event rates are also reflected in low positive predictive accuracies that range from 7 to 35 % (7 and 17 % in the two largest studies) [47]. As the SAECG was developed in an attempt to specifically detect the presence of one of the requisites for reentrant ventricular tachycardia (slow conduction) in abnormal substrates, a positive SAECG should theoretically predict with good specificity those patients at risk for arrhythmic, as opposed to non-arrhythmic mortality. However, the actual specificity of the SAECG for prediction of sudden death is difficult to determine, as many of the studies report composite outcomes of sudden death or cardiac arrest with sustained ventricular tachycardia. Most reports have also not provided the rates of non-sudden cardiac deaths in patients with abnormal SAECGs. Notably the MUSTT study (Multicenter UnSustained Tachycardia Trial) showed that the risk for sudden death significantly exceeded the risk of non-sudden death in patients with an abnormal SAECG [70]; patients with an abnormal SAECG had a greater increase in the 5-year rate of arrhythmic death (28 % vs 17 %, $p < 0.01$) than in all-cause mortality (43 % vs 35 %, $p < 0.01$) as compared to those with a normal SAECG. Greater specificity may ultimately be compromised by the fact that not all areas of delayed activation serve as substrates for reentry; larger infarcts, though more likely to give rise to reentrant ventricular tachycardia circuits, may also be more likely to result in "dead end" or bystander areas of delayed activation that do not participate in reentry [71]. Conversely, low amplitude signals representing areas of scar may occur earlier rather than as late potentials, and be obscured by within the QRS complex.

In a series of patients studied after coronary artery bypass surgery, abnormal SAECGs were present in 27 % of patients postoperatively, but did not predict SCD [72]. Additional limitations include a lack of standards to defining a normal SAECG in patients with bundle branch block; most studies have excluded patients with bundle branch block from analyses.

In light of the pathophysiologic relationship between underlying conduction abnormalities in infarcted substrate to subsequent arrhythmic events, it is noteworthy that the presence and degree of SAECG abnormalities are affected very favorably by thrombolytic therapy and mechanical reperfusion early after acute MI [73–75]. The reduction in frequency of late potentials is directly related to patency of the infarct related artery [76, 77]. In summary, despite potential prognostic value, routine use of the SAECG in clinical practice has been hampered (appropriately) by a lack of prospective studies demonstrating clear utility. As with most other risk factors, until a clinical trial is performed demonstrating that antiarrhythmic therapy guided by results of the SAECG results in improved outcome of a group of patients, its routine use in practice cannot be justified.

Electrophysiologic Testing (Programmed Electrical Stimulation)

Programmed ventricular stimulation was initially developed in the early 1970s as a technique to study mechanisms of monomorphic ventricular tachycardia occurring spontaneously

after MI. Initial studies demonstrated that programmed stimulation could reproduce spontaneous sustained monomorphic ventricular tachycardia (VT) in >90 % of patients with spontaneous sustained VT [78]. The technique was then applied to patients who had been resuscitated from cardiac arrest [79, 80]. Cardiac arrest survivors differed from patients presenting with stable sustained ventricular tachycardia in a number of respects, including the fact that monomorphic sustained VT was inducible in only 30–40 % of cases. Programmed stimulation was then tested as a tool for risk stratification to predict sudden death after MI, with the reasoning that inducibility of VT with invasive electrophysiological testing would identify patients whose diseased myocardium could sustain either monomorphic VT precipitating cardiac arrest, or re-entrant ventricular arrhythmias that subsequently degenerate into VF and cause sudden death. The group at Johns Hopkins first reported on this, using as an endpoint induction of repetitive ventricular responses [81]. A number of other laboratories then applied programmed stimulation, using induction of sustained VT as the endpoint in most cases [82–88], to demonstrate a link between sustained monomorphic VT and subsequent cardiac death. Sustained monomorphic VT was inducible in 6–30 % of patients, with ventricular fibrillation or polymorphic VT inducible in fewer patients. Risk varied with the type of induced arrhythmia; inducible VT with very short cycle lengths (<250 ms) was associated with significantly lower likelihood of cardiac arrest than VT with cycle length >250 ms.

These early, small, single center studies provided the rationale for the Multicenter UnSustained Tachycardia Trial. This large (2,202 patients) trial remains the only large scale prospective evaluation of the utility of programmed stimulation to risk stratify post-MI patients [89]. Inclusion criteria included LVEF ≤ 0.40 in patients with coronary artery disease, and asymptomatic unsustained ventricular tachycardia. Following publication of the initial MUSTT results on EP-guided therapy, subsequent analyses reported on the outcomes of inducible patients in the trial who received no therapy compared to patients with a negative EP study. The 2 and 5-year rates of arrhythmic death or cardiac arrest were 18 and 32 %, respectively, in inducible patients (not treated with antiarrhythmic therapy). These SCD rates were significantly higher when compared with 12 and 24 % rates of SCD in non-inducible patients. While the presence of inducible sustained VT was associated with significantly increased total mortality as well, the risk for sudden death significantly exceeded the risk for total mortality in patients with inducible VT, supporting the specificity of inducible VT for predicting arrhythmic events. Of note, the relative risk of sudden death exceeded the relative risk of non-sudden death only for patients with an EF of 0.30–0.40, and not for patients with EF < 0.30, possibly because of greater heart failure in the patients with lower EF [48].

A substudy of the MADIT II trial provided further data on the predictive value of the EP study [90]. MADIT II randomized 1,232 patients with prior MI and LVEF ≤ 0.30 to ICD versus conventional medical therapy, and 593 of 720 patients in the ICD arm underwent elective EP study. This MADIT II substudy revealed that inducibility of sustained monomorphic VT (as a more narrow definition of inducibility not including VF) on EP study significantly enhanced the likelihood for future development of both VT (hazard ratio 1.89) and VT or VF (hazard ratio 1.56), but not VF.

The MUSTT and MADIT data provide rationale for current guidelines that find EP testing reasonable for patients with remote MI, NSVT, and LVEF equal to or less than 0.40. However, the wide range of reported sensitivities (between 28 and 80 %) in various reports makes it inadequate for routine use in isolation, without other risk stratification tests. This of course, is true for every risk factor studied to date. Differences in the reported prognostic significance of inducible ventricular tachyarrhythmias is likely in part due to variations in study populations, timing of study in relation to MI (5 days to many months after MI), stimulation protocols, as well as use of pharmacologic antiarrhythmic therapy. Protocols limited to ≤2 extrastimuli result in lower rates of inducible tachycardias as well as lower sensitivity [87, 91]. Studies that used ≥3 extrastimuli and follow-up of ≥1 year reported arrhythmic event rates of 25–36 % in

patients with inducible sustained VT [88, 92]. Importantly, in one study of 360 patients surviving STEMI who had EF≤0.40 and underwent early EPS, 29 % of patients with a positive EPS required a 4th extrastimulus to induce VT [93]. These patients had an arrhythmic event rate comparable that of patients induced with two or three extrastimuli. An Australian group reported results in over 1200 patients followed for at least 2 years [92]. This study demonstrated that patients with only polymorphic ventricular tachycardia (cycle length <230 ms) or ventricular fibrillation induced had no higher risk of arrhythmic events than patients without any induced arrhythmia [94]. This is consistent with most data that suggest induced polymorphic VT and VF are not associated with a high risk for cardiac arrest or sudden death. In all the studies, the reported negative predictive value of programmed stimulation was approximately 97 %, and the combined sensitivity approximated 62 % for prediction of major arrhythmic events [47].

The timing of EP study may be important. Sustained monomorphic ventricular tachycardia, especially in patients with coronary artery disease, can be reproducibly initiated on electrophysiology studies over time [91, 95]. Short (day to day, week to week) and long term (8 months) reproducibility of inducible VT averages 80 %, and is significantly greater for slower (cycle length >240 ms) induced tachycardias [91, 96–99]. Interestingly, programmed stimulation when applied to small numbers of patients with remote (average 3 years after) MI having spontaneous NSVT [100–103] induced sustained VT in 40–45 % of patients studied. The increase in the percent of patients having inducible VT in comparison with those studied early after infarction is noteworthy. Arrhythmic events (sudden death, resuscitated cardiac arrest, or sustained ventricular tachycardia) occurred in 12.5–23 % of patients with inducible VT after 14–30 months, while only 4–12 % of patients without inducible sustained VT experienced events. Almost all events occurred in patients with EF≤0.40. Taken together, these data support the ideal that areas of myocardial scar in patients with chronic ischemic heart disease not only form a stable substrate for ventricular arrhythmias over time, but that the substrate can evolve to be more arrhythmogenic over time.

Finally, reported outcomes of prior studies need to be interpreted in the context of contemporary management. Patients who have received thrombolytic therapy have lower rates of inducible VT, ranging from 0 to 10 % in streptokinase-treated patients versus 12–74 % in untreated patients [104, 105]. In contrast, a more recent study did not find any differences in the rate of inducible VT in patients treated with thrombolysis or primary angioplasty for ST-elevation MIs, with EF < 0.40 [106]. Changes in medical management may also alter background risk. For example, only 35–51 % of patients in MUSTT received a β-blocker at discharge, which would likely have increased the rates of SCD over that expected with contemporary medical treatment.

In summary, EPS can discriminate between patients at relatively high versus low risk for sudden cardiac death. However, its clinical utility is limited by moderate sensitivity as well as its invasive nature. As such, its primary role may be to further refine risk assessment not as an initial screening tool, but in conjunction with or in the setting of equivocal results from other noninvasive risk stratifiers.

T Wave Alternans

T wave alternans (TWA) refers to the variability in amplitude, width or morphology of the T-wave in alternate beats on the surface ECG [107]. This phenomenon is thought to reflect temporal and/or spatial heterogeneity of ventricular repolarization, which may create a substrate for microreentry. Repolarization is perturbed on the single cell level due to alternations in intracellular calcium cycling in a rate dependent manner [108]. The beat-to-beat fluctuation in the T wave amplitude can be detected at the microvolt level with digital processing techniques. TWA may be detected in normal persons with sufficient elevation of the heart rate. The most common definition of abnormal TWA is the presence of >1.9 μV of alternans starting at a heart rate <110 beats/min. TWA has been measured using at least two methods: the spectral

method uses fast Fourier transformation during an increase in heart rate, and provides a binary result; positive or negative (indeterminate values also result frequently from inability to elevate the heart rate sufficiently). Measurement of microvolt T wave alternans (MTWA) can be assessed during exercise or during atrial pacing, although one study suggested that exercise-induced alternans is superior for prediction of risk [109]. A newer method quantifies the magnitude of alternans using the modified moving average (MMA) technique, and does not require an increase in heart rate. Measurements are usually made from a continuous (ambulatory) ECG recording [110]. Both of these techniques appear to be valid [111].

Microvolt TWA has been linked to increased susceptibility for development of ventricular tachyarrhythmias in patients with coronary artery disease, congestive heart failure and other cardiac conditions [112–118]. The presence of abnormal TWA has been correlated to inducibility of ventricular arrhythmias on electrophysiology study (EPS) in patients that have already experienced spontaneous VT [116], as well as in patients without prior tachyarrhythmias. A meta-analysis combining data from 19 studies comprising 2,608 patients demonstrated a four-fold increased risk for arrhythmic events associated with abnormal TWA, with a negative predictive value of 97.2 % [119]. Notably, the positive predictive value varied widely depending on specific subgroup characteristics, and ranged from 6.0 % in the post-MI subgroup to 29.7 % in the "ischemic CHF" subgroup. In several observational cohort studies, the positive predictive value of TWA has been comparable to other markers of increased risk of arrhythmic death such as EPS, LVEF, SAECG, baroreflex sensitivity, and heart rate variability [112, 115, 117].

The ABCD (Alternans Before Cardioverter Defibrillator) trial was a prospective primary prevention non-inferiority study comparing the performance of TWA to EPS to risk stratify post-MI patients with decreased left ventricular systolic function (EF≤0.40) and spontaneous NSVT [120]. Using a composite endpoint of sudden death or "appropriate" defibrillator discharge, TWA and EPS had similar predictive power at a median follow-up of 1.9 years; the predictive accuracy of TWA appeared superior at 1 year, whereas EPS was superior at 2 years. Of note, there was only 45 % concordance between the tests, suggesting that they measure different factors. This is supported by the observation that the two tests provided complementary predictive value; patients with negative or positive results on both tests had significantly lower and higher event rates, respectively, than patients with only one test positive.

A major limitation of most of the studies that have compared performance of TWA to other tests has been inclusion of patients with multiple types of underlying heart disease (as well as no structural heart disease), and the fact that the majority of patients included in these reports had already experienced symptomatic and/or spontaneous sustained ventricular tachycardia or fibrillation. One exception is a report from Germany of 107 patients with heart failure, of whom 67 had coronary disease [114]. In this analysis, TWA proved superior to EF, NSVT, BRS, HRV and SAECG for prediction of arrhythmic events over a mean follow-up of 15 months. As with other risk factors, the utility of TWA is enhanced when combined with additional risk predictors. The REFINE study evaluated the utility of TWA in predicting arrhythmic events in patients with recent MI and varying degrees of left ventricular dysfunction (LVEF≤0.50) [55]. These investigators found that abnormal TWA measured 10–14 weeks (but not 2–4 weeks) following MI, in combination with impaired autonomic tone, identified patients at risk of cardiovascular death, resuscitated cardiac arrest, and all-cause mortality [55].

Despite several reports linking TWA to risk, some recent data are contradictory, and raise questions about the clinical application of MTWA. In the first prospective evaluation of TWA to predict arrhythmia vulnerability, the Sudden Cardiac Death in Heart Failure Trial (SCD-Heft) Investigators did not find that TWA in a subset of 490 patients predicted either life-threatening ventricular arrhythmias, appropriate shocks, or all-cause mortality [121]. Of note, 41 % of that population had an indeterminate TWA study, severely limiting applicability. In another recent prospective study in patients who met MADIT II criteria for ICD implantation

(prior MI and LVEF ≤ 0.30), MTWA classification did not predict patients experiencing the composite endpoint of arrhythmic death or "appropriate" defibrillator shock over 3-year follow-up [122].

Taken together, it is difficult to make firm conclusions regarding the utility of TWA for prediction of arrhythmic death. Both the SCD-Heft substudy and MASTER trial used ICD shocks as surrogates for arrhythmic mortality, which may not be sufficiently specific as endpoints. Other studies have enrolled mixed patient populations, including those without structural heart disease, non-infarct related cardiomyopathies, as well as coronary disease. The majority of these studies examined TWA in patients with LV dysfunction, for which heart failure poses many competing non-arrhythmic risks. An interesting result was observed in a Japanese study that evaluated MTWA in 1,041 post-MI patients with EF ≥ −0.40 [123]. These investigators demonstrated a low incidence of indeterminate results (10 %), as well as a hazard ratio of 19.7 for arrhythmic events. In this study no patients with indeterminate tests experienced an arrhythmic event, and <1 % of patients with negative TWA experienced an arrhythmic event. However, the positive predictive value of the test was relatively low (9 %).

In contrast, the absence of TWA (negative test) confers a very low risk of sudden death due to its high negative predictive value [118, 119, 124, 125]. Therefore the most valuable role of TWA testing in risk stratification may prove to be its ability to identify, out of a group thought to be at high risk of sudden death, patients who are at a particularly low risk of arrhythmic events and who may therefore not benefit from implantation of an ICD. The ideal timing to assess for the presence of TWA is not yet established, and likely needs to take into account the changing disease states of specific patient subgroups. As suggested by the REFINE trial, early assessment of TWA following a myocardial infarction does not seem to be helpful [55]. Similarly, in a prospective study of 379 post-MI patients in whom the presence of TWA was assessed prior to hospital discharge [126], 56 patients had a positive TWA test. Over a 14-month follow-up period, 26 patients died, all of whom had negative TWA tests.

A major limitation of TWA has been the high percentage of indeterminate results when using the spectral method. Indeterminate tests can be due to atrial fibrillation, frequent VPCs, or inability to augment heart rate adequately with exercise. Consequently some initial prospective studies had difficulty attaining statistical significance when excluding those with indeterminate results. In a multicenter study of 549 patients with LVEF ≤0.40 [118], the 2-year event rate (nonfatal sustained ventricular tachyarrhythmias or total mortality) was 12.3 % for patients with a positive TWA test (162/549), 17.5 % for patients with an indeterminate test (198/549), and 2.5 % for patients with a negative test (189/549) (Hazard ratio for an abnormal (indeterminate or positive) test result = 6.5). Of note, more patients had indeterminate than positive tests, and the mortality was higher for patients with indeterminate versus positive tests. This should not be surprising, since the factors causing indeterminate tests all reflect how sick the population is. It is not clear whether further attempts to refine test characteristics or interpretation will be useful, when using the spectral method. These limitations may not occur when using the modified moving average technique. Ultimately all these considerations will need additional clinical validation.

Measures of Abnormalities in Autonomic Nervous System Tone

Heart Rate Variability

Autonomic tone, and in particular excess sympathetic or deficient parasympathetic tone, has been correlated with increased propensity for arrhythmias during ischemia as well as increased mortality in post-MI patients due to both sudden and non-sudden cardiac death. Heart rate variability (HRV) measures the beat-to-beat variation in resting sinus rates as a reflection of the balance between sympathetic and parasympathetic input to the sinus node, which is then used as a surrogate for the autonomic effects in the ventricle that might modulate the development of VT or VF in susceptible substrates.

Heart rate variability is due to high frequency (0.15–0.45 Hz) and low frequency (0.04–0.15 Hz) periodic oscillations in sinus rate [127]. High frequency oscillations are primarily a result of sinus arrhythmia due to respiratory variation, which is primarily determined by parasympathetic tone. Conversely, sympathetic activity contributes significantly to low frequency oscillations. Additional factors that contribute to the genesis of HRV and its relation to resting heart rate remain incompletely understood. HRV is additionally influenced by variables such as age, gender, and medications (e.g. thrombolysis, antiarrhythmics, β-blockers, and ACE inhibitors) [128, 129]. Nevertheless, the underlying premise is that increased HRV reflects greater relative degrees of parasympathetic tone.

HRV can be expressed in several ways: as time domain measures, frequency domain measures, and non-linear measures. Common measures available from 24-h ambulatory ECG recording include standard deviation of NN (SDNN) intervals which may be obtained over a 24-h period or over a few minutes (short term HRV), SDANN which is the standard deviation of the average NN intervals for the 288 5-min intervals in a 24-h ECG recording, pNN50 which is the percent NN intervals >50 ms different from the prior interval, rMSSD which is the root mean square of differences between successive NN intervals, and total power, ultra-low frequency (ULF) power, very low frequency (VLF) power, low frequency (LF) power, high frequency (HF) power, and the ratio of LF/HF. Most data are based on long-term (24-h) ECG recordings.

Both short and long term heart rate variability have been studied with respect to mortality risk, and most studies suggest a similar prognostic ability. Short term HRV (generally assessed over 2–8 min) has been assessed in patients with coronary artery disease and heart failure with regard to mortality risk. Long term HRV is assessed on 24-h ambulatory ECG recordings, and several studies have reported a two- to fivefold increased risk of death in post-MI patients with decreased long term HRV [130–135].

HRV decreases during the early phase of AMI, and begins to normalize in 6–12 weeks [136, 137]. Initial reports suggested a link between reduced HRV and increased mortality following MI. In the Multicenter Postinfarction Study (MPS) Holter tapes of 808 patients who survived AMI were analyzed [130]. The relative mortality risk was 5.3 times higher in the group with HR variability of less than 50 ms than the group with HR variability of more than 100 ms. Importantly, however, many of these studies were performed prior to current reperfusion therapy. One study has noted improved HRV in patients treated by primary PCI than by fibrinolysis or conservative management [138].

In patients with heart failure, diminished low frequency power is associated with a fivefold increase in arrhythmic mortality in multivariate analysis [139]. In the same study, the combination of normal low frequency oscillations in short term HRV and the absence of frequent isolated ventricular premature complexes (<86/h) conferred a very low risk of sudden death (3 % compared to 23 %).

The use of HRV to predict SCD in CAD populations is less well established, and the majority of studies show no significant difference between the relative risks for SCD and for total mortality. In a consecutive series of 700 patients with AMI and treated with beta-blockers, HRV measured on 24-h recordings within 2 weeks did not separate those patients who subsequently experienced SCD or an arrhythmic event from those who died nonsuddenly [11]. A large trial designed to evaluate the effects of an antiarrhythmic drug, azimilide, on survival in 3,717 patients with left ventricular systolic dysfunction following a myocardial infarction also reported on the prognostic importance of HRV in separating patients into low- and high-risk groups. It showed a hazard ratio of 1.46 for all-cause mortality in patients with low HRV. However, no significant increase in arrhythmic death was associated with abnormal HRV [135].

When compared to other markers of autonomic dysfunction, HRV appears to not discriminate as well. The ATRAMI study, which followed 1,284 patients with recent MI (<28 days), demonstrated a relative risk of 3.2 for mortality in patients with decreased HRV, independent of LVEF and ventricular ectopy [140]. However, HRV did not discriminate risk for arrhythmic events as well as baroreceptor sensitivity.

Likewise, a German study of 1,455 patients after MI found that deceleration capacity based on 24-h Holter measurements was a stronger predictor of mortality than measures of HRV [141].

In general, long term HRV seems to be superior to short term HRV in predicting risk. As HRV seems to be a better marker of non-arrhythmic mortality, it is not clear whether HRV has any useful a role for specific prediction of SCD risk. Additional limitations include its inability to assess patients with atrial fibrillation or frequent PVCs, and possible confounding factors as with medications, functional state of the sinus node, or patient activity.

Baroreceptor Sensitivity

Baroreflex sensitivity (BRS) reflects the relationship between heart rate (RR intervals) and changes in blood pressure. This relationship is usually measured after administration of a bolus of phenylephrine. The increase in blood pressure which accompanies its administration normally produces a reflex slowing of heart rate. Several studies have demonstrated an increased risk of death or ventricular arrhythmias in post-MI patients in whom this response is blunted (<3 ms/mmHg change) [142,143]. These findings were confirmed by the ATRAMI trial, a prospective study of 1,284 patients with recent MI over a 21-month follow-up [132, 133]. In a multivariate analysis, impaired BRS or HRV was associated with a 3.2 and 2.8 relative risk for cardiac mortality, respectively. The relative risk was higher if both autonomic parameters were assessed together or in combination with a LVEF ≤ 0.35. Importantly, in post-MI patients with LVEF < 0.35, preserved BRS was associated with a very low risk of cardiac death (3 % over a 2-year period). In similar fashion to a negative TWA test, preserved BRS may be useful in identifying patients who may be at particularly low risk of cardiac death and who may not benefit from implantation of an ICD. Of note, BRS may also have utility for predicting SCD risk in patients with more preserved EF after MI. In a study of 244 patients with recent MI and EF > 0.35, BRS testing was abnormal in 14 %, and these patients had a relative risk of 11.4 of cardiovascular mortality compared to patients with preserved BRS [144]. This risk was especially marked for patients <65 years old with abnormal BRS (relative risk 19.6). Unfortunately, there did not appear to be a specific association of abnormal BRS with SCD (the relative risk was similar to that for non-SCD, de Ferrari personal communication).

Heart Rate Turbulence

Heart rate turbulence (HRT) is another measure of baroreflex sensitivity and refers to short term oscillations in sinus rhythm cycle lengths following single spontaneous VPCs [145]. The physiological mechanisms responsible for HRT in normal patients involve: (1) initial early acceleration of the sinus rate due to vagal withdrawal in the setting of missed baroreflex afferent inputs from a hemodynamically inefficient ventricular contraction, then (2) sinus deceleration from reflex parasympathetic recruitment following sympathetically mediated overshoot in the blood pressure [145]. Both HRT and baroreflex sensitivity (BRS) are measures of vagal responsiveness. However, unlike BRS, HRT may be assessed from 24-h ambulatory ECG recordings without the need for an active intervention (such as intravenous phenylephrine) to alter blood pressure.

Heart rate turbulence has been characterized by two parameters: turbulence onset (TO) and the turbulence slope (TS) [146]. The turbulence onset is "the difference between the mean of the first 2 sinus RR intervals after a VPC and the last 2 sinus RR intervals before the VPC divided by the mean of the last 2 sinus RR intervals before the VPC." The turbulence slope is the "maximum positive slope of a regression line assessed over any sequence of 5 subsequent sinus rhythm RR intervals within the first 20 sinus rhythm intervals after a VPC." A decreased slope, suggestive of impaired parasympathetic response, has been associated with an increased mortality risk.

Schmidt et al. [146] showed in patients with coronary artery disease and prior MI, that a decreased turbulence slope was associated with a relative mortality risk of 2.7 in the placebo arm of EMIAT (European Myocardial Amiodarone Trial) and of 3.5 for patients entered in the MPIP (Multicenter Post-Infarction Program).

Additionally, impaired HRT was associated with a relative mortality risk of 4 in a substudy of the ATRAMI Trial [147]. The relative risk of death doubled when HRT was combined with indices of BRS and HRV. A large, prospective study evaluated a cohort of 1,455 post-MI patients with regard to abnormalities of HRT [148]. With a primary endpoint of all-cause mortality over a 22-month follow-up period, patients with abnormal TO and TS had a hazard ratio of 5.9 which was greater than the hazard ratio of 4.5 associated with LVEF ≤ 0.30.

Two more recent prospective studies also demonstrated that HRT could identify high risk groups following MI. The REFINE study (Noninvasive Risk Assessment Early After a Myocardial Infarction) evaluated several measure of autonomic tone in 322 patients with an EF < 0.50 after MI, and showed that an abnormal HRT (by either onset or slope) predicted a significantly higher risk of cardiac death or resuscitated cardiac arrest over a median 47 month period, with an adjusted hazard ratio of 2.91 (p = 0.026) [55]. As with the other risk factors evaluated in that study, HRT was useful when measured at 10–14 weeks after the index MI, but not when performed 2–4 weeks following MI. The ISAR-Risk study (Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function) examined 2,343 consecutive patients following MI [149]. This cohort study evaluated for the presence of severe autonomic failure (SAF), as defined by an abnormal HRT (both onset and slope) as well as abnormal cardiac Deceleration Capacity, which is an integrated measure of all regulatory processes that slow the heart rate on a beat-to-beat basis. The study found that SAF could identify a group of post-MI patients with LVEF > 0.30 that was similar in size and risk-profile to the group with LVEF ≤ 0.30, with respect to total mortality, cardiac mortality and sudden cardiac death at 5 years.

Thus HRT is a promising predictor of mortality in patients with CAD post-MI, perhaps even more so in the group with preserved EF. However, further studies are needed in order to establish its utility as a specific risk stratifier for arrhythmic death, and whether interventions based on such autonomic measures will actually be beneficial. Practically, the requirement for at least 24-h Holter recordings as well as baseline sinus rhythm, and potential problems with accurate computerized analysis and classification may be issues. Also the timing of these tests seems to be important, and will need to be standardized.

Cardiac Magnetic Resonance Imaging

High resolution cardiac magnetic resonance (CMR) imaging has been used to better delineate the extent of myocardial scar in patients with acute and chronic infarctions, and more recently as a novel approach to predicting arrhythmic events and mortality. Notably, CMR using late gadolinium enhancement (LGE) has sufficiently high spatial resolution to delineate not only infarct location and extent, but also evaluate viability and characterize features of the border zone in peri-scar regions. CMR sequences distinguish infarcted myocardium as bright against a dark normal myocardium, with the mechanism of late enhancement thought to be related to delayed washout and increased volume of distribution. The border zone is a potentially arrhythmogenic area of conduction block or slowing, containing fibrosis interspersed with viable myocytes, and is identified by intermediate enhancement between normal myocardium and infarct core. Several studies have examined the relation between infarct size, as measured by to cardiac events and mortality [150, 151]. One of the initial pilot studies evaluating infarct heterogeneity was conducted in 144 patients with a history of coronary artery disease, mean EF of 0.44, and abnormal myocardial delayed enhancement consistent with MI [152]. This study showed that the extent of the peri-infarct zone was an independent predictor of post-MI all-cause and cardiovascular mortality. After adjusting for LVEF, the percentage of border zone area was a risk factor for cardiovascular mortality with a hazard ratio of 1.51 per 10 % border zone (p = 0.09). Other studies demonstrated that a larger extent of border zone identified inducible monomorphic VT in patients with prior MI and LVEF < 0.35 [153]. In addition, infarct tissue heterogeneity by LGE predicted spontaneous

ventricular arrhythmia in patients receiving primary prevention ICDs with a HR of 1.40/10 g ($p = 0.04$). Interestingly, in several of these studies total infarct size as measured by CMR was not consistently related to future risk. One more recent prospective study in patients meeting MADIT II criteria for primary prevention ICD suggested that perhaps relative infarct transmurality (RIT) as opposed to size might be an important predictor of a combined endpoint of ICD therapy or death from a cardiac cause [154]. This finding is consistent with post-infarction animal models in which the reentry circuit isthmus is localized to areas of slow conduction corresponding to greater fibrosis and scar transmurality on CMR [155].

It appears promising that information on the size and morphology or periphery of infarct scar has additive or complementary value to current risk stratifiers. Novel parameters such as 3D architecture and geometry of scar are also being studied. However, larger prospective multicenter studies will be needed to further confirm current observations and importantly, to address the particular utility of CMR for specific risk stratification of sudden cardiac death. Many studies have instead used combined mortality or surrogate endpoints such as VT or ICD therapy, which themselves may have low positive predictive value for SCD. Important advantages to the use of CMR include its non-invasive nature and the ability to quantitate in a more precise and reproducible manner metrics of interest, though definitions with regard to infarct tissue heterogeneity and border zone will need to be standardized. CMR evaluation also concurrently provides assessments of LVEF and function, which have excellent intra- and interobserver variability, and which could potentially help refine echocardiography-based measurements of LVEF on which current guidelines for risk stratification are based [156].

Summary

In spite of the significant differences between the individual risk stratification tests, it is remarkable that individually, they have all demonstrated fairly similar properties when analyzed in a meta-analysis [47]. While the sensitivity for prediction of arrhythmic events of spontaneous VPCs and NSVT (43 %) and HRV (50 %) appear lower, the SAECG, EF and EPS all had sensitivities of approximately 60 %. The odds ratio for arrhythmic events ranged from a low of 3.2 (VPCs and NSVT) to 5.1 (EF), 5.7 (SAECG), 6.3 (HRV), to a high of 8.5 (EPS). Clearly, none of these tests alone display adequate sensitivity. This is not surprising given the multiplicity of possible mechanisms that may lead to cardiac arrest or sudden death after MI. This leads us to the conclusion that only through the use of multiple tests will we be able to cost-effectively identify individuals most likely to benefit from therapies to reduce risk of sudden death. In fact, multiple studies have demonstrated that the prognostic significance of isolated tests is limited, while combining tests results in identification of much higher risk groups [66, 68, 133]. For example, each of these studies has shown that EF alone, when not associated with other abnormal risk stratification tests, is associated with only slightly elevated mortality risk. On the other hand, risk appears to be elevated significantly when two or more risk factors are identified, with the degree of elevation depending on the specific risk factor in question.

In conclusion, we hope to have convinced the reader that we have yet to find the ideal risk stratification test. In fact, it is unlikely that there ever will be one ideal test, and testing will have to be individualized. It is likely that combinations of tests will be required to achieve optimum sensitivity and specificity. Because of the progressive nature of coronary artery disease, testing will have to be repeated at intervals. However, the optimal time for initial and repeat testing has not yet been defined. At the present time, most workers in this field agree that a prospective trial seeking to define the optimal risk stratification schema in survivors of MI is desperately needed.

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23
Sudden Death in Athletes

Domenico Corrado, Anna Baritussio, Mariachiara Siciliano, Antonio Pelliccia, Maurizio Schiavon, Cristina Basso, Barry J. Maron, and Gaetano Thiene

Abstract

Competitive sports activity is associated with an increase in the risk of sudden cardiovascular death (SCD) in susceptible adolescents and young adults with clinically silent cardiovascular disorders. Screening including 12-lead electrocardiogram (ECG) has been demonstrated to allow identification of athletes affected by malignant heart muscle diseases at a pre-symptomatic stage and lead to substantial reduction of the risk of SCD during sports. The use of modern criteria for interpretation of the ECG in the athlete significantly improves the screening accuracy by reducing the false positive rate (increased specificity), with the important requisite of maintaining the ability for detection of life-threatening heart diseases (preserved sensitivity). Screening including ECG has a more favorable cost-benefit ratio than that based on history and physical examination alone, with cost estimates per year of life saved below the threshold to consider a health intervention as cost-effective. Screening with exercise testing middle aged/senior athletes engaged in leisure sports activity is likely to be cost-effective in older patients with coronary risk factors, while it is not justified in low-risk subgroups.

Keywords

Athletes • Automated external defibrillator • Cardiomyopathy • Electrocardiogram Pre-participation screening • Sports cardiology • Sudden cardiac death • Ventricular arrhythmias

D. Corrado, MD, PhD (✉)
Division of Cardiology, Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Via Giustiniani, 2, 35121 Padova, Italy
e-mail: domenico.corrado@unipd.it

A. Baritussio, MD • M. Siciliano, MD
Division of Cardiology, Department of Cardiac, Thoracic and Vascular Sciences, University of Padua Medical School, Padua, Italy
e-mail: anna.baritussio@gmail.com; mariachiarasiciliano@hotmail.com

A. Pelliccia, MD
Department of Medicine, Institute of Sport Medicine and Science, Rome, Italy
e-mail: ant.pelliccia@libero.it

M. Schiavon, MD
Department of Social Health, Center for Sports Medicine and Physical Activity, Azienda ULSS 16 of Padova, Padua, Italy
e-mail: maurizio.schiavon@sanita.padova.it

C. Basso, MD, PhD • G. Thiene, MD, FRCP
Cardiovascular Pathology, Department of Cardiac, Thoracic and Vascular Sciences, University of Padua Medical School, Padova, Italy

B.J. Maron, MD
Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, MN, USA
hcm.maron@mhif.org

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Introduction

Regular physical exercise is recommended by the medical community because it is associated with a decrease in all cause-mortality, particularly from cardiovascular causes [1]. Several epidemiological and clinical studies have provided solid scientific evidence that habitual aerobic physical activity reduces the risk of acute myocardial infarction and sudden cardiac death (SCD) [2]. On the other hand, vigorous exertion may acutely and transiently increase the risk of acute coronary events and sudden cardiac arrest in susceptible individuals [3–5]. The risk-benefit ratio of sports activities varies according to athlete's age and intensity of physical exercise. According to Maron et al. [6] athletes can be divided into two major categories. Competitive athletes are young (usually ≤35 years) subjects who participate in an organized team or individual sport that requires systematic training and regular competition against others and places a high premium on athletic excellence and achievement. Conversely, leisure athletes are individuals, most frequently middle-aged/senior (usually >35 years), participating in a variety of informal recreational sports, within a range of exercise levels from modest to vigorous, on either a regular or inconsistent basis, which do not require systematic training or the pursuit of excellence.

This report examines the prevalence, causes, and mechanisms of SCD in both categories of athletes, and reviews the currently available prevention programmes such as systematic pre-participation screening and early defibrillation by using AEDs.

Epidemiology of SCD in Athletes

Although sudden cardiac death (SCD) during sports is a rare event, it always has a tragic impact on the community because it occurs in apparently healthy individuals and assumes great visibility through the news media, due to the high public profile of competitive athletes [7–10]. For centuries it was a mystery why cardiac arrest should occur in vigorous athletes, who had previously achieved extraordinary exercise performance without complaining of any symptoms. The cause was generally ascribed to myocardial infarction, even though evidence of ischemic myocardial necrosis was rarely reported; it is now clear that the most common mechanism of SCD during sports activity is an abrupt ventricular tachyarrhythmia as a consequence of a wide spectrum of cardiovascular diseases, either acquired or congenital. The culprit diseases are often clinically silent and unlikely to be suspected or diagnosed on the basis of spontaneous symptoms. Systematic pre-participation screening of all subjects embarking in sports activity has the potential to identify those athletes at risk and to reduce mortality.

Table 23–1. Cardiovascular causes of sudden death associated with sports

Age ≥ 35 years
Coronary artery disease
Age < 35 years
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy/dysplasia
Congenital anomalies of coronary arteries
Myocarditis
Aortic rupture
Valvular disease
Preexcitation syndromes and conduction diseases
Ion channel diseases
Congenital heart disease

Causes of SCD in the Athlete

As reported in Table 23.1, the causes of SCD reflect the age of the participants. Although *atherosclerotic coronary artery disease* accounts for the majority of fatalities in *adults* (*aged >35 years*) (Fig. 23.1) [4, 11, 12], in *younger athletes* a *broad spectrum of cardiovascular substrates* (*including Congenital and inherited heart disorders*) has been reported (Fig. 23.2) [7–10, 14–23].

Cardiomyopathies have been consistently implicated as the leading cause of sports-related cardiac arrest in the young, with hypertrophic cardiomyopathy accounting for more than one-third of fatal cases in the United States and arrhythmogenic right ventricular cardiomyopathy/dysplasia for approximately one-fourth in the Veneto Region of Italy [7, 8]. Two to five percent

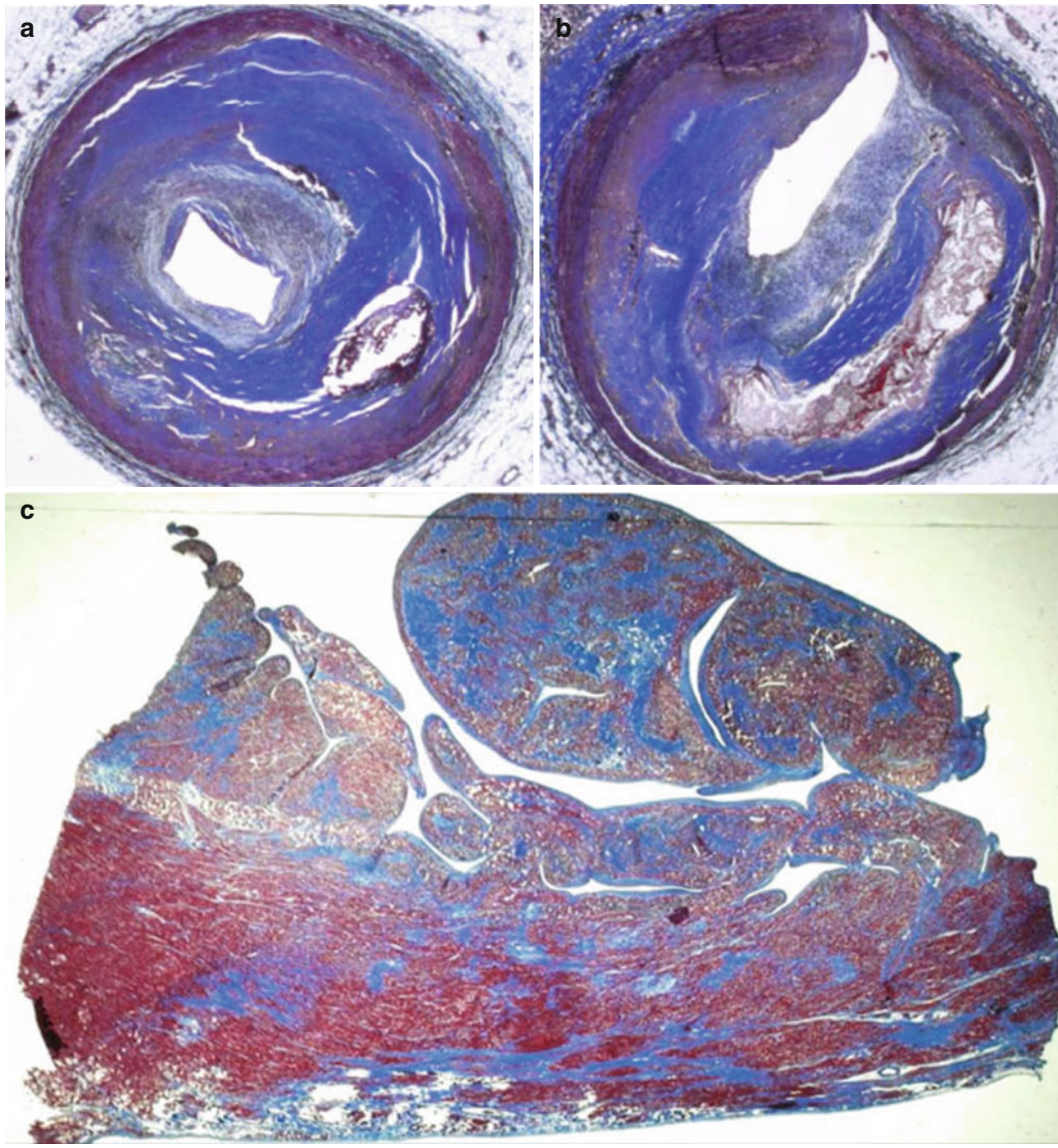

Figure 23–1. Sudden death of a middle-aged athlete. Obstructive atherosclerotic coronary artery disease of both left (anterior descending branch) and right coronary arteries (**a**, **b**) Heidenhain trichrome. (**c**) Histology of the myocardium shows replacement type fibrosis due to previous myocardial infarction (Adapted from Corrado et al. [13]. With permission from Oxford University Press)

of young people and athletes who die suddenly have no evidence of structural heart disease and the cause of their cardiac arrest in all likelihood is related to a primary electrical heart disease such as inherited cardiac ion channel defects (channelopathies), including long and short QT syndromes, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia [24]. Sudden death may also be caused by a non-arrhythmic mechanism—e.g., spontaneous aortic rupture complicating Marfan's syndrome or bicuspid aortic valve as well as by diseases not related to the heart—e.g., bronchial asthma or rupture of a cerebral aneurysm [2]. Blunt, non-penetrating, and often innocently appearing blows to the precordium may trigger ventricular fibrillation without structural injury to ribs, sternum, or heart itself (commotio cordis) [9].

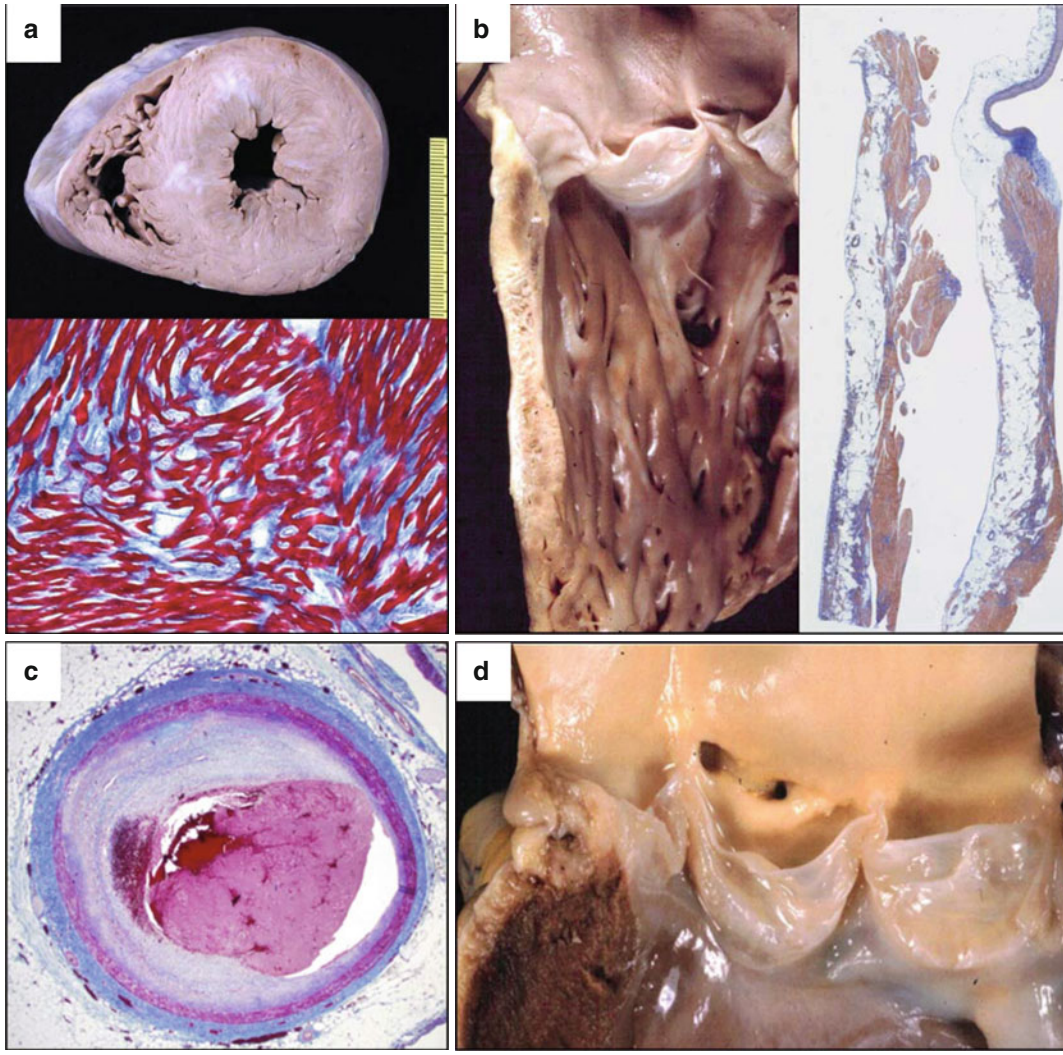

Figure 23–2. Leading causes of sudden cardiovascular death in young competitive athletes. (**a**) Hypertrophic cardiomyopathy: short axis cut of the heart specimen showing asymmetric septal hypertrophy with multiple septal scars (*top*); histology of the interventricular septum revealing typical myocardial disarray with interstitial fibrosis (*bottom*) (Heidenhain trichrome); (**b**) Arrhythmogenic right ventricular cardiomyopathy/dysplasia: section of the heart specimen along the right ventricular infundibulum (*left*); panoramic histological view of the right infundibular free wall showing wall thinning with fibro-fatty replacement (*right*) (Heidenhain trichrome); (**c**) Atherosclerotic coronary artery disease: histology of the proximal tract of the left anterior descending coronary artery showing a non obstructive fibrous plaque complicated by luminal thrombosis due to endothelial erosion (Heidenhain trichrome). (**d**) Congenital coronary anomaly: gross view of the aortic root showing both coronary ostia located in the right coronary sinus, pointing to an anomalous left coronary artery arising from the right aortic sinus of Valsalva and running between the aorta and the pulmonary trunk (From Corrado et al. [13]. With permission from Oxford University Press)

Incidence of SCD

Death usually occurs either during (80 %) or immediately after (20 %) athletic activity, suggesting that participation in competitive sports increases the likelihood of cardiac arrest. Fortunately, the frequency with which SCD occurs during sports activity is low and varies in the different athlete age-groups because of the different nature of cardiovascular substrates [2, 3, 25]. It generally increases with age and is greater in men [9, 25, 26]. In middle-age/senior athletes engaged in leisure time sports such as jogging or marathon

racing, the estimated rate of sports-related fatalities ranges from 1:15,000 to 1:50,000 [5]. Several epidemiological studies have assessed the relationship between physical exercise and the risk of acute myocardial infarction/SCD in leisure athletes, in which physical exercise can be regarded as a 'two-edged sword' [1–3, 5, 25] while epidemiological studies support the concept that habitual sports activity offers protection against cardiovascular events over the long-term [1–3, 25], vigorous exercise may acutely increase the incidence of both cardiac arrest and acute myocardial infarction, mostly in those who do not exercise regularly. In younger competitive athletes (≤35 yoa), the reported incidence of sudden death from all causes in Veneto region was 2.3 per 100,000 athletes per year and of 2.1 per 100,000 athletes per year by cardiovascular diseases [26].

On the other hand, the prevalence of fatalities among US high-school and college athletes has been estimated to be less than 1 in 100,000 participants per year [9, 27]. Compared with US high school and college participants, the Italian athletic population included older athletes (age range 12–35 vs. 12–24 years) and a significantly higher proportion of men (85 vs. 65 %). This partly explains why the mortality rates found in the Italian investigations were significantly higher than those reported in the USA. In addition, while the Italian data were systematically gathered from a well-defined geographic area (the Veneto region of Italy) according to a prospective study design, the US SCD rates were mostly based on retrospective analysis of data from public media reports and insurance claims, which unavoidably led to an incorrectly low number of events and underestimation of mortality. The accuracy of the determination of incidence rates of SCD among US athletes is further questionable, because denominator data did not reflect the real number of active athletes in each year, but the total participation figures divided by an estimate of the average number of sports, in which each high school and college athlete participated [9, 27, 28]. Other studies with more rigorous data collection and denominator estimates reported an incidence of either SCD or sudden cardiac arrest of young athletes in the USA quite similar to the incidences found in the Veneto region of Italy in the pre-screening period (Table 23.1) [28]. In this regard, Harmon et al. [29] recently reported that during a 5-year period, SCD incidence among national collegiate athletic association (NCAA) student-athletes was 2.3/100.000 participants per year.

The Italian prospective study also demonstrated that adolescent and young adults involved in competitive sports activity have an estimated risk of SCD approximately three times greater (2.8) than that of their non-athletic counterpart (Fig. 23.3) [26, 28]. However, sport was not itself the cause of the enhanced mortality, since it triggered cardiac arrest in those athletes who were affected by cardiovascular conditions predisposing to life-threatening ventricular arrhythmias during physical exercise (Fig. 23.3). This reinforces the need for systematic evaluation of adolescent and young individuals embarking in

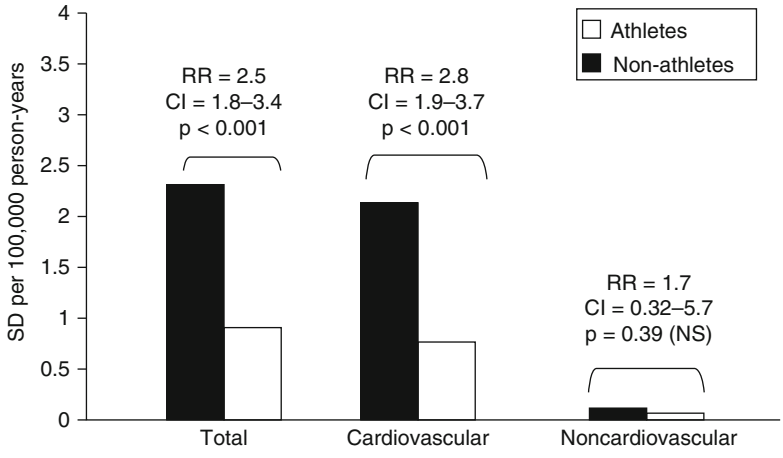

Figure 23–3. Incidence and relative risk (*RR*) of sudden death among young athletes and non-athletes from total, cardiovascular and non-cardiovascular causes (From Corrado et al. [30]. With permission from Sage Publications)

sports activity in order to identify those with potentially lethal cardiovascular diseases and protect them against the increased risk of SCD.

Pre-participation Screening

The primary purpose of pre-participation screening is to identify the cohort of athletes affected by unsuspected cardiovascular diseases and to prevent SCD during sports by appropriate interventions [29]. Sudden cardiac death during sports is often the first clinical manifestation of cardiovascular disease, because the culprit conditions are usually clinically silent and unlikely to be suspected during life on the basis of spontaneous alarming prodroma.

The importance of early identification of clinically silent cardiovascular diseases at a pre-symptomatic stage relies on the concrete possibility of SCD prevention by lifestyle modification, including restriction of competitive sports activity (if necessary), but also by prophylactic treatment with drugs and implantable defibrillator [31]. The vast majority of 'at risk-athletes' show neither a positive family history nor preexistent cardiovascular symptoms. This explains why a screening protocol based solely on the athlete's history and a physical examination, as used in the United States, is of limited value (<10 %) in detecting affected athletes and preventing fatalities. In this regard, Glover and Maron [32] found that of 134 high school and collegiate athletes who suffered from SCD after they underwent a pre-participation screening, only 3 % were suspected of having cardiac disease and, eventually, <1 % received an accurate diagnosis.

The Italian screening protocol utilizing ECG in addition to history and physical examination has proven to successfully identify unsuspected cardiovascular diseases in the general population of young competitive athletes. Twelve-lead ECG enhances the sensitivity of the screening process by allowing early detection of cardiovascular conditions distinctively manifesting with ECG abnormalities, such as hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia, dilated cardiomyopathy, Wolff–Parkinson–White syndrome, Lenegre conduction disease, long and short QT syndromes, and Brugada syndrome [33]. Overall, these conditions account for two-thirds of SCD in young competitive athletes. Italy is the only country in the world where law mandates that every subject engaged in competitive sports activity must undergo a clinical evaluation to obtain eligibility before entering in competitive sports. A nationwide mass pre-participation screening programme, essentially based on 12-lead ECG, has been the practice for more than 25 years [5, 28]. The pre-participation evaluation involves nearly six million athletes of all ages annually, representing about 10 % of the overall Italian population. A flow chart illustrating the Italian screening protocol is reported in Fig. 23.4.

Efficacy of Pre-participation ECG Screening

The long running Italian experience has shown that ECG screening actually identifies asymptomatic athletes with previously undiagnosed cardiovascular abnormalities [10, 14, 28, 34]. Among 33,735 athletes undergoing preparticipation screening at the Center for Sport Medicine in Padua, 22 (0.07 %) showed definitive evidence, both clinical and echocardiographic, of HCM [15]. An absolute value of screening sensitivity for HCM cannot be derived from these data because systematic echocardiographic findings were not available. However, the 0.07 % prevalence of HCM found in the white athletic population of the Veneto region of Italy, evaluated by history, physical examination, and ECG, is similar to the 0.10 % prevalence reported for young white individuals in the USA, as assessed by echocardiography. This finding indicates that ECG screening may be as sensitive as echocardiographic screening in detecting HCM in the young athletic population. Comparison between sensitivity of Italian and US screening protocols demonstrated that 12-lead ECG makes the difference. Among 22 athletes with HCM who were detected by ECG screening at the Center for Sport Medicine in Padua and disqualified from competition, only five (23 %) would had been identified on the basis of a positive family history, symptoms, or abnormal physical findings in the absence of an ECG [20]. Hence, the estimated sensitivity of Italian screening modality

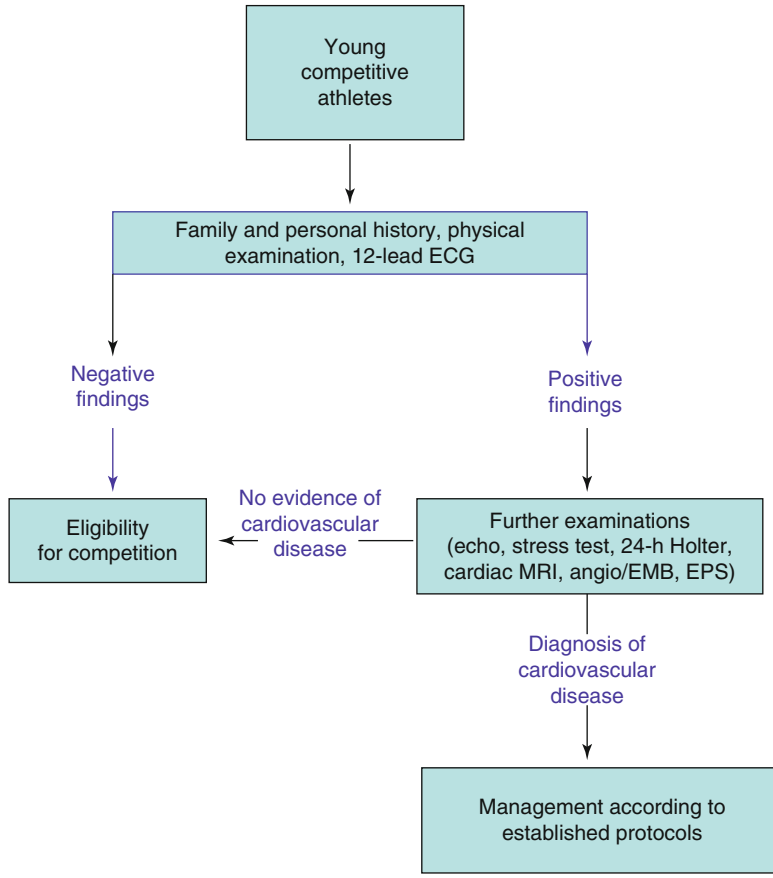

Figure 23–4. Flow diagram illustrating the modality of pre-participation cardiovascular screening recommended by the ESC section of Sports Cardiology. The screening modality is substantially based on the Italian protocol of pre-participation cardiovascular evaluation. First line examination includes family history, physical examination and 12-lead ECG; additional tests are requested only for subjects who have positive findings at the initial evaluation. Athletes recognized to be affected by cardiovascular conditions potentially responsible for sudden death in association with exercise and sport participation are managed according to the available recommendations for sports eligibility. The screening starts at the beginning of competitive athletic activity, which for the majority of sports disciplines corresponds to an age of 12–14 years. There is the need of repeating the screening on a regular basis every 1–2 years, mostly in teenagers, in order to timely identify delayed phenotypic manifestations, disease progression, or substrate worsening over the time. *Angio/EMB* contrast angiography/endomyocardial biopsy, *EPS* electrophysiologic study with programmed ventricular stimulation, *MRI* magnetic resonance (From Corrado et al. [30]. With permission from Sage Publications)

for identification of athletes with HCM is 77 % greater than that of the screening protocol (not including ECG) recommended by the American Heart Association. Echocardiographic study in addition to the basal protocol does not seem to significantly improve efficacy of the pre-participation screening in identifying HCM. Pelliccia et al. did not identify any HCM by routine echocardiographic examination in 4,450 elite athletes previously cleared by ECG at pre-participation evaluation [35].

Interpretation of Athlete's ECG at Pre-participation Screening

ECG changes usually develop in trained athletes as a consequence of the heart adaptation to sustained physical exercise ('athlete's heart') [36–38]. There is a misconception that such physiological ECG changes overlap significantly with ECG abnormalities seen in the cardiovascular diseases which cause sudden death in the young [39–42]. Therefore, the ECG has been

considered to be a poor screening tool in the athlete, because of its presumed high level of false-positive results [43]. The Italian screening experience disproved that ECG is a non-specific and non-cost-effective test. Among 42,386 athletes initially screened by history, physical examination, and 12-lead ECG, 3,914 (9 %) had positive findings as to require further examination, 879 (2 %) were diagnosed with cardiovascular disorders, and 91 (0.2 %) were ultimately disqualified for potentially lethal heart diseases [28]. The percentage of false-positive results, i.e. athletes with a normal heart but positive screening findings, was 7 % for all cardiovascular disorders and 8.8 % for heart diseases at high risk of sudden death during sports. Recommendations for interpretation of 12-lead ECG in the athlete have been recently provided by a Consensus Statement of the Section of Sports Cardiology of the European Association of Cardiovascular Prevention and Rehabilitation [43]. The document provides cardiologists and sports medical physicians with a modern approach to distinguish between physiological and potentially pathological ECG patterns. Defining what ECG changes are physiological (common and training-related ECG abnormalities) and what are pathological (uncommon and training unrelated ECG abnormalities) (Fig. 23.5) has significant favourable effects on the athlete's cardiovascular management including clinical diagnosis, risk stratification, and cost savings. The effect of the use of the proposed modern criteria is to substantially increase the ECG

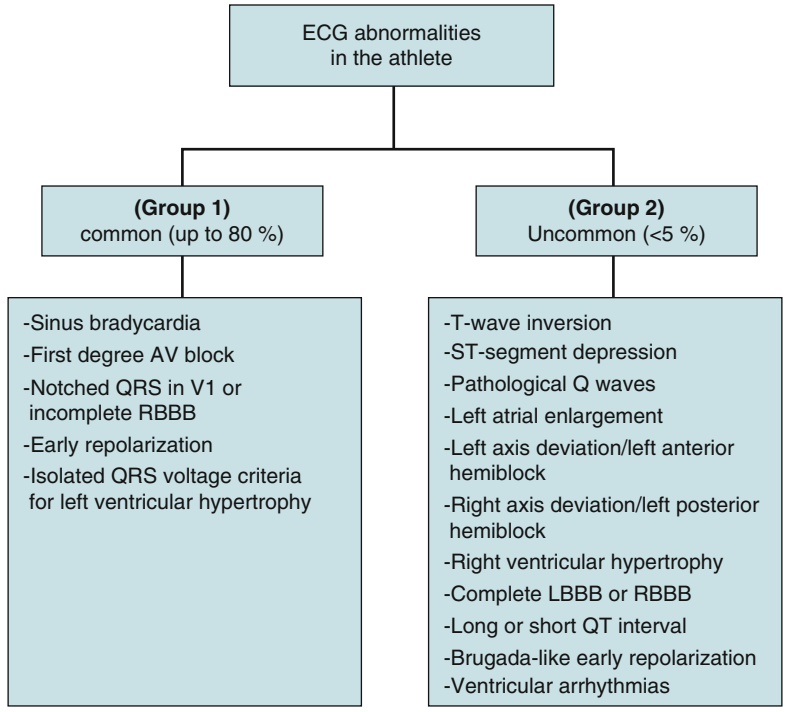

Figure 23–5. Classification of ECG abnormalities in the athlete. Common ECG abnormalities: up to 80 % of trained athletes exhibit ECG changes such as sinus bradycardia, first degree AV block, early repolarization, incomplete right bundle branch block and pure increase of QRS voltages (Group 1). Such common ECG changes are the consequence of the physiologic cardiovascular adaptation to sustained physical exertion and do not reflect the presence of an underlying cardiovascular disease. Therefore, they are not associated with an increase of cardiovascular risk and allow eligibility to competitive sports without additional evaluation. Uncommon ECG abnormalities: this subset includes uncommon ECG patterns (<5 %) such as ST-segment and T-wave repolarization abnormalities, pathological Q waves, intraventricular conduction defects, and ventricular arrhythmias (Group 2). These ECG abnormalities are unrelated to athletic conditioning and should be regarded as an expression of a possible underlying cardiovascular disorders, notably cardiomyopathies and cardiac ion channel diseases, and, thus, associated with an inherent increased risk of sudden arrhythmic death (From Corrado et al. [13]. With permission from Oxford University Press)

specificity (by about 70 %), primarily in the important group of athletes who exhibit pure voltage criteria for left ventricular hypertrophy and early repolarization abnormalities, but with the important requisite of maintaining sensitivity for detection (or suspicion) of cardiovascular diseases at risk of SCD during sports [43, 44]. Baggish et al. [45] examined the effect of cardiovascular screening with and without electrocardiography in 510 US college athletes. The use of ECG increased the recognition of cardiomyopathies and improved the screening sensitivity from 45.5 to 90.9 %. However, including ECG was associated with a greater false-positive rate of 16.9 % (vs. 5.5 % for screening with history and examination only), accounting for a reduction of screening specificity from 94.4 to 82.7 %: the conclusion of this first study was that adding ECG to medical history and physical examination improves the overall sensitivity of pre-participation cardiovascular screening in athletes, though this strategy is associated with an increased rate of false-positive results when current ECG interpretation are used. In a subsequent study, the authors examined the performance of the new, revised ESC criteria for ECG interpretation in the same athletic population previously screened using traditional criteria. Application of the new ECG criteria improved the accuracy of an ECG-inclusive pre-participation screening strategy, by improving specificity [i.e. reducing the number of participants with false-positive ECG findings from 83 of 508 (16.3 %) to 49 (9.6 %) and, most importantly, preserving sensitivity] [46]. The reduction in the number of abnormal ECGs was driven by the reclassification of participants with isolated QRS voltage criteria for left-ventricular hypertrophy from abnormal to normal.

Mortality Reduction by Pre-participation Screening

A time-trend analysis of the incidence of SCD in young competitive athletes age 12–35 years in the Veneto region of Italy during 1979–2004 has provided compelling evidence that ECG screening is a lifesaving strategy [28]. The long-term impact of the Italian screening programme on prevention of SCD in athletes was assessed by comparing temporal trends in SCD among screened athletes and unscreened non-athletes. Assessed intervals were pre-screening (1979–1981), early-screening (1982–1992), and late screening (1993–2004). The analysis demonstrated a sharp decline of SCD in athletes after the introduction of the nationwide screening programme in 1982. Fifty-five SCDs occurred in screened athletes (1.9 deaths per 100,000 person-years) and 265 deaths in unscreened non-athletes (0.79 deaths per 100,000 person-years). The annual incidence of SCD in athletes decreased by 89 %, from 3.6 per 100,000 person-years during the pre-screening period to 0.4 per 100,000 person-years during the late-screening period. By comparison, the incidence of SCD in the unscreened non-athletic population of the same age did not change significantly over that time (Fig. 23.6). The decline in death rate started after mandatory screening was launched and persisted to the late screening period. Compared with the pre-screening period (1979–1981), the relative risk of SCD was 44 % lower in the early-screening period (1982–1992) and 79 % lower in the late-screening period (1993–2004). It is noteworthy that most of the reduced death rate was due to fewer cases of SCD from cardiomyopathies. Most of the reduction was attributable to fewer deaths from HCM and arrhythmogenic right ventricular cardiomyopathy/dysplasia. A parallel analysis of the causes of disqualifications from competitive sports at the Center for Sports Medicine in the Padua country area showed that the proportion of athletes identified and disqualified for cardiomyopathies doubled from the early- to the late-screening period. This indicates that mortality reduction was a reflection of a lower incidence of SCD from cardiomyopathies, as a result of increasing identification over time of affected athletes at pre-participation screening. The results of the Italian study have raised an intensive debate. It has been argued that the Italian study was not a randomized trial comparing screening versus non-screening of young competitive athletes, and, thus, definitive conclusions that the reduced mortality was solely the consequence of the screening process cannot be drawn [47]. However, the strong cause–effect relationship between implementation of the screening

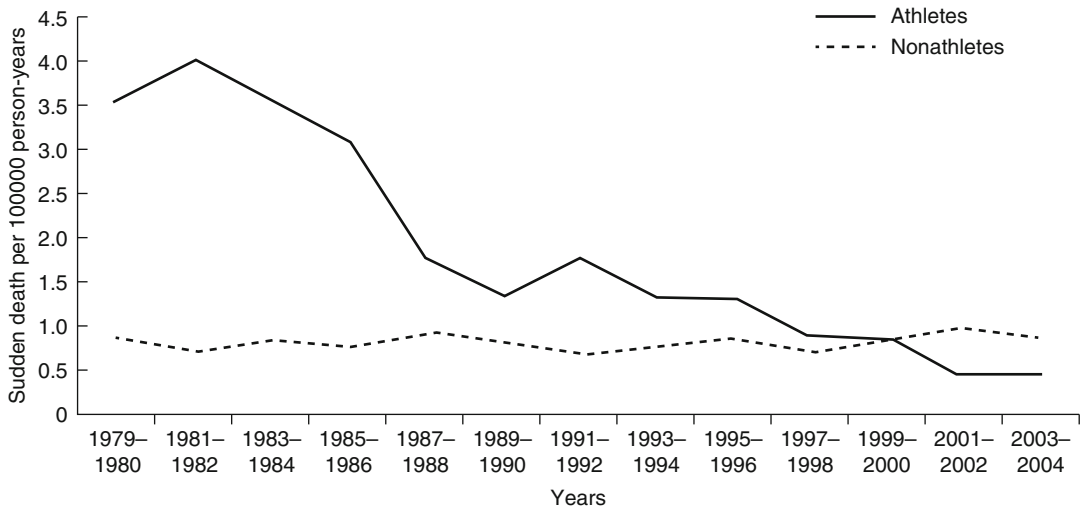

Figure 23–6. Annual incidence rates of SCD per 100,000 person, among screened competitive athletes and unscreened nonathletes 12–35 years of age in the Veneto Region of Italy, from 1979 to 2004. During the study period (the nationwide preparticipation screening program was initiated in 1982), the annual incidence of SCD declined by 89 % in screened athletes (*P* for trend <0.001). In contrast, the incidence of SCD did not demonstrate consistent changes over that time in unscreened nonathletes (From Corrado et al. [30]. With permission from Sage Publications)

programme and the substantial reduction (by 89 %) of SCD in Italian athletes should remove all doubt of the efficacy of screening to identify athletes with at-risk cardiovascular conditions and its ability to save lives. The study [28] showed that: (1) there was a coincident timing between decline of SCD in young competitive athletes and screening implementation in Italy; (2) most of the reduced incidence of SCD was due to fewer deaths from cardiomyopathies and was accompanied by the concomitant increase of the proportion of young competitive athletes with cardiomyopathies who were identified and disqualified from competition at the Center for Sports Medicine in Padua during the same time interval; and (3) during the study period, the incidence of SCD did not change among the unscreened non-athletic population of the Veneto region of the same age range.

Cost–Benefit Considerations

The long-term Italian experience indicates that screening is made feasible because of its limited costs in athletes setting of a mass programme [33, 48]. The cost of performing a pre-participation cardiac history/physical examination by qualified physicians has been estimated to be about 20 Euro per athlete and rises to about 30 Euro per athlete if a 12-lead ECG is added. The screening cost is covered by the athlete or by the athletic team, except for athletes younger than 18 years, for whom the expense is supported by the National Health System. The cost of further evaluation of athletes with positive findings at first-line examination is smaller than expected on the basis of the presumed low specificity of athlete's ECG. The long-running Italian screening programme showed that the percentage of false positive results (i.e., athletes with a normal heart but positive screening findings) requiring additional testing, mainly echocardiography, did not exceed 9 %, with a modest proportional impact on cost [34]. The demographics of the screened athletic population, consisting of adolescents and young adults, as well as the genetic nature of the leading causes of SCD in this age group, profoundly impacts cost–benefit considerations [48]. Unlike older patients with coronary artery diseases or heart failure, young individuals diagnosed with a genetic disease at risk of arrhythmic cardiac arrest will survive for many decades with normal or nearly normal life expectancy, thanks to restriction from

competition and prophylactic therapy against life-threatening arrhythmias [48]. This large amount of life-years saved favourably influences cost-effectiveness analysis of the screening process [48, 49].

Wheeler et al. applied a theoretical model to project the costs and survival rates of US high school and college athletes who had pre-participation screening [50]. Adding ECG to history and physical examination saved 2.1 live-years per 1,000 athletes screened. The incremental cost effectiveness ratio of adding ECG to history and physical examination was 42,000 USD per life-year saved [50]. According to this and other study results [51, 52] the ECG based screening is more cost-effective than that relying on history and physical examination alone with cost estimates per year of life saved below 50,000 USD, which is the traditional threshold to consider a health intervention as cost-effective.

The benefit of pre-participation evaluation goes beyond the detection of index athletes with an inherited heart disease because it enables cascade screening of relatives and results in a multiplier effect for identifying other affected family members and saving additional lives [34, 48].

Pre-participation Screening of Middle Aged/ Senior Athletes (>35 Years)

The risk of sports-related acute cardiovascular events, including SCD, increases exponentially among individuals >35 years and is almost exclusively related to the development and progression of atherosclerotic coronary artery disease [25]. The growing number of middle-aged/ senior subjects engaged in leisure-time sports activity, outside the competitive sports community, makes the pre-participation screening of this athletic population an emerging task, with specific problems in terms of feasibility, logistics, and costs. The identification and management of coronary artery disease in asymptomatic adults and elderly is a controversial issue. So far, no strategies have been adequately studied to evaluate their ability to reduce the risk of exercise-related acute cardiovascular events in this group of athletes [2]. Several epidemiological studies reported the association between ECG abnormalities and an increased relative risk (1.5–2.5 fold) of mortality from coronary artery disease [53, 54]. Despite its recognized prognostic value, the utility of ECG for screening asymptomatic subjects without known coronary atherosclerosis is limited. Up to half of individuals with angiographically normal coronary arteries show ECG changes, approximately one-third of those with coronary artery disease show normal basal ECG findings, and, most importantly, the vast majority of coronary events occurs in the absence of prior ECG abnormalities [55, 56].

Thus, basal ECG results in an unacceptably large number of false negative and false-positive results in athletes >35 years and is not suitable as a single test for screening this athlete's age-group.

Because of its established prognostic value, widespread availability and low cost, exercise testing is widely deemed the best available test for screening asymptomatic adults prior to an exercise programme. Several studies reported an increase in the relative risk of coronary death (range 2–5), for those asymptomatic subjects with a positive exercise testing [57–59]. However, the test accuracy for detection of coronary artery disease is expectedly limited among the general population because of the relatively low disease's prevalence [60, 61]. The test performance increases with a greater pre-test probability of coronary atherosclerosis, so that subgroups of asymptomatic individuals with risk factors who would most benefit from screening by exercise testing have been defined [58, 59, 62]. These subgroups include men with advanced age, multiple coronary risk factors, or diabetes; instead, the test prognostic value has not been demonstrated in asymptomatic healthy women. There is evidence that the risk of cardiac events related to underlying coronary artery disease further depends on the level of fitness/habitual physical activity as well as on the intensity of the intended physical exercise [63–65]. However, the predictive value of exercise ECG test for cardiovascular events occurring specifically during exercise is very limited. Siskovick et al. [57] reported an 18 % sensitivity and 92 % specificity of a positive exercise testing to predict an exercise-related cardiovascular event in asymptomatic, hypercholesterolaemic men (35–59 years). Although there are no solid scientific data to guide the use of exercise testing

for screening, several Associations of Cardiology and Sports Medicine have addressed this important issue by consensus [66–68]. Despite slight differences, the common denominator of current recommendations is that individuals who appear to be at a greater risk of suffering from underlying coronary artery disease (for instance those with diabetes mellitus [69–71]) should be considered for exercise testing prior to the beginning of a vigorous exercise training programme. In contrast, the US Preventive Services Task Force states that there is insufficient evidence to determine the benefits of pre-participation exercise testing prior to exercise programmes [72].

Most recent recommendations of cardiovascular evaluation of middle-aged/senior individuals engaged in leisure sports activity have been proposed by the ESC sections of Sports Cardiology and Exercise Physiology of the European Association of Cardiovascular Prevention and Rehabilitation [68]. Figure 23-7 summarizes the specific work-up of cardiovascular evaluation recommended as appropriate for either sedentary or regularly active individuals, based on the individual risk profile and the type or intensity of intended physical exercise [68]. The recommended first line evaluation consists of a self-assessment (by the individual or by non-physician health-related professionals) of the habitual physical activity level and the risk factors, using validated questionnaires such as the AHA pre-participation Questionnaire [73] or the simpler revised Physical Activity Readiness Questionnaire [74]. If indicated, subsequent thorough risk assessment is performed by a qualified physician, using the ESC Systematic Coronary Risk Evaluation (SCORE) [75–77]. According to the SCORE system, the assessment of cardiovascular risk of coronary death within 10 years is based on age, sex, blood pressure, blood cholesterol, and smoking history. Maximal exercise testing (and possibly further cardiological evaluations) is reserved to those individuals embarking in moderate/intense physical activity who show an increased risk for coronary events [75]. Whether further evaluation and successful treatment of an asymptomatic individual with a positive exercise test by interventional/non-interventional therapies can improve outcomes, thereby validating the screening clinical utility, remains to be established. Screening with exercise testing is likely to be cost-effective in older patients with coronary risk factors, while it is not justified in low-risk subgroups.

Secondary Prevention of Sudden Cardiac Death

Compared to primary prevention of SCD by pre-participation identification of athletes affected by at-risk cardiovascular diseases, secondary prevention is based on early external defibrillation of unpredictable arrhythmic cardiac arrest. The screening ability to detect young competitive athletes with either premature coronary atherosclerosis or anomalous coronary artery is limited by the scarcity of baseline ECG signs of myocardial ischaemia [16–19, 78]. Moreover, SCD during sports may be the result of non-penetrating chest injury (commotio cordis) which cannot be prevented by screening. This justifies the growing efforts to implement secondary prevention strategy based on early external defibrillation of SCA. The most important factor influencing survival from SCA is the access to rapid defibrillation through on-site AED. Public access to AED has been successful in improving survival (up to 52 %) from out-of-hospital cardiac arrest in many settings including casino, airlines, and airports [79–82]. These favourable results were obtained in individuals with a mean age > 60 years that most likely experienced an ischaemic cardiac arrest due to atherosclerotic coronary artery disease. Limited research is available regarding early defibrillation programmes in the athletic setting. Concerns have been raised about the effectiveness of early defibrillation of SCA occurring in the young athletic population with different causes of cardiac arrest, mostly consisting of cardiomyopathies, compared with older people suffering ventricular fibrillation from coronary artery disease [83–86]. Original research on the use of AED at the college athletic venue did not demonstrate a significant success in a small number of intercollegiate athletes with SCA, although an overall resuscitation rate of 54 % was found in older non-students [83, 84]. Drezner and Rogers [84, 85] showed that

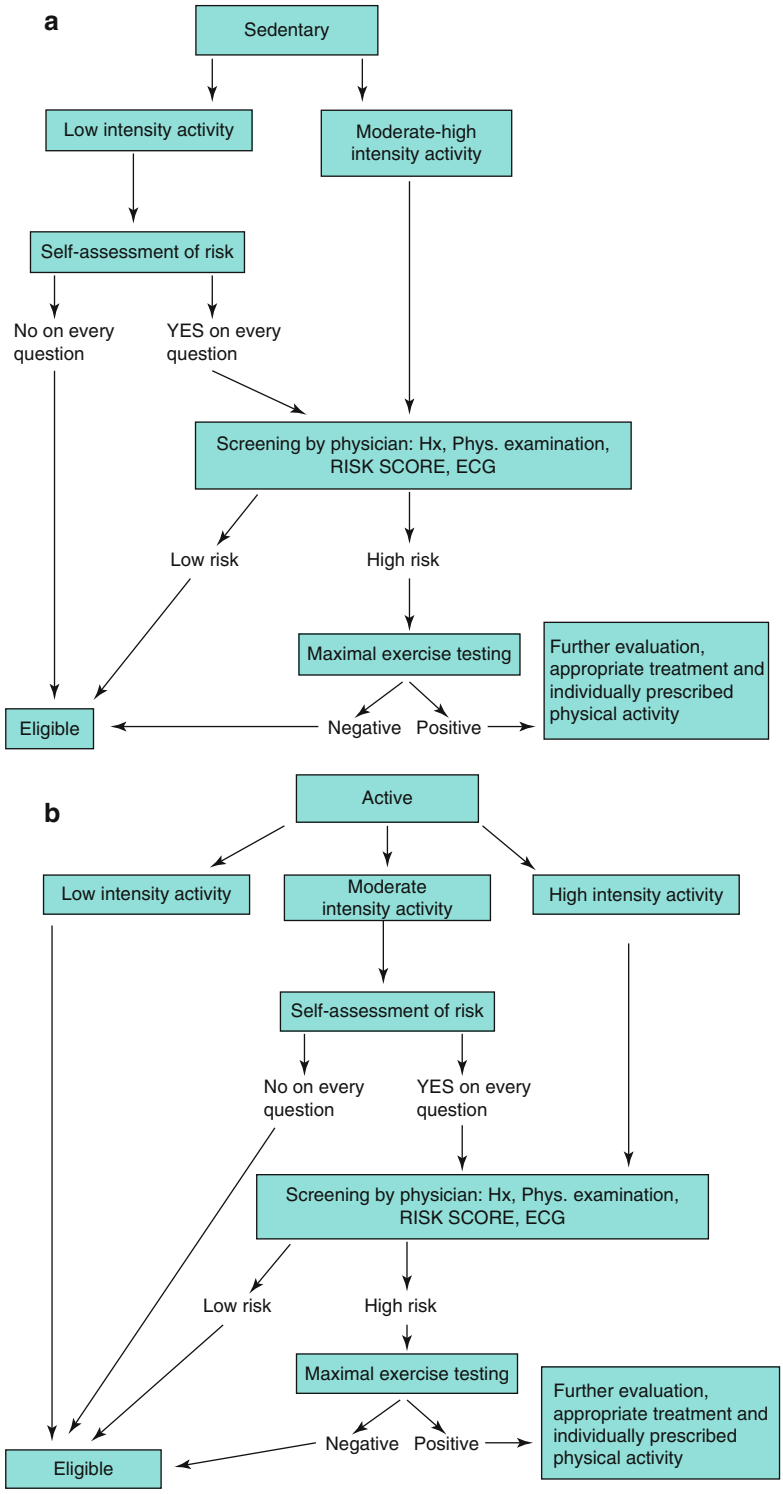

Figure 23–7. Specific pre-participation screening work-up for middle aged/senior individuals. (**a**) Sedentary individuals are defined as individuals whose energy expenditure during physical exercise accumulates to less than 2 MET-h/week. This low activity has been associated with higher coronary event rates and a poorer prognosis. The recommendations consider low cardio respiratory fitness equivalent of having a high risk according to score. The intensity of the intended physical exercise program, assessed by the individual or by a non-physician is classified as follows: (1) Low intensity, corresponding to 1.8–2.9 METS; (2) Moderate intensity, corresponding to 3–6 METS; (3) High intensity, including individuals participating/willing to participate in masters events such as long-distance cycling, city marathons, long distance cross country skiing and triathlons, corresponding to an effort greater than 6 METS. (**b**) Active individuals are defined as those accumulating ≥2 MET-h/week, even intensive, though non competitive sport activities. Classification of intensity of the intended physical activity as in Fig. 23.6 (From Borjesson et al. [68]. With permission from Sage Publications)

chances for on-field successful resuscitation in intercollegiate athletes with SCA are remote. Despite a witnessed collapse, timely cardiopulmonary resuscitation, and prompt defibrillation in most cases (average time from cardiac arrest to defibrillation of 3.1 min), only one out of nine athletes (11 %) in this study survived. However, a closer scrutiny of the emergency responses in this series, revealed that the reported response time may have been underestimated. Moreover, five out of nine athletes (55 %) with SCA had an underlying hypertrophic cardiomyopahy, which likely influenced the low survival rate. It is noteworthy that ventricular tachycardia/fibrillation may be more resistant to defibrillation (specially if non-immediate) in patients with a cardiomyopathy. Other factors that may decrease the efficacy of defibrillation in athletes include the high catecholamine levels and metabolic changes occurring during strenuous physical exercise and interacting unfavourably with the underlying structural substrate. Other studies have also found the survival rates after SCA in young athletes to be lower than expected. Maron et al. [87] analysed 128 cases from the USA Commotio Cordis Registry and found an overall survival rate of 16 %. Drezner et al. [86] reported a 7-year (2000–2006) analysis showing an overall survival rate of 11 % per year following exercise related SCA in US young people (5–22 years).

Improved Survival by Early Defibrillation in Young Athletes

A more recent research by Drezner et al. [88] on a cohort of 1,710 US high schools with free-standing AED programme demonstrated for the first time an improved survival rate for young athletes with SCA if early defibrillation is achieved. Twenty-three of the 36 SCA victims (64 %) survived to hospital discharge, including 9 of 14 students-athletes and 14 of 22 older nonstudents. Although this was a retrospective cohort study, the consistent reported use of on-site schoolbased AEDs makes this the largest study on successful early defibrillation to treat SCA in the school or athletic setting. Compared with previous studies in intercollegiate athletes, the higher survival rates reported in high school athletes may be explained by the higher proportion of SCA victims treated with AED and the smaller proportion of victims with HCM. An on-site AED was used in the resuscitation of students-athletes in 11 of 14 cases (79 %) cases, and HCM was only found in three of 14 (21 %) cases.

Future Directions and Conclusions

The long-term Italian experience with pre-participation screening of millions of athletes has demonstrated that such a population-based prevention strategy allows the successful identification of athletes affected by potentially malignant cardiovascular diseases and to substantial reduction of mortality [89]. Until other studies, either observational or randomized, on athletic populations of comparable size and follow-up are conducted, the existing data provide good evidence that ECG screening decreases the risk of SCD in athletes. Accordingly, pre-participation ECG screening is currently recommended by the International Olympic Committee (Lausanne Recommendations) [90] as well as by most European Cardiologic Societies and Sports Medical Federations. Recent research reports an improved survival rate for young athletes who experience a SCA if early defibrillation is delivered by on-site AED [88]. Although the presence of a free-standing AED at sporting events is a valuable back up for life-threatening conditions that are unrecognized by ECG screening such as atherosclerotic coronary artery disease, congenital coronary anomalies, or commotio cordis, it should not be considered neither a substitute of pre-participation evaluation nor a justification for participation in competitive sports of athletes with at-risk heart diseases. Pre-participation ECG screening and early defibrillation by AED should not be considered alternative prevention strategies; rather, they should be used synergistically in order to combine primary prevention of SCD during sports by pre-participation identification of athletes affected by potentially lethal heart diseases and secondary prevention with back-up defibrillation of unpredictable arrhythmic cardiac arrest in the athletic field.

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Cardiac Channelopathies and Sudden Infant Death Syndrome

Peter J. Schwartz, Marco Stramba-Badiale, John R. Giudicessi, David J. Tester, Lia Crotti, and Michael J. Ackerman

Abstract

Sudden Infant Death Syndrome (SIDS) represents the leading cause of postneonatal sudden death in developed countries, the third leading cause of infant mortality overall in the United States, and a source of devastating psychosocial consequences for the families of victims. This chapter (i) describes the cardiac QT hypothesis for SIDS according to which some cases of SIDS might be due to ventricular fibrillation associated with prolonged repolarization, (ii) summarizes the results of an 18-year long prospective study with electrocardiogram (ECG) recordings in over 34,000 infants, (iii) discusses recent findings which provide the molecular and functional evidence linking SIDS to cardiac channelopathies like the congenital long QT syndrome (LQTS), Short QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), (iv) presents the results of a prospective ECG study involving 45,000 infants which provided the first opportunity for a data-driven assessment of the prevalence of LQTS and summarizes the main finding of a cost-effectiveness study which analyzes a screening neonatal ECG

P.J. Schwartz, MD (✉)
Department of Molecular Medicine,
University of Pavia and Fondazione IRCCS
Policlinico S. Matteo,
Pavia, Italy

Department of Cardiology,
Fondazione IRCCS Policlinico S. Matteo,
V. le Golgi, 19,
Pavia 27100, Italy
e-mail: peter.schwartz@unipv.it

M. Stramba-Badiale, MD, PhD
Pediatric Arrhythmias Center, IRCCS Istituto
Auxologico Italiano, Via Mose Bianchi, 90,
Milan 20149, Italy
e-mail: stramba_badiale@auxologico.it

J.R. Giudicessi, BA
Divisions of Cardiovascular Diseases and Pediatric
Cardiology, Departments of Medicine,
Pediatrics, and Molecular Pharmacology &
Experimental Therapeutics, Windland Smith Rice
Sudden Death Genomics Laboratory,
Mayo Clinic, Rochester,
MN, USA

D.J. Tester, BS
Cardiovascular Diseases Division,
Department of Medicine, Mayo Clinic,
505 Guggenheim, 200 First St, SW,
Rochester, MN 55905, USA

L. Crotti, MD, PhD
Department of Molecular Medicine,
University of Pavia and Fondazione IRCCS
Policlinico S. Matteo,
Pavia, Italy

Department of Cardiology,
University of Pavia and Fondazione IRCCS
Policlinico S. Matteo, Pavia, Italy
e-mail: l.crotti@smatteo.pv.it

M.J. Ackerman, MD, PhD, FACC
Department of Medicine, Division of Cardiovascular
Diseases, Department of Pediatric and Adolescent Medicine,
Division of Pediatric Cardiology,
Department of Molecular Pharmacology and
Experimental Therapeutics, Mayo Clinic,
Rochester, MN, USA
e-mail: ackerman.michael@mayo.edu,
haglund.carla@mayo.edu

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program in a large European country, and (v) addresses the implications of 35 plus years of research on LQTS and SIDS. The studies presented here provide the conclusive evidence that genetically mediated arrhythmias represent a significant and non-dismissible cause of SIDS and support the concept of widespread neonatal ECG screening for the identification of a subset of infants at high risk for sudden death that can be prevented as it is the case with most patients affected by LQTS.

Keywords
Sudden Infant Death Syndrome • Long QT Syndrome • Neonatal ECG screening • Channelopathies

Introduction

Sudden Infant Death Syndrome (SIDS) represents the leading cause of postneonatal sudden death in developed countries, the third leading cause of infant mortality overall in the United States, and a source of devastating psychosocial consequences for the families of victims [1, 2]. At present, SIDS is defined as the death of any infant prior to his/her first birthday which is unexpected by history and remains unexplained following a thorough post-mortem and death-scene investigation [3]. SIDS is likely a multifactorial disease whose pathogenic basis is often presented through the framework of a "Triple Risk Hypothesis" that argues that SIDS deaths result from the convergence of three overlapping risk factors: (1) a vulnerable infant, (2) a critical developmental period, and (3) the presence of an exogenous stressor(s) [4].

Despite a plethora of hypotheses/theories, mostly focused on abnormalities in the homeostatic control of respiratory or cardiac function, the underlying causes of infant vulnerability to SIDS still remain largely unknown. The suggestions over the years that cardiac mechanisms and specifically life-threatening arrhythmias [5, 6] might account for a significant portion of cases of SIDS have been controversial.

This chapter (i) describes the cardiac QT hypothesis for SIDS according to which some cases of SIDS might be due to ventricular fibrillation associated with prolonged repolarization, (ii) summarizes the results of an 18-year long prospective study with electrocardiogram (ECG) recordings in over 34,000 infants [7], (iii) discusses recent findings which provide the molecular and functional evidence linking SIDS to cardiac channelopathies like the congenital long QT syndrome (LQTS), Short QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), (iv) presents the results of a prospective study involving 45,000 infants and the main finding of a cost-effectiveness study which analyzes a screening neonatal ECG program in a large European country, and (v) addresses the implications of 35 plus years of research on LQTS and SIDS.

The QT Hypothesis

Many hypotheses have been proposed to explain SIDS but none has yet been proven. There is a consensus that SIDS is multifactorial [6, 8], an important concept which implies that a sudden and unexpected death in infancy may stem from many different causes. A logical corollary is that the validity of one mechanism is not negated by the validity of another. Most SIDS cases probably result from an abnormality in either respiratory or cardiac function [8], or in their neural control, that may be transient in nature but sufficient to initiate a lethal sequence of events.

As to the so-called "apnea hypothesis", its demise came with the large, NIH-funded, prospective study CHIME on over 1,000 infants who during the first 6 months of life were observed with home cardiorespiratory monitors for a total of almost 720,000 h of monitoring [9]. The accompanying editorial by Jobe [10] concluded by stating that "*This study justifies a severe curtailing of home monitoring to prevent SIDS*". More details can be found in an earlier review [11].

As to the cardiac hypothesis, Schwartz considered that in the Western world the leading cause of mortality between age 20 and 65 is sudden cardiac death (SCD), and that the mechanism involved is almost always a lethal arrhythmia, ventricular fibrillation. It would be odd if SCD, and therefore lethal arrhythmias, would not contribute to some unexplained deaths during infancy (i.e. SIDS).

In 1976 [5], Schwartz proposed that some cases of SIDS might have been due to a mechanism similar to that responsible for the sudden death of patients affected by LQTS, a leading cause of autopsy negative sudden death below age 20 [12–15]. One such mechanism could be a developmental abnormality in cardiac sympathetic innervation predisposing some infants to lethal arrhythmias in the first year of life [5]. Another possible mechanism could be a LQTS-causing genetic mutation [12–15]. In either case, the only clinically detectable marker might be a prolonged QT interval on the electrocardiogram (ECG).

Following the editorial by Schwartz in 1976 [5], the hypothesis that QT interval prolongation might play a role in the genesis of SIDS received attention. However despite some very early support by Maron et al. [16], it was rapidly, and perhaps prematurely, discarded on the basis of a series of apparently negative results [17–21]. The weaknesses in the arguments against a possible role of abnormal cardiac repolarization in the pathogenesis of SIDS have been discussed in detail previously [6, 22].

The Italian Study on Neonatal ECG and SIDS

To test the Schwartz QT-SIDS hypothesis, a prospective study involving 12-lead ECG screening of 3–4 day old infants was designed and was initiated in 1976. Given the low incidence of SIDS (0.5–1.5 per 1,000 live births), it was necessary to prospectively collect neonatal ECGs in a very large population and to subsequently follow these infants for 1 year to assess the occurrence of SIDS or deaths from other causes. The results from this 18-year study were published in 1998 [7] and are summarized here.

Twelve-lead ECGs were recorded in 34,442 neonates. The QT interval was measured by investigators blinded to the survival status of the infant. Of the 34,442 infants enrolled, 33,034 (96 %) completed the 1-year follow-up. Those lost-to-follow-up were due to change of residence. The mean Bazett's heart rate corrected QT interval (QTc, QT divided by the square root of the RR interval) at 3 or 4 days of life was 400 ± 20 ms, unaffected by gender. The normal and symmetrical distribution of the QTc in our population made the 97.5th percentile value of QTc correspond to 440 ms, 2 standard deviations above the mean. Consequently, we considered a value greater than 440 ms during the first week of life as a prolonged QTc.

During the 1-year follow-up there were 34 deaths: 24 classified as SIDS and 10 attributed to definite causes. All post-mortem examinations of SIDS victims were negative and failed to document an adequate cause of death. No SIDS victim had a family history of LQTS or sudden death. The mean QTc was 435 ± 45 ms in the SIDS group, significantly longer than that of the non-SIDS victims (392 ± 26 ms, $p < 0.05$) and of the cohort alive at 1-year (400 ± 20 ms, $p < 0.01$). Importantly, half of the SIDS victims (12/24) exceeded the 97.5 % cut-off value of 440 ms indicating a strong association between a right-shifted QTc and susceptibility for SIDS. In fact, the odds ratio (OR = 41.3, 95 % CI 17.3–98.4) exceeds nearly all of the classic risk factors linked with SIDS such as prone sleep, cigarette smoke exposure, etc. However, given that 2.5 % of healthy infants exceed this cut-off value of 440 ms, screening implications during the first week of life are challenged by the very poor positive predictive value (i.e. <2 %). Nonetheless, it is fair to remind that when the event rate is low, positive predictive values for any marker are always poor.

The Molecular Link

Potential Causes for QT Prolongation in Infants

This large prospective study based on more than 34,000 infants demonstrated that QT interval prolongation, on the standard ECG recorded on

the 3rd–4th day of life, is a major risk factor for SIDS [7]. While borderline values and transient QT prolongations do occur in the first week of life, the study provided the first compelling evidence that the observed QT prolongation either reflected a "vulnerable" infant with autonomic dysregulation [5], drug-induced QT prolongation [11], acquired QT prolongation secondary to other disease states, or a "vulnerable" infant with a LQTS-predisposing substrate [23].

The first mechanism is partly based on the fact that an imbalance in cardiac sympathetic innervation with left dominance, experimentally produced by removing the right stellate ganglion, prolongs the QT interval and increases susceptibility to ventricular fibrillation in several conditions, including 3 week old puppies with normal hearts [24]. The sympathetic innervation of the heart continues to develop after birth and becomes functionally complete by approximately the sixth month of life. The right and left sympathetic nerves may occasionally develop at different rates and lead temporarily to a harmful imbalance [25]. A sudden increase in sympathetic activity, particularly when involving the arrhythmogenic left sided nerves [25], might easily trigger a lethal arrhythmia in these electrically unstable hearts. The original data with right stellate ganglionectomy [26] have been reproduced by Chen and associates using Nerve Growth Factor injected in the left stellate ganglion [27]. Infants with this type of sympathetic imbalance, either developmental or genetic, would be more vulnerable during the first few months of life and the higher risk for SIDS could be identified by the observation of a prolonged QT interval. This pathogenic mechanism, however, is difficult to prove (or dismiss). Nevertheless, a prolonged QT interval might be a surrogate marker for autonomic dysregulation and the "vulnerable" infant.

The second mechanism relates to the fact that several drugs commonly used in the neonatal period and during infancy may induce QT interval prolongation, as previously discussed [11]. Also, almost half of the neonates born from mothers with autoimmune diseases and positive for the anti Ro/SSA antibodies show QT interval prolongation [28], with values of QTc that sometimes exceed 500 ms even in the absence of AV conduction abnormalities, the typical manifestation of neonatal Lupus syndrome [29]. At variance with congenital heart block, these ventricular repolarization abnormalities are transient and disappear by the 6th month of life, concomitantly with the disappearance of the anti Ro/SSA antibodies [30]. This transient QT prolongation could well predispose some anti-Ro positive infants to life-threatening arrhythmias. The implications are twofold: the presence of asymptomatic autoimmune diseases should be excluded in mothers of neonates showing QT prolongation in the absence of other causes and neonates born from mothers with Lupus erythematosus should be followed during the first year of life with repeated ECGs.

As to the possibility that the QT prolongation reflects an infant at risk for SIDS because of congenital LQTS, one potential difficulty in linking LQTS to SIDS is that the latter is not a familial disease. Two concepts are highly relevant here. The first is that "sporadic" cases of LQTS result from *de novo* mutations that, by definition, are inherited from either parent. The second is represented by the demonstration of "low penetrance" in LQTS [23]. Low penetrance implies that clinical diagnosis is often inadequate and that many affected individuals may appear completely normal at clinical examination. In congenital LQTS, disease penetrance is estimated to be approximately 60 %.

Molecular Evidence

Indeed, three independent, anecdotal cases which demonstrate that *de novo* mutations in LQTS genes may manifest as, and be indistinguishable from, typical cases of "near-miss" SIDS or as SIDS itself have been reported [31–33]. The first two cases, which represented "proof-of-concept" for the possibility that LQTS could cause events clinically indistinguishable from SIDS, are worth reporting in some detail.

In the first case report, a 7-week old infant was found cyanotic, apneic, and pulseless by his parents [31]. He was rushed to a nearby hospital while his father was attempting CPR. In the emergency room, ventricular fibrillation was recorded (Fig. 24.1). Thus, this infant presented as typical "near-miss" for SIDS. After defibrillation, the

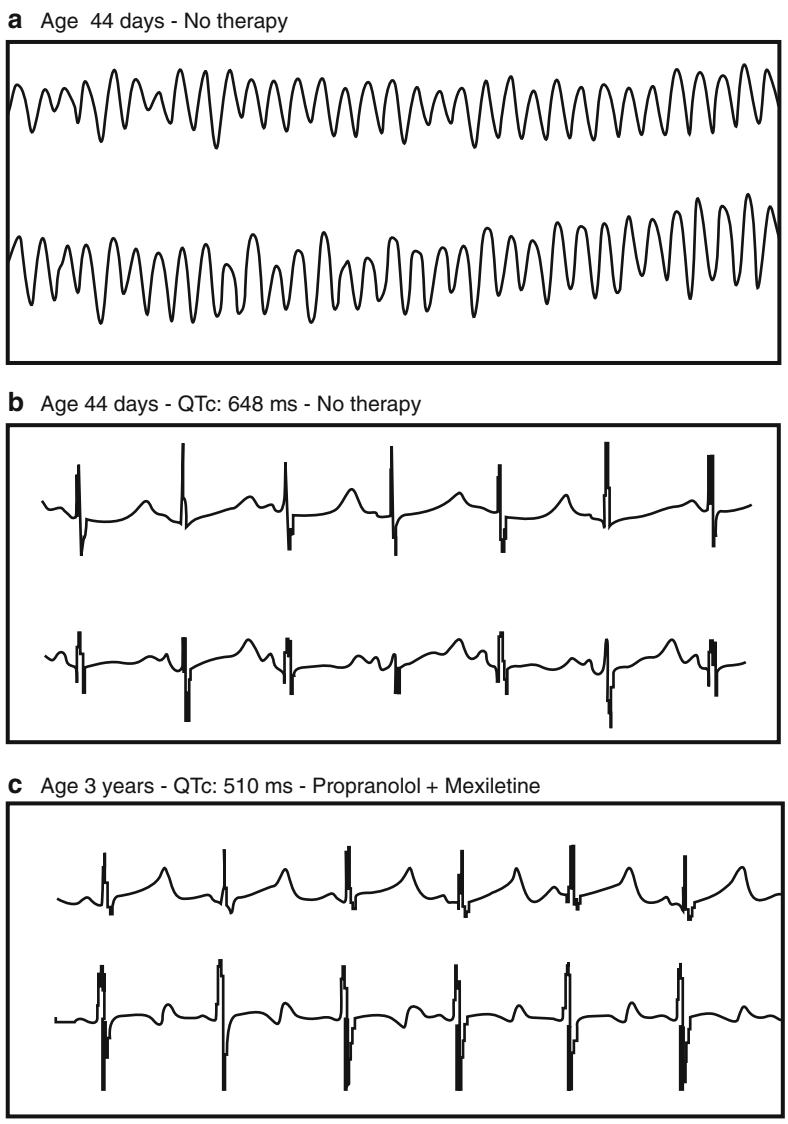

Figure 24–1. ECG leads II and V2, showing ventricular fibrillation at hospital admission (panel **a**); QT interval prolongation observed the same day after restoration of sinus rhythm (panel **b**); and ECG recorded at the last follow up visit (panel **c**) (Modified from Ref. [31])

ECG revealed extreme QT prolongation (QTc 648 ms), LQTS was diagnosed and therapy was instituted by combining beta-blockade and the sodium channel blocker mexiletine. A critical point is that the QT interval of both parents was normal, paternity being confirmed. Molecular screening identified a mutation in *SNC5A*, the cardiac sodium channel gene responsible for type 3 LQTS (LQT3) [13–15]. This disease-causing mutation was not present in either parent, thus establishing that this was a *de novo* mutation. The documentation of ventricular fibrillation at arrival in the emergency room is quite important given the frequent statements such as "*no one has recorded ventricular arrhythmias in infants at risk for SIDS*" [34]. Had the infant died, a certainty without cardioversion, the absence of an ECG, the negative family history, and the parents' normal QT intervals would have prompted the classic labeling of SIDS. Thus, infants who have similar *de novo* mutations, involving one of the ion channels controlling ventricular repolarization, may have a prolonged QT interval at birth. Some of them may die *in utero* because of ventricular fibrillation, and thus become stillbirths [35], or during the first few

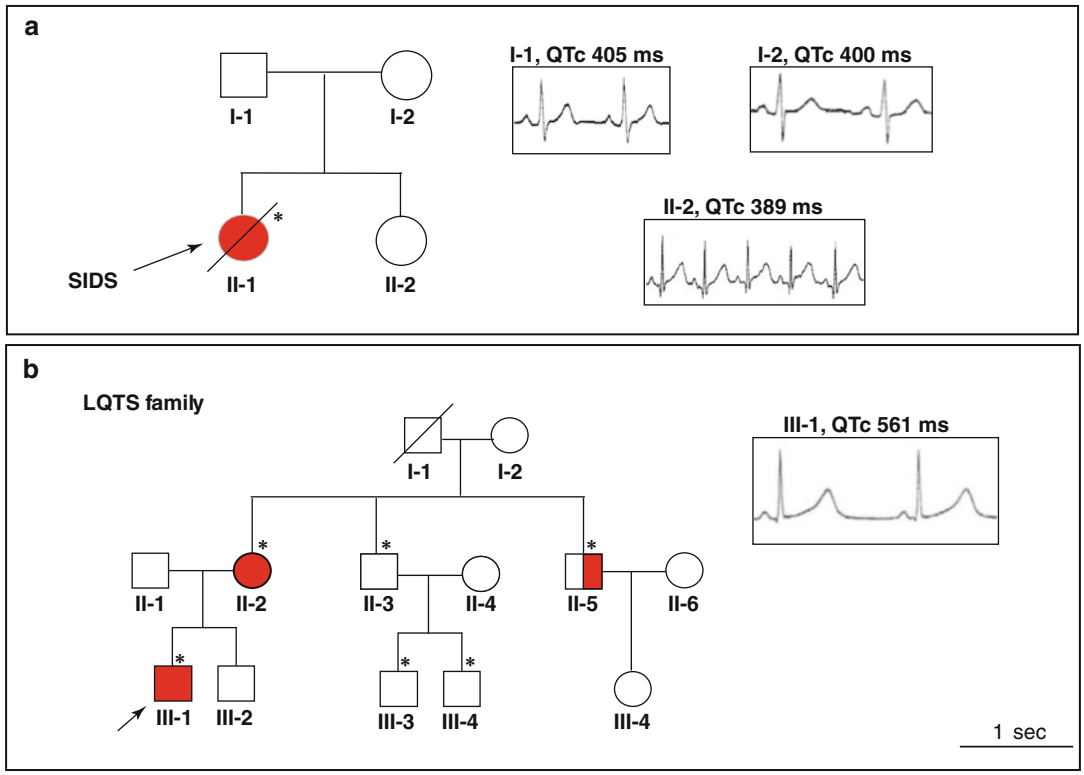

Figure 24–2. Pedigrees and ECG tracings of the two families with the P117L mutation. Panel **a** shows the pedigree of the SIDS family [32]. ECG tracings of the parents (I-1 and I-2) and the sister (II-2) of the proband showing a normal QT interval (lead II) are reported on the *right*. Panel **b** shows the pedigree of the family with LQT1 due to P117L-KCNQ1. On the *right*, lead II ECG recording obtained in the proband (III-1). *Arrows* indicate probands. *Filled symbols* represent individuals presenting with syncope and prolonged QT interval. *Half-filled symbols* represent individuals with QT interval prolongation and no symptoms. *Asterisks* indicate carriers of the P117L mutation

months of life and without an available ECG, these deceased infants would be labeled as victims of SIDS. Others would probably begin to have syncopal episodes or non-fatal cardiac arrests during their childhood and would only then be diagnosed as sporadic cases of LQTS.

In the second case report [32], a 4-month old infant was found dead in her crib. A thorough post-mortem examination was negative and the diagnosis of SIDS was rendered. When post-mortem molecular genetic testing was performed, a missense mutation (*KCNQ1*-P117L) was identified. Both parents of the victim and her sister had normal QT intervals and no one had the P117L mutation. Paternity was confirmed once again establishing the presence of a spontaneous, germline mutation (sporadic, *de novo*) in the deceased infant. The same identical mutation is present in one of the LQTS families followed in Pavia (Fig. 24.2). This case provided the first evidence that in a child whose death was classified as SIDS, according to current standards, a molecular autopsy made possible the diagnosis of an arrhythmogenic disease, LQTS.

These single case reports provided the "proof-of-concept" evidence linking LQTS and SIDS. These studies provided the first unequivocal demonstration that life-threatening events and actual unexpected sudden deaths in infancy, with all the characteristics for SIDS or for "near miss" for SIDS, can depend on a *de novo* mutation in one of the LQTS genes thus escaping recognition in the parents but nevertheless precipitating sudden death due to ventricular fibrillation. Following these case reports, Ackerman and colleagues provided the first

genetic epidemiology studies investigating the hypothesis of cardiac channel mutations in SIDS by conducting comprehensive post-mortem mutational analysis of the five major long QT disease genes (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2*) in a large (N = 93) 2-year, state-wide, population-based cohort of SIDS [36, 37]. Notably, genetic testing for the three major (*KCNQ1*, *KCNH2*, *SCN5A*) and several minor LQTS-susceptibility genes is now a routine, clinically available diagnostic test. Three of the 58 deceased white infants (5.2 %) and 1 of 34 deceased black infants (2.9 %) hosted LQTS-causing mutations.

Schwartz and colleagues have independently validated and extended this observation in a much larger cohort of SIDS involving 201 Norwegian infants [38]. Here, the investigators found compelling molecular and functional evidence to implicate LQTS-causing mutations in approximately 9 % of cases. Of the 201 SIDS victims, 18 (9 %) were carries of LQTS gene variants with functional effect, and 50 % had mutations in the sodium channel gene *SCN5A* [39]. The size of the study population has provided a reliable estimate of the prevalence of mutations in the LQTS genes (at least among Norwegians), as shown by the narrow 95 % confidence intervals, which range between 5.4 and 13.8 %.

Collectively these findings indicate that (1) mutations in the major LQTS-susceptibility genes may account for approximately 10 % of SIDS cases. As 20–25 % of the patients with typical LQTS are genotype-negative, we currently estimate the likely probability of SIDS cases explained by LQTS to be close to 12–15 % (2). While mutations in *SCN5A* account for only 5–10 % of LQTS cases, they comprise nearly half of the rare "channelopathic" variants identified in SIDS cases [38–40]. As one would expect, as the list of putative LQTS-susceptibility genes has grown, so too has the number of channelopathic substrates linked to SIDS pathogenesis. Since 2007, Ackerman and colleagues have identified putative SIDS-causing mutations in several minor genes implicated in the pathogenesis of LQTS including: *CAV3*-encoded caveolin-3 (LQT9) [41], the *SCN4B*-encoded sodium channel β-subunit 4 (LQT10) [42], and *SNTA1*-encoded α1-syntrophin (LQT12) [43]. Interestingly, each of these genes encodes a molecular constituent of the cardiac sodium channel macromolecular complex providing further evidence that functional perturbations in the Nav1.5 channel/complex that result in an LQT3-like increase in late cardiac channel sodium current play a prominent role in the pathogenesis of channelopathic SIDS cases.

LQTS is not the exclusive channelopathic cause of SIDS. Short QT syndrome (SQTS; QTc < 350 ms for males and <360 ms for females), first described in 2000 by Gussak [44], may manifest as sudden cardiac death during the first year of life, suggesting a possible role for SQTS in some cases of SIDS [45–47]. In fact, Schwartz and colleagues identified in one of their Norwegian SIDS cases a gain-of-function I274V-*KCNQ1* mutation consistent with a short QT syndrome type 2 (SQT2)-like electrophysiologic cellular phenotype [38, 48]. Recent work has also unearthed SIDS-susceptibility mutations in the Brugada syndrome (BrS)-susceptibility genes *GPD1L* (BrS2) [49] and *SCN1B*/*SCN1Bb* (BrS7) [42, 50], which both result in cardiac sodium channel loss-of-function. Mutations in the *RyR2*-encoded cardiac ryanodine receptor/calcium release channel which underlies type 1 catecholaminergic polymorphic ventricular tachycardia (CPVT1) have also been identified in SIDS [51]. While not directly linked to the alteration of cardiac repolarization, Ackerman and colleagues recently identified two novel genetic substrates for channelopathic SIDS: (1) loss-of-function mutations in the *KCNJ8*-encoded Kir6.1 ATP-sensitive potassium channel (IKATP) that may confer a maladaptive cardiac response to systemic metabolic stress [52] and (2) a loss-of-function mutation in the *GJA1*-encoded connexin 43 gap junction protein with mosaic expression in the heart that completely abolishes electrical junctional coupling between cells *in vitro*. A full summary of SIDS-susceptibility genes linked to disruptions in the electrical systems of the heart is presented in Table 24.1.

Besides rare, pathogenic LQTS/SQTS/BrS/CPVT susceptibility mutations, these and similar investigations have also exposed the possible contribution of "repolarization reserve"-altering cardiac channel polymorphisms to the "vulnerable infant" component of the SIDS Triple-Risk Hypothesis. Even after excluding the most

Table 24–1. SIDS-associated mutations in cardiac channelopathy genes

Gene	Protein product	Functional role	Functional effect of SIDS mutations	Clinical syndrome
Cardiac sodium channel macromolecular complex genes				
SCN5A	Nav1.5	α-subunit of Nav1.5 channel	I_{Na} gain-of-function (increased late current)	LQT3
			I_{Na} loss-of-function	BrS1
SCN3B	Navβ3	β-subunit of Nav1.5 channel	I_{Na} gain-of-function (increased late current)	BrS7
SCN4B	Navβ4	β-subunit of Nav1.5 channel	I_{Na} loss-of-function	LQT10
CAV3	Caveolin-3	Scaffolding protein	I_{Na} gain-of-function (increased late current)	LQT9
GPD1L	G3PD1L	Not entirely understood	I_{Na} loss-of-function	BrS2
SNTA1	α1-syntrophin	Scaffolding protein	I_{Na} gain-of-function (increased late current)	LQT12
Cardiac potassium channel macromolecular complex genes				
KCNQ1	Kv7.1	α-subunit of Kv7.1 channel	I_{Ks} loss-of-function	LQT1
			I_{Ks} gain-of-function	SQT2
KCNH2	Kv11.1	α-subunit of Kv11.1 channel	I_{Kr} loss-of-function	LQT2
KCNE1	minK	β-subunit of Kv7.1 channel	I_{Ks} loss-of-function	LQT5
KCNE2	MiRP1	β-subunit of Kv11.1 channel	I_{Kr} loss-of-function	LQT6
KCNJ8	Kir6.1	α-subunit of Kir6.1 channel	I_{KATP} loss-of-function	N/A
Cardiac calcium release channel genes				
RYR2	RyR2	SR ryanodine receptor	Calcium leak from sarcoplasmic reticulum	CPVT1
Other genes				
GJA1	Connexin43	Gap junction protein	I_j loss-of-function	N/A

Abbreviations: I_{Na} cardiac fast sodium current, I_{Ks} slow component of the delayed rectifier current, I_{Kr} rapid component of the delayed rectifier current, *SR* sarcoplasmic reticulum, I_j gap junctional current, *LQT* long QT syndrome, *BrS* Brugada syndrome, *SQT* short QT syndrome, *CPVT* catecholaminergic polymorphic ventricular tachycardia

common channel polymorphisms: *KCNH2*-K897T, *SCN5A*-H558R, and *KCNE1*-G38S, nearly one-third of infants possessed at least one genetic variant noted previously in ethnic-matched reference alleles in one of the five cardiac channel genes [37–39].

Whether or not a bulk of these channel polymorphisms reduce repolarization reserve and/or facilitate adrenergically-mediated cardiac arrhythmias requires further investigation. Interestingly, a single nucleotide polymorphisms (SNPs) in the *NOS1AP* gene associated with QT interval variation in health [53, 54] and risk of cardiac events in LQTS [55, 56] was positively correlated with SIDS in a small population-based study [57]. Furthermore, two independent studies found the functional African-American-specific sodium channel common polymorphism, *SCN5A*-S1103Y, to be statistically over-represented in African-American SIDS [58, 59]. Lastly, several SIDS victims harbor SNPs, such as *KCNH2*-R1047L, that serve as independent risk factor for drug-induced (dofetilide) torsades [37, 60]. Indeed, even the most common of single nucleotide polymorphisms in cardiac channels (*KCNH2*-K897T and *SCN5A*-H558R) are not necessarily innocent bystanders, having been shown to modulate the properties of other disease-causing mutations [61–63]. In fact, in the Norwegian SIDS study, all seven decedents with mutations/rare variants in *SCN5A* that displayed a modest but definite functional effect were also heterozygous for H558R. Moreover, the allele frequency for H558R was twice as large in this subgroup of SIDS cases compared to controls ($p = 0.02$).

These findings provide the conclusive evidence that genetically mediated arrhythmias represent a significant and non-dismissible cause of SIDS. Furthermore, given the fact that malignant LQTS is associated with marked QT prolongation, these observations support the concept

of widespread neonatal ECG screening and indicate that at least this subset of infants at high risk for sudden death during infancy or beyond can be diagnosed early on and that their impending death can probably be prevented, as it is the case with most patients affected by LQTS. These implications will be discussed next.

Implications and New Directions

The aforementioned studies carry obvious clinical implications and have forced new investigations. The highly significant association between QT prolongation and occurrence of SIDS unavoidably raises the issue regarding the potential value of routine neonatal ECG screening. This, in turn, requires knowledge on the feasibility and on results that can be expected by such a study and also an accurate estimate of its cost-effectiveness. This information has become available and will be presented in the next sections. A practical issue involves the management of infants found to have significant QT prolongation by such a screening program. Overwhelming data from thousands of LQTS families indicate that treatment with beta-blockers has reduced mortality below 2 % [64, 65]. This information is relevant to the prevention not only of early deaths (which would be labeled as SIDS) in newborns with a prolonged QT interval but also of later sudden deaths due to LQTS.

A "Pilot" Study on 45,000 Infants

The Italian Ministry of Health has considered the possibility of introducing – as part of the National Health Service – an electrocardiographic screening program in the first month of life with the objective of identifying infants affected by the LQTS in order to treat these babies and prevent sudden death in the first months of life and during childhood. A requirement made by the Italian Ministry of Health, prior to final consideration for the implementation of a nation-wide neonatal ECG screening program, was the performance of a "large scale" pilot study with ECGs performed during the 3rd and 4th weeks of life, as recommended by the guidelines of the European Society of Cardiology [66].

The study constitutes the largest ECG prospective study ever performed in infants [67]. The population under study included 44,596 neonates (43,080 whites), 22,967 males (51 %), and 21,629 females (49 %) consecutively enrolled by 18 Italian maternity hospitals from 2001 to 2006, in whom an ECG was recorded between the 15th and the 25th day of life. Whenever a QTc > 450 ms was found, the ECG was repeated within 1–2 weeks to confirm the initial finding. If QT prolongation was confirmed or any other ECG abnormality was identified, the infants were managed and treated according to the guidelines [66] and in the case of a QTc > 470 ms, a blood sample was taken from the neonate and from his or her parents for genetic analysis. Molecular screening was performed on *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *CAV3*, and *SCN4B* genes. Toward the end of the study, it was decided to extend the genetic analysis to the infants with a QTc between 461 and 470 ms.

The QT interval was considered prolonged according to the guidelines for the interpretation of neonatal ECG of the European Society of Cardiology [66]. In 1094 neonates (2.5 %) QTc was >440 ms, and in 858 (2.0 %) it was between 441 and 450 ms. There were 177 infants with a QTc between 451 and 460 ms, 28 between 461 and 470 ms, and 31 with a QTc >470 ms. Among these 31 neonates (1:1,438; 0.07 %; 23 females and 8 males), 4 had a QTc >500 ms.

Molecular analysis was performed in 28 neonates with QTc >470 ms available during follow-up. LQTS mutations were identified in 12 of 28 neonates (43 %): 8 were carrying heterozygous mutations on the *KCNQ1* gene (LQT1) and 4 on *KCNH2* (LQT2), thus confirming the higher prevalence of LQT1. Among the 14 neonates with a QTc between 461 and 470 ms for whom a blood sample was available, LQTS mutations were identified in 4 (29 %): one infant carried a mutation on *KCNH2*, one carried 2 independent mutations on *KCNH2* and *KCNQ1* and the remaining two cases, a mutation on *KCNE1* and *KCNE2*, respectively. Thus, overall 16/42 (38 %) newborns with a QTc >460 ms carried disease-causing mutations of LQTS. Of note, of the 7 neonates who had a QTc >485 ms at the ECG, 6 were disease-causing mutation carriers.

QTc normalization at 1 year of life occurred in 3 of 16 genotype-positive (19 %) and in 24 of 25 genotype-negative infants (96 %) Importantly, the only genotype-negative child in whom QTc remained prolonged was one whose father also had marked QT prolongation and who was considered affected by LQTS on clinical criteria. Among the 14 infants whose QT interval remained prolonged at 1 year of life, a disease-causing mutation was identified in 13 (92 %).

In all 16 cases with LQTS mutations, genetic analysis was extended to the parents and, whenever appropriate and possible, to other family members, and it allowed the identification of 42 of 82 mutation carriers (51 %).

This prospective study clearly indicates that at least 17 infants (16 because of disease-causing mutations and 1 because of clear-cut clinical diagnosis) among this cohort of 44,596 neonates are affected by LQTS. All of them are white. LQTS, as all other arrhythmogenic diseases of genetic origin, is considered rare but its real prevalence has remained unknown. Rates ranging from 1:20,000 to 1:5,000 have been reported, but these numbers are unfortunately not supported by actual data. Our large prospective ECG study in 3- to 4-week-old infants provided the first opportunity for a data-driven assessment of the prevalence of LQTS. The prospective study indicates a prevalence among whites of 1:2,534 (95 % confidence interval, 1:1,583–1:4,350). Considering the possibility that among the non-genotyped infants with a QTc between 450 and 470 ms there might be some LQTS mutation carriers, we suggest that the prevalence of LQTS may be closer to 1:2,000, much higher than that suggested previously [67].

Unexpectedly, this "pilot" study also prompted the identification of 4 cases of two major and life-threatening congenital heart diseases that had escaped recognition during the initial medical visit including 3 cases of coarctation of the aorta and 1 case of anomalous origin of the left coronary artery. Each infant promptly and successfully underwent surgical correction of their defect. This finding has significant implications for the cost-effectiveness of a neonatal ECG screening program. The ECG screening was extremely well received by all families with practically a 100 % acceptance. This study proved that such a screening program is feasible and allows early identification of infants affected either by LQTS or by other significant cardiovascular disorders.

Cost-Effectiveness of a Neonatal ECG Screening Program

Based on the initial studies linking QT prolongation, LQTS, and SIDS [5–7] some European countries have begun to consider the possibility of introducing in their National Health Services, the performance of an ECG during the first month of life in all newborns, as part of a cardiovascular screening program. Should neonatal screening indeed be introduced as part of National Health Services, then hospital cardiologists – most of whom are utterly unfamiliar with neonatal ECGs – would be asked to read these tracings. The European Society of Cardiology has realized the potential implications for European cardiologists and for health care, and has acted accordingly by instituting a Task Force for the creation of guidelines for the interpretation of the neonatal ECG [66]. The Task Force has provided such guidelines focusing on the most clinically relevant abnormalities, on the ensuing management and referral options. As a starting point it was suggested that the number of false positives could be greatly reduced by performing the screening ECG in the 3rd–4th week of life and by repeating it when QTc values appear abnormal.

To provide the information necessary for governmental agencies to decide on possible implementation, a formal cost-effectiveness study was performed [68]. It is vital, given the frequent misunderstandings and misquotations, to stress that the objective of such an ECG surveillance program is not the identification of infants at risk for SIDS (an unrealistic target) but is instead the early identification of infants affected by LQTS, a potentially lethal, highly treatable condition that affects 1 in 2,500 infants. Without diagnosis, few of these infants might die suddenly in the first year of life – and would then almost certainly be labeled as a SIDS victim – or might die later on, as children, teenagers or young adults. The ultimate objective of early identification is the prevention of sudden death for a significant

number of patients with LQTS, irrespective of their age.

The study used Markov process analysis to forecast natural and clinical histories of subjects with or without screening. Monte Carlo simulations were used to simultaneously alter all the uncertain parameters (process-related probabilities and costs) by ±30 % to cover for any potential error and for inter-country variability. The main finding was that by screening only for LQTS, the cost per year-of-life saved was 11,740 Euros. When, as it happens in the real world [67], two congenital heart diseases (coarctation of the aorta and anomalous origin of the left coronary artery) are considered also, then the cost per year-of-life saved was only 7,022 Euros. These figures denote a "highly cost-effective" screening program. Traditionally, figures below 50,000 US dollars are deemed "cost-effective". Recently, an estimate of costs related to the actual organization of a mass neonatal ECG screening in Italy has been performed. Taking into account all the expenses, including implementation of the screening program, equipment and personnel, genetic tests in neonates with prolonged QT interval and in their family members if positive, additional tests and therapies in affected neonates and family members, the cost per infant is 12 Euros. Thus, the introduction of a program for the early identification of LQTS in order to prevent sudden cardiac death in infancy but also in childhood, based on the ECG as a screening test and genetic analysis in selected cases, would cost less than 6 million Euros per year, which corresponds to 1/17,500 of the national healthcare expenditure of a large European country such as Italy. This is a very modest cost for saving precious young lives.

Medico-Legal Implications

The evidence that neonatal electrocardiography might be useful for the identification of those infants who are at risk for an early arrhythmic death, besides prompting clinical decisions, also carries significant medico-legal implications.

There are two critical points. One is that approximately 10 % of future SIDS victims (and probably a larger number of future victims of sudden death in the young) carry LQTS mutations likely to produce repolarization changes identifiable by neonatal electrocardiography [38] and that, due to the understanding of the lethal mechanisms involved, there are high chances to prevent these untimely sudden deaths. The other is the evidence [69, 70] that it is possible to make a molecular diagnosis of LQTS in a SIDS victim of whom no pre-mortem ECGs were ever recorded [31–33, 69]. Further support for the importance of early ECG screenings to identify at-risk individuals affected by LQTS is provided by evidence from so-called molecular autopsies whereby ~20 % of autopsy negative sudden death victims were found to harbor mutations in LQTS-susceptibility genes [69, 71].

The still prevailing concept of the impossibility of identifying infants at truly high and specific risk for SIDS has the undeniable advantage that no one has to be blamed, except a cruel fate. The evidence presented above changes all that. Parents of SIDS victims or, more appropriately, their physicians may now begin to ask for a post-mortem molecular genetic test. What will happen when such a molecular autopsy identifies a LQTS-susceptibility mutation and a lethal ventricular arrhythmia as the likely cause of death? The bereaved parents, and their lawyers, will start asking new questions. Indeed, in our opinion, the parents of a newborn child have the right to be informed about the existence of a potentially lethal albeit uncommon cardiovascular disease of which the most malignant forms can be rather easily exposed by a simple ECG and for which very effective and safe therapies are available. It will then be their choice to spend a very small amount of money to evaluate for this highly unlikely but life-threatening possibility. Without information they would be denied the option. Failure to fully inform families of this possible scenario could, in a very near future, carry medico-legal consequences.

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25
Heart Failure and Sudden Death

Yong-Mei Cha and Win-Kuang Shen

Abstract

Syndrome of congestive heart failure is a clinical manifestation of many cardiac disease processes when the cardiovascular compensatory mechanisms are no longer able to maintain homeostasis. Approximately five million people in the United States have heart failure and over 550,000 of patients are diagnosed with heart failure for the first time each year. The Framingham heart study reported 62 and 42 % 5-year survival rates, respectively, for men and women with newly diagnosed congestive heart failure in the early 1970s. These mortality rates were six to seven times higher than that of age-matched general population. Of the total mortality, approximately 40–50 % were sudden deaths. The trending in the incidence and survival with heart failure among 11,311 subjects in the Framingham heart study during a 50-year interval has been updated. Heart failure occurred in 1,075 study participants between 1950 and 1999. The 5-year mortality rate among men declined from 70 % in the period from 1950 to 1969 to 59 % in the period from 1990 to 1999, whereas the respective rates among woman declined from 57 to 45 %. Although the relative declining of mortality is encouraging, likely a result of the better understanding of the disease pathophysiology and improvement of the medical and device therapy, the growing epidemics of heart failure has been increasingly recognized in the United States and around the globe.

The topic of heart failure and sudden death is enormously broad. Many specific and related topics are discussed in other chapters of the book. In this chapter, we will provide an overview on the following relevant issues: (1) mode of death in patients with heart failure; (2) arrhythmogenic substrates and triggers of malignant arrhythmias causing sudden death; (3) risk stratification schemes in identifying patients at increased risk of sudden death in heart failure; (4) outcomes from sudden death prevention clinical trials; and (5) a summary of current clinical management in sudden death prevention in heart failure.

Keywords

Heart failure • Sudden death • Arrhythmia • Ventricular tachycardia • Ventricular fibrillation

Y.-M. Cha, MD (✉)
Cardiovascular Diseases and Internal Medicine,
Mayo Clinic, 200 First Street,
SW, Rochester,
MN 55041, USA
e-mail: cha.yongmei@mayo.edu

W.-K. Shen
Division of Cardiovascular Diseases,
Department of Medicine,
Mayo Clinic College of Medicine,
Mayo Clinic Arizona, Phoenix, AZ, USA
e-mail: wshen@mayo.edu

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Introduction

Syndrome of congestive heart failure is a clinical manifestation of many cardiac disease processes when the cardiovascular compensatory mechanisms are no longer able to maintain homeostasis. Approximately five million people in the United States have heart failure and over 550,000 of patients are diagnosed with heart failure for the first time each year [1]. The Framingham heart study reported 62 and 42 % 5-year survival rates, respectively, for men and women with newly diagnosed congestive heart failure in the early 1970s [2]. These mortality rates were six to seven times higher than that of age-matched general population. Of the total mortality, approximately 40–50 % were sudden deaths [3]. The trending in the incidence and survival with heart failure among 11,311 subjects in the Framingham heart study during a 50-year interval has been updated [4]. Heart failure occurred in 1,075 study participants between 1950 and 1999. The 5-year mortality rate among men declined from 70 % in the period from 1950 to 1969 to 59 % in the period from 1990 to 1999, whereas the respective rates among woman declined from 57 to 45 % (Fig. 25.1). Although the relative declining of mortality is encouraging, likely a result of the better understanding of the disease patho-physiology and improvement of the medical and device therapy, the growing epidemics of heart failure has been increasingly recognized in the United States and around the globe.

The topic of heart failure and sudden death is enormously broad. Many specific and related topics are discussed in other chapters of the book. In this chapter, we will provide an overview on the following relevant issues: (1) mode of death in patients with heart failure; (2) arrhythmogenic substrates and triggers of malignant arrhythmias causing sudden death; (3) risk stratification schemes in identifying patients at increased risk of sudden death in heart failure; (4) outcomes from sudden death prevention clinical trials; and (5) a summary of current clinical management in sudden death prevention in heart failure.

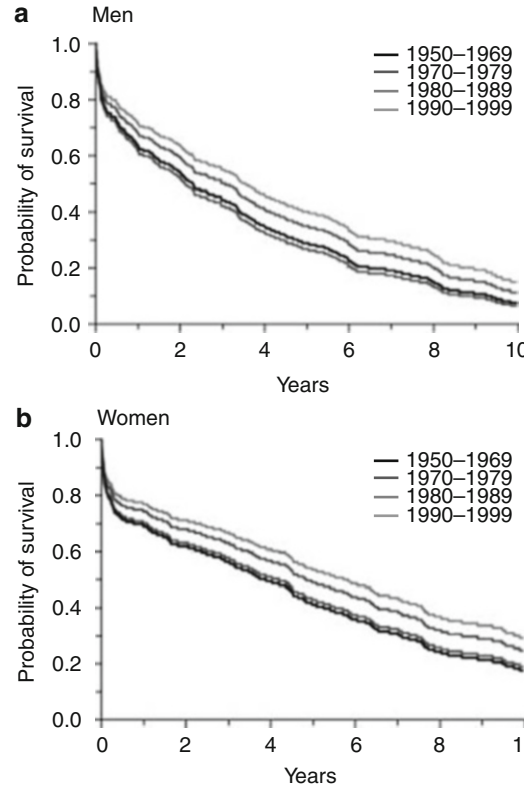

Figure 25–1. Temporal trends in age-adjusted survival after the onset of heart failure among men (panel **a**) and women (panel **b**). Values were adjusted for age (<55, 55–64, 65–74, 75–84, and 85 years). Estimates are shown for subjects who were 65–74 years of age (From Levy et al. [4]. Reprinted with permission from Massachusetts Medical Society)

Death Mode in Advanced Stage of Heart Failure

Sudden death is often equated with primary arrhythmia events. While ventricular tachyarrhythmias are the most common rhythms associated with unexpected sudden death, bradycardia and other pulseless supraventricular rhythms are also common in patients with advanced heart failure [5]. In MERIT-HF trial, a total of 3,991 patients with chronic heart failure in New York Heart Association (NYHA) functional class II-IV and with an ejection fraction of 0.4 or less were randomized to either placebo or Metoprolol CR/XL groups. During a mean follow-up duration of

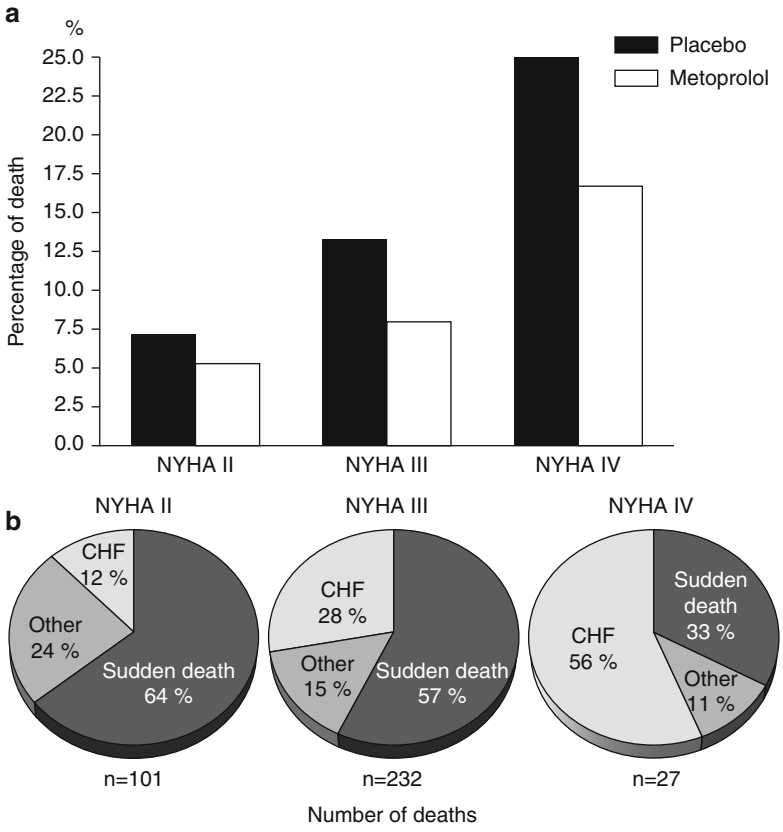

Figure 25–2. (**a**) Total mortality in relationship to NYHA class in Metoprolol and placebo groups from MERIT-HF trial. (**b**) Severity of heart failure and mode of death from MERIT-HF trial (From Cha and Shen [6]. Reprinted with permission from Springer Publishers)

1 year, total mortality was lower in the Metoprolol group than in the placebo group (7.2 % versus 11 %). Fifty-eight percent of these deaths were classified as sudden. The study analyzed the total mortality and mode of death in relationship to NYHA functional class at randomization. While the absolute frequency of death is highest in patients with severe symptoms or in NYHA function class IV (Fig. 25.2a), the proportion of sudden death generally decreased with the increasing severity of heart failure, from 60 % in class II or III down to 30 % in class IV heart failure. The proportion of patients who died from pump failure increased from 25 % in NYHA class II to 35 % in class III and up to 55 % in class IV (Fig. 25.2b) [7]. Implantable cardioverter defibrillator (ICD) provided a unique opportunity to record terminal rhythm at the time of death. Although the frequency of a primary bradycardia-mediated sudden event can not be assessed in the ICD patient population because of the presence of pacing function in all ICDs, other mechanisms of sudden death were investigated from a non-thoracotomy ICD database [8]. Among 317 patients that died after ICD implantation, 28 % were sudden cardiac, 49 % were non-sudden cardiac, and 27 % were non-cardiac. Among the sudden death, 29 % had post-shock electro-mechanical dissociation (EMD), 25 % had VT/VF uncorrected by shocks, 16 % had primary electro-mechanical dissociation, and 13 % had recurrent incessant VT/VF despite successful transient termination after shocks. NYHA functional class was the only independent predictor of post-shock EMD. Many patients with end-stage heart failure experience sudden death that is nonetheless expected. Prevention of sudden death in this population may be more effective by focusing on therapies which can modify disease progression [9, 10].

The contemporary therapies in the 21 century have shifted the mode of death associated with

HF. A comparison of 2 prospective cohort studies of patients with chronic HF performed between 1993 and 1995 (historic cohort) and 2006–2009 (contemporary cohort) showed that mortality rates over the first year of follow-up declined from 12.5 to 7.8 %, sudden death made a much smaller contribution to mortality (33.6 % vs. 12.7 %), and noncardiac causes became greater. Modern medical, ICD and cardiac resynchronization therapy all contributes to the changes in death mode [11].

Mechanisms of Sudden Death in Heart Failure

Arrhythmogenic Substrates Predisposing to Sudden Death

Abnormalities in Cellular Electrophysiology

Prolongation of ventricular action potential has been well documented in both animal models and humans in heart failure. Down regulation of ionic current I_{to}, IK_r, IK_s, IK_1, have been observed from animal or human studies. Despite action potential duration prolongation and increased dispersion of repolarization, these changes only contribute in part of the genesis of malignant ventricular tachyarrhythmias leading to sudden cardiac death [12–14]. In heart failure, altered calcium handling not only affects ventricular mechanics, but also affects electrophysiologic properties. The $I_{Ca\text{-}L}$ density has been reported unchanged [15, 16], while the $I_{Ca\text{-}L}$ was decreased in cardiac hypertrophy and severe heart failure primarily from Ca-mediated inactivation of the $I_{Ca\text{-}L}$ current [17]. Spontaneous calcium release from the sarcoplasmic reticulum results in enhanced Na-Ca exchanger current which likely contributes to the genesis of delayed after depolarization (DAD) and DAD-mediated ventricular arrhythmias [18, 19].

Gap Junction

Gap junctions are comprised of intercellular channels that permit the transfer of electrical current between neighboring cells. Connexin 43 is a principal gap junction protein in the ventricle, playing a critical role in impulse propagation and electrical synchronization between myocytes. To determine the transmural Connexin 43 expression and its relationship to electrophysiological function, Poelzing et al. [20] performed a high resolution transmural optical mapping of the arterially perfused canine preparation to measure the conduction velocity and transmural changes of action potential duration in a pacing-induced heart failure model. The absolute Connexin 43 expression in failing myocardium, quantified by confocal immunofluorescence, was uniformly reduced by 40 %, compared with control. Reduced Connexin 43 expression in heart failure was associated with a significant reduction in intercellular coupling between transmural muscular layers correlated to reduced conduction velocity. The action potential duration dispersion was greatest in failing myocardium, and the largest transmural action potential duration gradient was consistently found in regions exhibiting lowest Connexin 43 expression. These findings led to a conclusion that reduced Connexin 43 expression produced uncoupling between transmural muscle layers resulting in a slow conduction and marked dispersion of repolarization between the epicardial and deeper myocardial layers, contributing to an arrhythmia substrate in failing myocardium.

Nerve Sprouting and Sympathetic Nerve Activity

Excessive sympathetic activation is one of the mechanisms contributing to the increased mortality and sudden death in heart failure. Ventricular arrhythmia associated with sympathetic activity is often seen in patients with ischemic cardiomyopathy owing to prior myocardial infarction. Following myocardial injury, peripheral nerves undergo Wallerian degeneration which may be followed by neurilemma cell proliferation and axonal regeneration (nerve sprouting), resulting in sympathetic hyperinnervation [21]. Nerve sprouting activity and sympathetic innervation after MI have been investigated from several experiemental conditions. Meiri et al. used computerized morphometry to quantify the density of nerve fibers that were immunopositive for growth associated protein 43 (GAP43) or tyrosine hydroxylase (TH) in a mouse model [22]. GAP43 is a protein associated with axonal growth cone and is upregulated during nerve sprouting. The density of GAP43 positive nerve

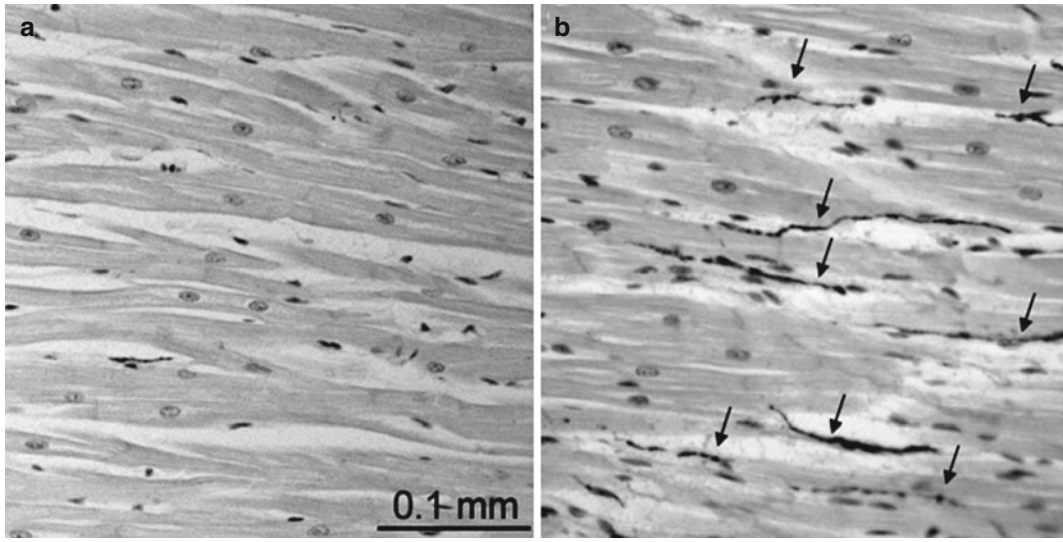

Figure 25–3. Nerve sprouting after MI. Panel **a** shows GAP43 staining of ventricular myocardium from a normal dog. There were no GAP43-positive nerves. Panel **b** shows the same stain of myocardium 1 week after MI, when abundant GAP43-positive nerves (*arrows*) were present (From Chen et al. [25]. Reprinted with permission from John Wiley and Sons)

fibers is a measurement for nerve sprouting activity. In contrast, TH is a measurement for stable sympathetic innervations in the myocardium. There was an acute increase in GAP43 immunoreactive nerve fiber density within 3-h and persisted for 1-week after myocardial infarction, so was TH-positive nerve fiber density [23]. The magnitude of increase in TH-positive nerve fiber density, as compared to controls, appeared to be greater in the peri-infarct area than in the remote area. In a large animal study, Zhou et al. [24] created MI in dogs by either ligating coronary artery or by intracoronary balloon inflation. Consistent with findings in the mouse model of MI, GAP43-positive nerve numbers increased in both infarcted and non-infarcted sites after MI (Fig. 25.3). In clinical studies, Cao et al. [26] reported that the nerve density of ventricular myocardium obtained from patients who had history of cardiac arrhythmia was significantly higher than those without arrhythmia in patients who had heart failure and underwent heart transplantation. To determine a causal relationship between sympathetic hyperinnervation and ventricular arrhythmia, a canine MI model was created by ligating the left anterior descending coronary artery, and complete AV block (AVB) by radiofrequency ablation. Sympathetic nerve sprouting was facilitated by giving chronic infusion of NGF via osmotic pump [27] to the left stellate ganglion. As compared to control dogs (with MI and AVB), NGF infusion increased sympathetic nerve density by twofold (33.2 ± 12.1 vs 16.6 ± 1.3 $\mu m/mm^2$) and increased the incidence of ventricular tachycardia by tenfold. Four of nine dogs died from documented ventricular fibrillation. In a pacing-induced heart failure canine model, an increase of ventricular sympathetic nerve density was also confirmed [28].

To prove a causal relationship between sympathetic nerve activity and arrhythmogenesis, Jardine et al. have recorded cardiac sympathetic nerve activity from sheep by multiple electrodes glued to the left cardiothoracic nerves and found spontaneous ventricular fibrillation episode preceded immediately by a paroxysm of increased cardiac sympathetic nerve activity in one sheep with acute MI [29]. By using implanted radiotransmitters to record long-term continuous (24 h a day and 7 days a week) stellate ganglion nerve activity (SGNA) in dogs, Zhou et al. found that ventricular tachycardia episodes were preceded by an increased SGNA [30]. The evidence from these investigations convey a consistent message that heterogeneous sympathetic reinnervation (neuronal remodeling) in the diseased myocardium are arrhythmogenic, increasing the propensity for ventricular arrhythmia and sudden death.

Anatomical Alteration of Myocardium

The pathophysiological basis for sustained monomorphic ventricular tachycardia due to prior myocardial infarction is usually reentry. The anatomical substrate for reentry is the interlacing of viable myocardium and scar tissue from prior myocardial damage [31]. The areas of slow conduction in infarct scars serve as the substrate for reentry. The slowly-conducting tissue can be identified during endocardial catheter mapping by a fractionated electrogram, mid-diastolic electrograms and long delay between the capturing stimulus and QRS complex resulting from the stimulus [32, 33]. Spontaneous sustained monomorphic ventricular tachycardia is highly reproducible (more than 90 %) in the electrophysiology laboratory [34]. The mechanism of sustained monomorphic ventricular tachycardia in nonischemic dilated cardiomyopathy is poorly understood and is more diverse. Diffused fibrosis and viable myocardium can produce fractionated and low-amplitude endocardial electrograms compatible with a slow conduction zone seen in the myocardial infarction and is responsible for sustaining reentry [35]. His-Purkinje's system disease is commonly associated with dilated cardiomyopathy. In this setting with differential conduction delays, bundle branch reentry tachycardia, by using the distal His bundle, left and right bundle branches, and ventricular septum as the reentry circuit, is another potential mechanism of monomorphic ventricular tachycardia in this subset of patients. Bundle branch reentry can be cured by ablation of the right bundle branch with a success rate of 100 % while ablating reentry circuit mediated by scarred myocardium is much lower in general, approximately 50 % [36].

Triggers Responsible for Initiating Ventricular Arrhythmia

Electrolyte disturbances are common in patients with heart failure. Hypokalemia and hypomagnesemia are predisposing factors to ventricular arrhythmia. In the post-hoc analysis from the SOLVD registry, a baseline use of nonpotassium-sparring diuretics was independently associated with increased risk of arrhythmic death (relative risk 1.33), where baseline use of potassium-sparring diuretics was not [37]. Hypokalemia shortens the action potential plateau and prolongs the rapid repolarization phase, predisposing myocardium susceptible to ventricular tachycardia and fibrillation [38]. ***Acute ventricular dilatation*** in the normal heart shortens action potential duration and refractoriness without apparent effect on conduction velocity, while increasing spontaneous automaticity and triggered activity [39]. Changes in cardiac loading, similar to those seen in heart failure, have a great tendency to be arrhythmogenic [40]. Among 311 patients in the SOLVD trial (studies of left ventricular dysfunction), there was a direct correlation between the severity of left ventricular enlargement and diastolic volume and the frequency of ventricular arrhythmia (Fig. 25.4) [41]. *Myocardial ischemia* alters intracellular oxygen supply and

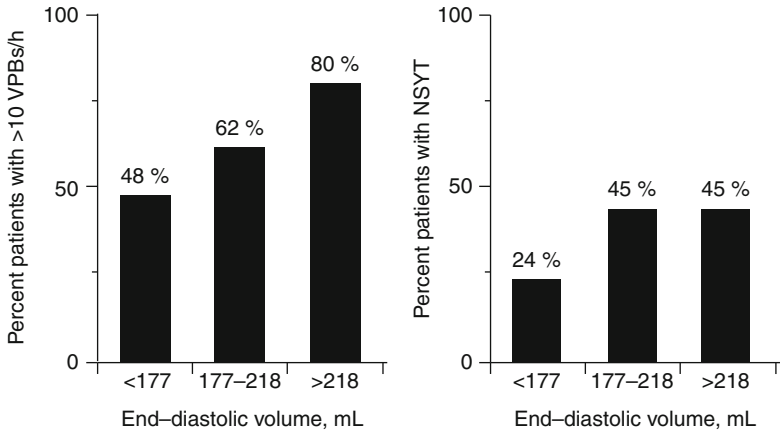

Figure 25–4. Correlation between left ventricular end-diastolic volume and ventricular arrhythmia in CHF. The incidence of ventricular premature beats (*VPBs*) and nonsustained ventricular tachycardia (*NSVT*) in patients with left ventricular dysfunction increases as the left ventricular size (end-diastolic volume) becomes larger (From Koilpillai et al. [41]. Reprinted with permission from Elsevier Limited)

electrocellular homeostasis, resulting in electrolytes shifting, and cellular acidosis. These effects from myocardial ischemia lead to impaired electrophysiologic milieu predisposing to ventricular arrhythmia [42].

Identifying Patients with Increased Risk of Sudden Death

Many approaches have been developed to detect the presence or propensity of arrhythmogenic substrate that trigger or maintain ventricular arrhythmias in patients with ischemic and nonischemic heart disease. These approaches include, but not limited to, detection of spontaneous ventricular ectopy, presence or absence of scar or hibernating myocardium, bio-markers, inducibility of sustained ventricular arrhythmias, cardiac function, ventricular conduction delay, inhomogeneity of ventricular repolarization, and fluctuation of autonomic tone. These approaches have been used singly or in combination in a large number of clinical studies. Although many of the risk stratification techniques and approaches have correlated to increased risks of sudden death in various patient populations, suboptimal predictive values in the cardiac patients at large have resulted in the lack of a coherent and dominant strategy in current clinical practice. Many of the techniques and approaches are discussed in details in other chapters in this Book. In the following paragraphs, a few approaches will be highlighted for discussion.

Left Ventricular Ejection Fraction (LVEF)

LVEF is the most widely used measure to assess overall prognosis and, in most of the ICD clinical trials for primary sudden death prevention, it has been used, with or without other risk stratifies, as a major inclusion criterion for patient selection. Although the severity of left ventricular dysfunction is a well known marker of risk, it identifies a broad segment of heart failure population. MUSTT study identified patients with coronary artery disease and left ventricular ejection fraction 40 % or less. In patients randomized to no antiarrhythmic therapy with inducible ventricular tachycardia during electrophysiology testing, the 5-year mortality rate was 48 %, yielding an annual mortality rate of approximate 10 % [43]. ScD-HeFT trial showed that patients with LVEF of 35 % or less with New York function class II or III attributed to either ischemic or nonischemic cardiomyopathy had a mortality rate of 7 % in control group on standard medical therapy (ScD-HeFT). MADIT II study included patients with prior myocardial infarction and a LVEF less than or equal to 30 % with a New York function class I-III. The mortality was 11 % in a controlled group [44].

In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), the event rates of sudden death was directly correlated to the degree of ventricular dysfunction during both early and late follow up [45].

Noninvasive Testing

Abnormalities of cardiac repolarization are common in heart failure, being closely related to the heterogeneity of depolarization across a diseased left ventricle. Dispersion of QT interval on the surface ECG was initially reported in high-risk patients, but further perspective studies showed no value in predicting of sudden arrhythmic death [46, 47]. Beat-to-beat variation in T-wave amplitude known as microvolt T-wave amplitude (TWA) is linked to a susceptibility to ventricular arrhythmias. It was reported as a marker of risk in a few prospective studies in patients with nonischemic and ischemic cardiomyopathy [48–50]. In a study of 107 consecutive patients with heart failure, left ventricular ejection fraction of 0.45 or less, and a positive TWA, the rate of arrhythmic events at 18 months was 21 % compared to none among those with a negative TWA [51].

Excessive sympathetic activation in heart failure promotes arrhythmia [52]. Heart rate variability reflects neurohumoral activity and its interaction with sinus node. Heart rate variability declines proportionally to the severity of heart failure and increased risk of sudden death [52, 53]. La-Rover et al. performed a short-term (8 min recording) study of heart rate variability in patients in chronic heart failure to determine

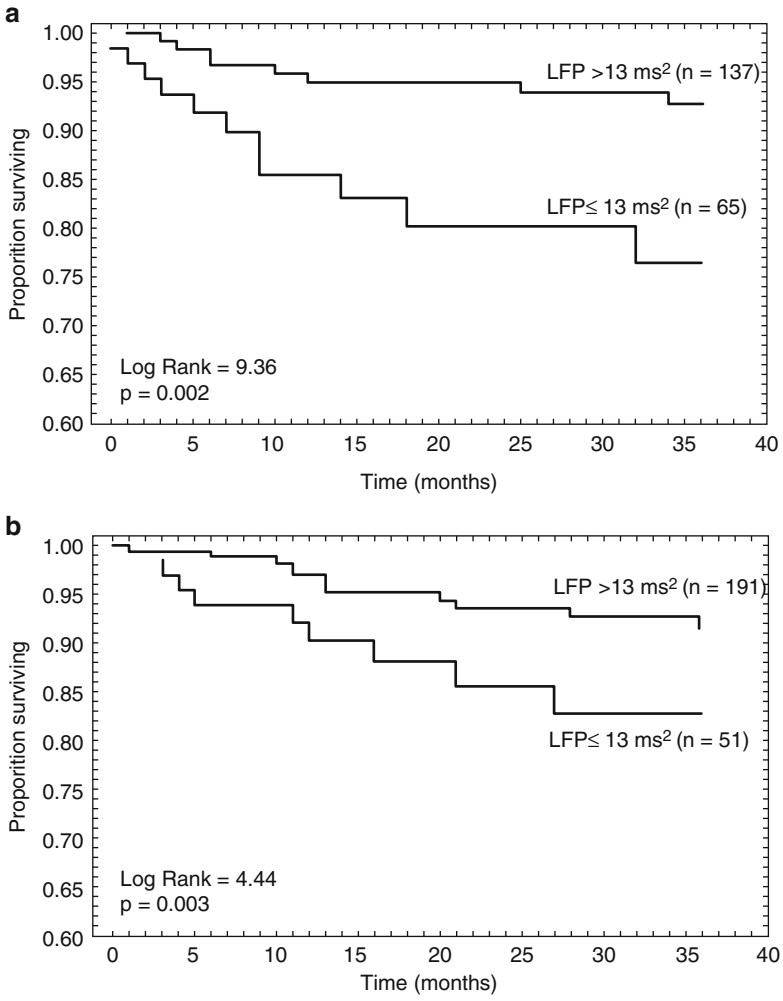

Figure 25–5. (**a**) Kaplan-Meier survival curves for sudden cardiac death in derivation sample. Mortality was significantly higher for patients with markedly depressed LF power (*LFP*) during controlled breathing (LFP 13 ms^2) than for patients with preserved LFP. (**b**) Kaplan-Meier survival curves for sudden cardiac death in validation sample. Although less impressive than in (a), mortality was significantly higher for patients with markedly depressed LF power (LFP) during controlled breathing (LFP 13 ms^2) than for patients with preserved LFP (From La Rovere et al. [53]. Reprinted with permission from Wolters Kluwer Health)

its prognostic value in sudden cardiac death. The study included a derivation sample of 202 consecutive patients in the early 1990s and a validation sample of 242 consecutive patients referred in the late 1990s. Sudden death was predicted by reduced power in the low frequency heart rate variability spectrum (0.04–0.15 HZ) and more than or equal to 83 ventricular premature beats per hour on a 24-h ambulatory Holter recording. This study concluded that reduced short-term (8 min) low-frequency power during controlled breathing is a powerful predictor of sudden death with patients with heart failure that is independent of many other variables (Fig. 25.5) [53]. One study compared the prognostic value of cardiac iodine-123 metaiodobenzylguanidine (MIBG) imaging to heart rate variability in 65 patients with heart failure. MIBG is a structural analog of the neuro transmitter guanathidine. It is taken up by adrenergic neurons in the manner similar to that of norepinephrine, but it does not undergo intracellular metabolism. Cardiac I-123 MIBG imaging reflects cardiac adrenergic nerve activity. The MIBG heart-to-mediastinum ratio and the wash-out rate were obtained from MIBG imaging. The time and the frequency domain parameters of heart rate variability were calculated from 24-h Holter recordings. High wash-out rate (more than 27 %) was the only independent predictor of sudden death. Cardiac events were significantly more frequently observed in patients with both abnormal wash-out rate and

normalized very low frequency power (less than 22) than those with both normal wash-out rate and normalized very low frequency power (54 % versus 4 %) [54].

B-type natriuretic peptide (BNP) is produced primarily from the left ventricle in response to a change in myocardial wall stretch or volume load. The plasma concentration of this peptide strongly correlates with the degree of LV systolic function and risk of death. In a study of 452 patients with ischemic or nonischemic cardiomyopathy and LVEF less than 35 %, fewer patients with a level of BNP <130 pg/mL (1 %) died, as compared with patients with BNP >130 pg/ml (18 %) [55]. A meta analysis of 19 studies that used BNP to estimate the relative risk of death in heart failure patients concludes that each 100 pg/mL increase in BNP was associated with a 35 % increase in the relative risk of death, thereby a strong prognostic indicator for heart failure at all stage of disease [50].

Invasive Electrophysiology Study

Approximately one-third of patients with prior myocardial infarction, LVEF less than or equal to 40 % and spontaneous nonsustained ventricular tachycardia, have inducible sustained ventricular tachycardia, suggesting a 6–9 % per year risk of spontaneous sustained VT or sudden death [43]. The utility of electrophysiology testing in sudden death risk stratification in patients with ischemic heart disease is reviewed elsewhere in the Book. Electrophysiological testing is not a useful screening tool in nonischemic cardiomyopathy. Fewer than 5 % of patients have inducible monomorphic ventricular tachycardia in this subset of patients.

Prevention of Sudden Death

Pharmacological Therapy

Beta Blockers

Beta blockers were first advocated for treatment of heart failure in 1975 [56]. Results from large clinical trials subsequently showed that three beta blockers, including bisoprolol, sustained release metoprolol, (selective beta-1 receptor blockers), and carvedilol (an alpha −1, beta-1, and beta-2 receptors blocker), were effective in reducing mortality in patients with chronic heart failure. The positive findings with these three agents, however, should not be considered indicative of beta blocker class effect, as shown by the lack of effectiveness of short-acting metoprolol in clinical trials [6, 57–61]. Patients who have been diagnosed with heart failure should be treated with one of these three beta blockers. The relative efficacy among these three agents is not known, but available evidence does suggest that beta blockers can differ in their effects on survival. In the Comet Trial, the absolute reduction in mortality over 5 years from carvedilol was 5.7 % when compared to immediate-release metoprolol. In addition to the survival benefit, these trials also demonstrated a reduction in heart failure related hospitalization, improved NYHA function class, and patients' well being. In the MERIT-HF trial, there were fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (RR 0.59, (0.45–0.78), Fig. 25.6) [7]. Post-hoc analysis from the MUSTT trial demonstrated that beta blockers were associated with decreased total mortality (5-year mortality 50 % with beta blockers versus 66 % without beta blockers). The mortality benefit associated with beta blockers was present in patients with and without inducible tachycardia [62]. However, the rates of arrhythmic death or cardiac arrest were not significantly affected by beta blocker therapy.

Angiotensin Converting Enzymes (ACE) Inhibitors and Angiotensin II Receptor Blockers (ARB) (ACE) inhibitors and ARB reduce sudden death. The CHARM Program assessed the effect of Candesartan on cause-specific mortality in patients enrolled in the Candesartan in heart failure assessment of Reduction in Mortality and Morbidity (CHARM) program. this program consisted of three component trials including CHARM-alternative (2,028 patients with a LVEF less than or equal to 40 %), CHARM-added (2,548 patients, LVEF less than or equal to 40 %, already on ACE inhibitors), and CHARM-preserved (3,023 patients, LVEF more than 40 %) [63–66]. Patients were randomized to Candesartan 32 mg once a day or placebo. All three trials were pooled to provide adequate statistical

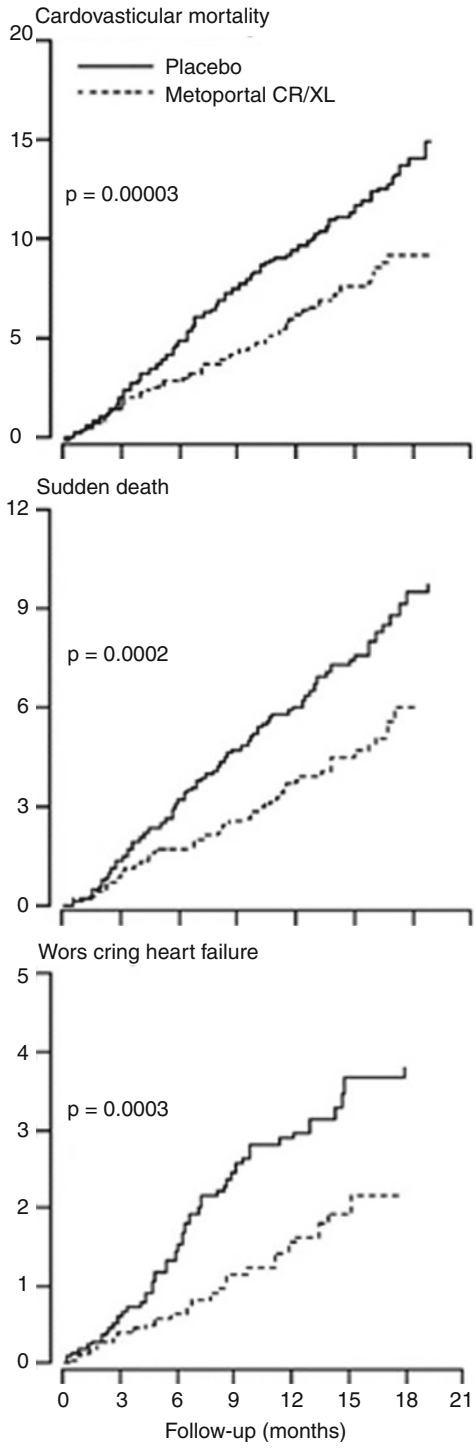

Figure 25–6. Kaplan-Meier curves of cumulative percentage of cardiovascular deaths, sudden deaths, and deaths from worsening heart failure (From MERIT-HF Study Group [7]. Reprinted with permission from Elsevier Limited)

power to evaluate cause-specific mortality. Of all the patients, 8.5 % died suddenly, and 6.2 % died of progressive heart failure. Candesartan reduced both sudden death (HR 0.85) and death from worsening heart failure (HR 0.78). This program concluded that Cardesartan reduced sudden death and death from worsening heart failure in patients with symptomatic heart failure, although this reduction was more apparent in patients with systolic dysfunction. The mechanisms whereby ARBs reduced incidence of sudden death in patients with heart failure remain less clear. Overall improvement in hemodynamic status and attenuation of ventricular remodeling may directly and indirectly decrease the propensity to fatal ventricular arrhythmia [67]. Reductions in the incidence of sudden death have also been observed in trial with ACE inhibitors [68].

Antiarrhythmic Agents

Amiodarone is a unique antiarrhythmic agent that has a class I, II, III, and IV effects. It has been associated with overall neutral effects on survival when given to patients with low LV ejection fraction and heart failure, although some studies have showed a reduction in sudden death [69–72], an increase in LVEF, and a decrease in the incidence of worsening heart failure [70, 73–75]. Despite its side effects of thyroid abnormalities, pulmonary toxicity, hepatotoxicity, neuropathy, and other adverse responses, amiodarone remains to be the most effective agent to prevent recurrent ventricular tachyarrhythmia, especially in patients who have been receiving frequent ICD therapies. Other pharmacological arrhythmic therapies such as Sotalol and Mexiletine may be used to suppress recurrent ICD shocks when Amiodarone has been ineffective or not tolerated due to side effects. Dofetilide is a class III antiarrhythmic drug. In the DIAMOND-CHF study, observed survival was not different between patients randomized to dofetilide or placebo while atrial fibrillation was significantly less in patients randomized to dofetilide therapy [76]. Although the overall incidence of pro-arrhythmia appears to be relatively low, clinical use of dofetilide has been limited because of concerns of drug-drug

Table 25–1. Secondary prevention of sudden cardiac death by ICD

	Patient population	Number	Randomization	Follow-up mo.	Reduction in mortality
AVID [79] 1997	Survived VT/VF/arrest, VT/ syncope, VT/LVEF ≤ 40 %	1,016	Antiarrhythmic agents (97 % amiodarone) vs ICD	18	HR 0.66, (0.51–0.85) P < 0.02
CASH [80] 2000	Survived VT/VF/arrest	288	Antiarrhythmic agents (amiodarone, propafenone, metoprololo) vs ICD	57	HR 0.82, (0.60–1.11) P = 0.08
CIDS [81] 2000	Survived VT/VF/arrest, VT/ syncope, VT/LVEF ≤ 35 %	659	Amiodarone vs ICD	35	HR 0.80, (0.60–1.08) P = 0.14

AVID Antiarrhythmic Vs Implantable Defibrillators, *CASH* Cardiac Arrest Study Hamburg, *CIDS* Canadian Implantable Defibrillator Study, *HR* hazard ratio, *VT* ventricular tachycardia, *VF* ventricular fibrillation, *LVEF* left ventricular ejection fraction

interaction and in patients with renal insufficiency. Despite a marked suppression of ventricular ectopic activity, the class 1C antiarrhythmic agents, flecainide and encainide, increased the total and arrhythmic mortality in patients with ischemic heart disease and compromised LVEF [77]. Other class I antiarrhythmic agents, including Quinidine, Procainamide, and Propafenone, have been poorly studied in patients with ischemic cardiomyopathy. Nevertheless, meta analysis of existing data consistently showed that class I agents are associated with a decreased survival in post-myocardial patients [78].

Implantable Cardioverter Defibrillators (ICD)

Secondary Prevention

Patients with a previous cardiac arrest or documented sustained ventricular arrhythmias have a high risk of recurrent events. Implantation of an ICD has been shown to reduce mortality in cardiac arrest survivals. Outcomes from secondary sudden prevention trials are summarized in Table 25.1. In antiarrhythmic versus implantable defibrillators study (AVID) the absolute reduction of mortality was 7 % and 11 % in 2 and 3 years in patients randomized to the ICD arm compared to the drugs-treated arm [79]. Two other secondary prevention multi-center trials (CIDS and CASH), with smaller numbers of study patients, also demonstrated a strong trend towards survival benefits among patients who received ICD therapy [80, 81]. Clinical data also support the consideration of ICD therapy in patients with chronic heart failure and low ejection fraction who experience syncope of unclear origin [82]. Placement of ICD is not indicated when ventricular tachyarrhythmias are incessant in patients with progressive and irreversible decompensated heart failure.

Primary Prevention

The utility of ICDs in the primary prevention of sudden death in patients without a prior history of life-threatening arrhythmias has been explored in numerous trials. If sustained ventricular tachyarrhythmias can be induced in the electrophysiology laboratory (and not suppressible by procainamide) in patients with a prior myocardial infarction, a LVEF less than or equal to 35 %, and spontaneous nonsustained ventricular tachycardia on ambulatory ECG, the absolute risk reduction of total mortality was 23 % in approximately follow-up duration of 2 years [44]. When the inclusion criteria for left ventricular ejection fraction was less than or equal to 40 %, the incidence of cardiac arrest or death from arrhythmia were 25 % among those receiving electrophysiology-guided therapy (half received drug therapy and half received ICD) and 32 % among the patients assigned to no antiarrhythmic therapy, yielding absolute reduction of 7 % after 5 years of follow-up. The survival benefit was entirely attributable to the ICD, not to the antiarrhythmic drug therapy [43]. More recently, the role of ICD in primary sudden death prevention was examined in patients with low ejection and heart failure, without risk stratifies such as spontaneous non-sustained ventricular tachycardia on ambulatory ECG or inducible sustained ventricular tachycardia during an electrophysiology study. When compared with standard medical therapy in patients with ejection fraction of less than or equal to 30 % after remote myocardial infarction, ICD decreased the mortality by 5.6 % over 20 months [83]. In patients

Table 25–2. Primary prevention of sudden cardiac death by ICD

	Patients population	LVEF (%)	Number	Randomization	Follow-up mo.	Reduction in mortality
MADIT [85] 1996	Prior MI, NSVT, Inducible VT refractory to procainamide	≤35	196	Antiarrhythmic agents vs ICD	27	HR 0.46 (0.26–0.92) P = 0.009
CABG-Patch [86] 1997	All undergo CABG, positive SAECG	≤35	900	CABG alone vs CABG plus ICD	32	HR 1.07 (0.81–1.42) P = 0.64
MUSTT [43] 1999	Prior MI/CAD, NSVT, inducible VT	≤40	704	Antiarrhythmic or ICD vs conventional therapy	39	HR 0.69 (0.32–0.63) P < 0.001
MADIT II [44] 2002	Prior MI/CAD	≤30	1232	Conventional therapy vs ICD	20	HR 0.69 (0.51–0.93) P = 0.02
DINAMIT [87] 2004	Recent MI (<40days), decrease HRV	≤35	674	Conventional therapy vs ICD	39	HR 1.08 (0.76–1.55) P = 0.66
DEFINITE [88] 2004	Nonischemic cardiomyopathy, NSVT or PVCs	≤36	458	Conventional therapy vs ICD	29	HR 0.65 (0.40–1.06) P = 0.08
SCD-HeFT [71] 2005	Ischemic and nonischemic cardiomyopathy, NYHA II-III	≤35	2521	Conventional therapy vs amiodarone vs ICD	45	ICD HR 0.77 (0.62–0.96) P = 0.007 Amiodarone HR 1.06 (0.86–1.30) P = 0.53

MADIT Multi-center Automatic Defibrillator Trial, *CABG* coronary artery bypass graft, *MUSTT* Multi-center Unsustained Tachycardia Trial, *DINAMIT* Prophylactic Use of an Implantable Cardioverter-defibrillator after Acute Myocardial Infarction, *DEFINITE* Prophylactic Defibrillator Implantation in Patients with Nonishchemic Dilated Cardiomyopathy, *SCD-HeFT* Sudden Cardiac Death in Heart Failure Trial, *ICD* implantable cardioverter-defibrillator, *LVEF* left ventricular ejection fraction, *NSVT* nonsustained ventricular tachycardia, *NYHA* New York Heart Association, *MI* myocardial infarction, *CAD* coronary artery disease, *HRV* heart rate variability, *SAECG* signal-averaged electrocardiogram

with EF less than 35 % and NYHA function class II-III symptoms of heart failure with either ischemic or nonischemic causes of advanced heart disease, survival benefit from ICD was also observed when compared to amiodarone [71]. Further analysis from the Sudden Cardiac Death in Heart Failure Trial showed that ICD therapy significantly reduced tachyarrhythmia mortality (adjusted hazard ratio, 0.40; 95 % confidence interval, 0.27–0.59) and had no impact on mortality resulting from heart failure or non-cardiac causes [84]. Outcomes from recent ICD trials for primary prevention of sudden death are shown in Table 25.2. Whereas ICD is effective in preventing death due to ventricular tachyarrhythmia, frequent shocks from an ICD can lead to a reduced quality of life, whether triggered by appropriately life-threatening arrhythmia or inappropriately by supraventricular tachycardia. In this situation, antiarrhythmic therapy, most often Amiodarone and/or catheter-based ablation can be considered to reduce recurrent ICD discharges. The balance of potential risks and benefit of ICD implantation should be individualized. Decrease in incidence of sudden death does not necessarily translate into decreased total mortality, and the decreased total mortality does not guarantee a meaningful prolongation of survival with adequate quality. This is particularly important in patients with poor prognosis due to advanced heart failure. There was no survival benefit observed from ICD implantation within the first year in two of the major trials [71, 89]. All ICD primary sudden death prevention trials up to date have excluded patients with NYHA class IV functional status. Consideration of ICD implantation is currently recommended in patients with ejection fraction less than 35 % and mild to moderate symptoms of heart failure without significant co-morbid conditions with an anticipated life expectancy extending beyond 1 year.

Cardiac Resynchronization Therapy (CRT)

CRT is a new therapy that reverses ventricular remodeling and improves ventricular function and symptoms in patients with advanced HF by using an additional pacing lead that stimulates the lateral wall of the left ventricle to achieve mechanical synchrony between and within the right and left ventricles. Meta analysis from earlier and smaller randomized trials found that CRT reduces death from progressive HF by 51 %

relative to controls and a trend toward reducing all-cause mortality, but no apparent effect on sudden cardiac death [90]. From a larger study, the Comparison of Medical therapy, Pacing, And Defibrillation in Chronic Heart Failure (COMPANION) trial found CRT with a pacemaker alone (CRT-P) reduced death from any cause (a secondary endpoint of the trial) by 24 % (marginally significant) compared to medical therapy, while CRT with a defibrillator (CRT-D) significantly reduced mortality by 36 % [91]. More recently, the Cardiac Resynchronization in Heart Failure Study (CARE-HF) also demonstrated that CRT-P was associated with an absolute 10 % mortality reduction, as compared with the medical-therapy group (20 % vs. 30 %; hazard ratio 0.64). In this study, CRT-P also reduced the interventricular mechanical delay, the end-systolic volume index, and the area of the mitral regurgitation; increased the left ventricular ejection fraction; and improved symptoms and quality of life [92]. MADIT-CRT trial randomized 1,820 patients with mild HF symptoms (NYHA I-II), LVEF of 30 % or less, and a QRS duration of 130 ms or more to CRT-ICD and ICD-only group [92]. CRT combined with ICD decreased the risk of HF events with a relative risk reduction of 41 %, but not mortality. Interestingly, the sub-analysis of MADIT-CRT trial assessing the effectiveness of CRT by QRS morphology found the risk of ventricular tachycardia, ventricular fibrillation, or death was decreased significantly in CRT-ICD patients with LBBB but not in non-LBBB patients, as compared to ICD-only patients. The benefit of reducing arrhythmic events was accompanied with a greater reduction of LV volumes and increase in LVEF in those with LBBB [93].

Catheter Ablation

Despite beta blocker and antiarrhythmic drug use, many patients receive frequent ICD shocks for ventricular tachycardia or fibrillation. Some may present with incessant slow ventricular tachycardia and others develop clustered multiple recurrences of ventricular tachycardia within a short period of time, the so-called electrical storm. Both appropriate and inappropriate ICD shocks are associated with increased mortality [94]. Catheter ablation of ventricular arrhythmia by eliminating or modifying arrhythmogenic reentry circuit or focus have proven to be beneficial in reducing recurrent arrhythmia burden and ICD shocks [95–97]. The Cooled RFC trial enrolled patients with a hemodynamically stable VT. The acute success rate was 71 % when the end point was elimination of all inducible VT. The 1-year arrhythmia free rate was 56 % [96]. The Thermocool trial included subjects with multiple VTs and hemodynamically unstable VT. The freedom from VT was 53 % at 6-month follow-up. The frequency of VT was reduced by ≥75 % in 67 % of patients [97]. For patients with electrical storm, catheter ablation substantially reduces the number of ICD interventions [98]. Is there a role of catheter ablation before ICD shocks? The VTACH trial randomized patients with first episode of VT to VT ablation plus ICD and ICD only arms [99]. Compared to ICD only group, the median time to first VT or VF was significantly prolonged from 5.9 months to 18.6 months in VT ablation group. In SMASH-VT trial, catheter ablation led to a 73 % reduction of ICD shocks as compared with the ICD only group [100]. Whether fewer ICD interventions after preventive catheter ablation may lead to improved survival remains to be studied.

Summary and Conclusion

Complex interactions reside between cardiac mechanical dysfunction and malignant arrhythmia generation. The cyclical relationship of heart failure and arrhythmogenesis is depicted in Fig. 25.7. Sudden death is a common mode of death in patients with advanced heart failure. In patients with heart failure, risk stratification for sudden death should be a routine component of the clinical evaluation. Following determination of underlying heart disease, appropriate and aggressive therapy should be implemented to target the primary disease process in order to modify the disease progression, thereby improving symptoms and prognosis. Antiarrhythmic drug therapy is not recommended in any heart failure patient

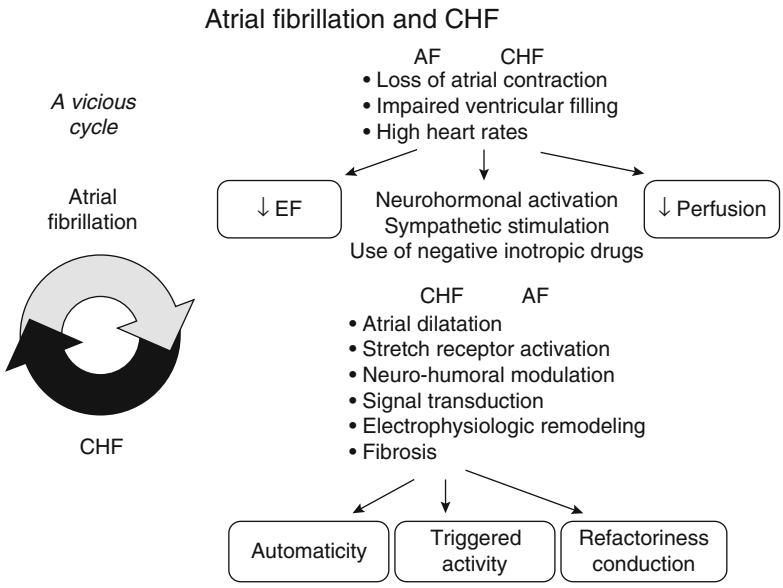

Figure 25–7. A vicious cycle of electro-mechanical coupling in the development of heart failure and sudden death (From MERIT-HF Study Group [7]. Reprinted with permission from Elsevier Limited)

population for primary sudden death prevention. When an anti-arrhythmic drug is needed to treat symptomatic arrhythmias in patients with heart failure, amiodarone usually is the drug of choice, while dofetilide is "safe" when used properly. Among patients with ischemic or non-ischemic heart disease and compromised LVEF with mild to moderate heart failure symptoms (NYHA functional class II-III), clinical evidence supports the recommendation of ICD implantation in patients with LVEF ≤ 35 %. Although many approaches and techniques are available for sudden death risk stratification, a "dominant" strategy has not been established primarily due to the lack of a strong predictive value either from individual or combinations of various testing modalities. Among patients with very advanced heart failure (class IV), ICD alone is not recommended. Preliminary data suggest CRT-P or CRT-D may improve survival, in addition to improving functional capacity and symptoms, in selected patients with advanced heart failure. The size of the heart failure patient population will continue to grow as the global population continues to get older and live longer as a result of advanced medical care. It is expected that sudden death risk stratification techniques will continue to evolve while pharmacological and non-pharmacological therapy for sudden death prevention will continue to be refined.

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26
Neurologic Conditions and Sudden Death

David M. Ficker and Elson L. So

Abstract

The most important type of sudden death in neurology is sudden unexpected (or unexplained) death in epilepsy (SUDEP). It accounts for up to 17 % of deaths in persons with epilepsy, and it is the most frequent cause of epilepsy-related deaths. The most prominent risk factor for SUDEP is uncontrolled generalized tonic-clonic seizures, the higher frequency of which results in greater SUDEP risk. However, the exact mechanism by which the seizures predispose a person to SUDEP is unknown. Although the phenomenon of seizure-related asystole is well known, it is usually very transient and uncommon. There is increasing evidence to implicate respiratory compromise as a major postseizure event that leads to cardiorespiratory arrest, but further investigations are needed to fully understand the relevance of this observation to the phenomenon of SUDEP. Most other "sudden" deaths in neurologic conditions are more properly termed "rapid death," in that death in most cases occurs in the setting of deteriorating neurologic and vital functions. More common neurologic conditions associated with rapid deaths are large strokes with increased intracranial pressure and, less commonly, smaller strokes that affect cerebral regions specifically linked to cardiorespiratory or autonomic functions, such as the brainstem and the insula. Death can also occur "suddenly" in advanced metabolic or congenital myopathies in which cardiomyopathy or channelopathy is a feature or in certain neurodegenerative disorders with compromise of the autonomic nervous system.

Keywords

Andersen-Tawil syndrome • Antiepileptic drugs • Epilepsy • Mitochondrial encephalomyopathy • Muscular dystrophy • Myopathy • Neurodegenerative disorder • Seizures • SUDEP

Abbreviations

AED	antiepileptic drug
ECG	electrocardiographic, electrocardiography
EEG	electroencephalography
GTCS	generalized tonic-clonic seizure
SUDEP	sudden unexpected (or unexplained) death in epilepsy

D.M. Ficker, MD, FAAN
Department of Neurology, College of Medicine, University of Cincinnati Academic Health Center, Cincinnati, OH, USA

E.L. So, MD (✉)
Department of Neurology, Mayo Clinic, 200 First St., SW, Rochester, MN 55905, USA
e-mail: eso@mayo.edu

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Introduction

"Sudden" death can occur in several acute, catastrophic neurologic diseases or chronic neurologic illnesses with acute decompensation [1]. The term "rapid death," rather than "sudden death," may be more appropriate in characterizing the mode of death in these conditions, because deteriorating vital signs are often observed over minutes or hours before death. In contrast, sudden cardiac or respiratory arrest without warning is a hallmark of the condition of sudden unexpected (or unexplained) death in epilepsy (SUDEP). SUDEP occurs in the setting of normal daily activities, and the death can be correctly characterized as unexplained when an autopsy discloses no cause of death. In contrast, rapid death in acute neurologic conditions such as large cerebral infarcts or head trauma, although unexpected by family and caregivers, cannot be said to be totally unexplained.

This chapter focuses on SUDEP and the potential role of the heart in causing death, with a brief discussion of sudden cardiac death in other neurologic conditions. Because the heart ultimately malfunctions in all deaths, the discussion emphasizes early or initiating cardiac mechanisms that are essential in precipitating sudden death.

Definition of SUDEP

SUDEP has been reported to be responsible for 2–17 % of all deaths in persons with epilepsy [2]. SUDEP can be defined as the sudden occurrence of death in a person with epilepsy in the absence of a reasonable anatomic or toxicologic explanation for death. Natural causes of sudden death such as cardiac ischemia, pulmonary embolus, and cerebral hemorrhage must be excluded before a case is determined to be SUDEP. In addition, seizure-related causes of death such as status epilepticus, asphyxiation, and head injury also must be excluded for the determination of SUDEP. Accurate determination of SUDEP requires postmortem examination to exclude natural, accidental, suicidal, and homicidal causes of sudden unexpected death.

A classification scheme was proposed so that potential SUDEP cases could be categorized for the purpose of research studies [3]. The criteria for SUDEP are that the person had epilepsy, defined as recurrent unprovoked seizures; the person died unexpectedly while in a reasonable state of health; the death occurred "suddenly" (in minutes), when known; the death occurred during normal activities (eg, in or around bed, at home, or at work) and in benign circumstances; and an obvious medical cause of death was not found. *Definite SUDEP* is defined when all criteria are met, with postmortem examination having been performed. *Probable SUDEP* meets all criteria but lacks postmortem data. *Possible SUDEP* is when SUDEP cannot be ruled out, but there is insufficient evidence regarding the circumstances of the death, and no postmortem report is available.

Historical Recognition of SUDEP

Evidence in early epilepsy studies suggested that some patients with epilepsy die suddenly, unexpectedly, and without apparent cause [4–7]. Later studies of patients with epilepsy who died suddenly and unexpectedly explored putative risk factors and provided estimates of the frequency of SUDEP [8–11]. Many deaths in earlier studies of patients with epilepsy were attributed to asphyxiation, status epilepticus, or aspiration, but in reality the deaths might have been SUDEP. Interest in SUDEP was renewed during the development of antiepileptic drugs (AEDs), when there was concern that subjects in the AED trials had higher rates of sudden death.

Incidence of SUDEP

Many studies have provided the incidence of SUDEP; however, direct comparison between studies is difficult because of differing definitions of SUDEP, varying ascertainment methods, and different source populations. Table 26.1 summarizes the incidence of SUDEP in various studies. Studies of incidence fall into several categories [30]:

1. Cases identified through autopsy records.
2. Cases identified from AED prescription registries.
3. Cases identified through clinical trials of AEDs or antiepileptic devices.
4. Cases identified through hospitals, epilepsy clinics, or centers.
5. Cases identified through community-based cohorts of incident epilepsy cases.

Autopsy-based studies suffer from referral bias and may overestimate the actual incidence of SUDEP because the decision to perform an autopsy is influenced by the circumstances surrounding death; therefore, autopsies may be performed in a higher proportion of unexplained deaths. In addition, the epilepsy prevalence in the base population is unknown in many studies.

Studies of SUDEP in epilepsy referral centers and in AED clinical trials involve persons with high seizure frequency and poor response to AED therapy [24]. These studies are not reflective of the general epilepsy population, in which an estimated 63 % of persons have well-controlled epilepsy [31]. Table 26.1 shows that SUDEP rates increase from study cohorts that include persons with well-controlled epilepsy to cohorts with frequent seizures. Thus, the highest rate of SUDEP is seen among candidates for epilepsy surgery, whose medically uncontrolled and frequent seizures prompt consideration of surgery.

Table 26–1. Rates of SUDEP reported in the literature

Study	Study population	No. of cases per 1,000 person-years
Lhatoo et al. [12]	Population based	0.13
Ficker et al. [13]	Population based	0.35
Leestma et al. [14]	Autopsy cases (retrospective)	0.5–1.9
Tennis et al. [10]	Prescription records in the community	0.5–1.4
Leestma et al. [11]	Autopsy cases (prospective)	0.9–2.7
Walczak et al. [15]	Multicenter referral practice	1.2
Jick et al. [9]	Prescription records in the community	1.3
Langan et al. [16]	Autopsy cases	1.5
Nilsson et al. [17]	Hospital admissions	1.5
Timmings [18]	Epilepsy unit in referral center	2.0
Klenerman et al. [19]	Institutionalized patients	2.1
Derby et al. [20]	Refractory epilepsy population	2.2
Hennessy et al. [21]	Temporal lobectomy patients	2.2
Nashef et al. [22]	Institutionalized young patients	3.4
Leestma et al. [23]	Drug trial subjects (lamotrigine)	3.5
Racoosin et al. [24]	Antiepileptic drug trials	3.8
Annegers et al. [25]	Vagus nerve stimulator trial	4.5–6.0
Lip and Brodie [26]	Epilepsy center	4.9
Nashef et al. [27]	Epilepsy center outpatients	5.9
Sperling et al. [28]	Epilepsy surgery patients	7.5
Dasheiff [29]	Epilepsy surgery candidates	9.3

Abbreviation: *SUDEP* sudden unexplained (or unexpected) death in epilepsy

Population-based studies are the best studies to estimate the actual incidence of SUDEP. The difficulty of population-based studies arises in collecting data that accurately represent the whole spectrum of all epilepsy patients in the community. Some studies that were alleged to be population based were conducted on cohorts identified from AED prescription records [9, 10]. In these studies, persons in the community were presumed to have epilepsy if they were taking AEDs. However, persons taking AEDs for nonepileptic conditions were most likely included in the study, and patients with epilepsy who were noncompliant with medications might have been excluded.

The National General Practice Study of Epilepsy in Great Britain reported the lowest SUDEP rate, approximately 1 in 5,000 person-years [12]. This rate of SUDEP may have been so low because the study included both patients with active epilepsy and patients with epilepsy in remission. We performed a population-based study in Rochester, Minnesota, in which the incidence of SUDEP was 0.35 per 1,000 person-years [13]. The incidence of sudden unexplained death in young nonepileptic adults in Rochester had previously been determined by Shen and colleagues [32]. Our comparison of the incidence rates of sudden unexplained death in persons with and without epilepsy yielded a standard mortality ratio of 23.7 for those with epilepsy. Therefore, the risk of sudden unexplained death is approximately 24 times higher in those with epilepsy than in the general population.

Risk Factors for SUDEP

Poor seizure control appears to be the most consistent risk factor for SUDEP across several studies reported over the past three decades [2]. The foregoing discussion of SUDEP incidence

clearly shows a much higher incidence of SUDEP among persons with poorly controlled epilepsy than among persons with well-controlled epilepsy. Furthermore, it is not uncommon for an epileptic seizure to have occurred near the time of the fatal event. Although it is rare for SUDEP events to have been witnessed, 80 % of witnessed SUDEP events are associated with a seizure occurrence [33]. Of the many types of epileptic seizures, generalized tonic-clonic seizure (GTCS; "grand mal" seizure) is the type most commonly associated with SUDEP [11]. The risk of SUDEP has been shown to be 14 times higher in persons with at least 1 GTCS within the past 3 months than in persons with no such seizures [34]. A collaborative study from three centers in the Midwest demonstrated that increasing frequency of GTCS is correlated with increasing risk of SUDEP [15]. The same study also reported mental retardation and greater number of AEDs used to be SUDEP risk factors. Although these factors are independent of seizure frequency, they cannot be said to be independent of the severity of the epileptic condition. Seizure frequency may not be the only determinant of the severity of the epileptic condition. Early onset of epilepsy has also been reported to be a risk factor for SUDEP [17]. After adjustment for seizure frequency, the relative risk of SUDEP is five times higher when epilepsy began between birth and age 15 years than when epilepsy began after age 45 years.

A low AED concentration in the serum is long believed to be a major risk factor for SUDEP. In one series of postmortem examinations of persons with SUDEP, only 10 % had serum AED concentrations in the therapeutic range [11]. Moreover, the risk of SUDEP was 3.7 times higher for patients who did not have their serum AED concentrations measured within the previous 2 years than for those who did [35]. However, more recent studies have found no association between low serum AED concentration and occurrence of SUDEP [15, 35]. Also, fluctuations in serum AED concentrations do not appear to be associated with increased SUDEP risk [35]. Nonetheless, two studies suggest that recent or frequent adjustments in AED dose increase the risk of SUDEP [26]. A study of AED concentrations in hair samples showed that patients with SUDEP had greater variability in AED concentrations over time than did epilepsy patients without SUDEP [36]. However, the greater variability in SUDEP may just be a reflection of more frequent AED dose adjustments because of worse seizure control in patients with SUDEP than without SUDEP.

No single AED has been associated with higher SUDEP risk than any other [37]. Carbamazepine rarely induces bradycardia or complete atrioventricular block [38]. Nilsson and colleagues [17] reported that a high serum carbamazepine concentration is associated with increased risk of SUDEP. The "high" carbamazepine concentrations in that study were observed in only five patients, however, and the concentrations were only slightly increased [17]. These limitations may explain the wide confidence intervals for the risk ratio determined in that study. More important than the type of AED is the number of AEDs used. After adjustment for seizure frequency, patients taking three AEDs had an eight-times greater risk of SUDEP than those taking one AED [17].

Most patients with SUDEP are between ages 20 and 40 years [2]. Whether age is a risk factor for SUDEP is not clear. Sudden deaths in older persons with epilepsy may have been attributed to coronary artery disease without serious consideration of the possibility of SUDEP.

In a study in Turku, Finland, that assessed the mortality of children with epilepsy followed up for 40 years, the risk of SUDEP was 7 % among all subjects and 12 % among those who were not in 5-year terminal remission and who were not receiving AEDs [39]. Among the subgroup with idiopathic or cryptogenic epilepsy, the SUDEP rate was 15 % in those not in 5-year terminal remission and no longer receiving AEDs. The only significant factor associated with SUDEP on multivariate analysis was the absence of 5-year terminal remission.

The Task Force on Epidemiology of the International League Against Epilepsy recently analyzed data combined from four case–control SUDEP studies [40]. Patients with frequent GTCSs, with early onset of symptomatic epilepsy that is poorly controlled, and using multiple AEDs were at the greatest risk for SUDEP. The study also suggested that the use of the AED

lamotrigine in idiopathic generalized epilepsy is associated with increased risk of SUDEP, but further studies are needed to independently confirm this finding.

Potential Cardiac Mechanisms in SUDEP

Because sudden nontraumatic death in the general population is often due to cardiac arrhythmia induced by ischemic heart disease, acute cardiac arrhythmia has often been suspected to be a primary cause of SUDEP. Patients with temporal lobe epilepsy were reported to have decreased heart rate variability that was more pronounced during nighttime than daytime [41]. This finding is relevant because most SUDEP events occur at night. However, there was no difference in the nighttime heart rate variability between patients with intractable or well-controlled epilepsy. Nonetheless, the finding still raises the possibility that both groups of patients have a background susceptibility to cardiac arrhythmias, but that seizure episodes are required to trigger potentially lethal arrhythmias to cause SUDEP.

Some epileptic seizure events are associated with supraventricular tachycardia, bradycardia, asystole, or arrhythmias such as atrioventricular block and ventricular ectopic rhythms [42–45]. These cardiac rhythm abnormalities have been observed in seizures that begin at several brain structures, including but not limited to the insular cortex, frontal lobe regions, cingulate gyrus, and the amygdala-hippocampal complex. In the evaluation of patients for epilepsy surgery, sinus tachycardia is a common observation during seizures recorded with video-electroencephalography (EEG) monitoring, but bradycardia is uncommon and asystole is rare. Whereas sinus tachycardia is observed with either focal-onset seizures or primary GTCSs, bradycardia and asystole are observed mostly with focal-onset seizures [46]. The rate of electrocardiographic (ECG) abnormalities has been reported to increase with the duration of seizure episode and to be increased for the GTCS type of seizure [47].

A fatal outcome of ictal asystole has rarely been encountered in the epilepsy monitoring unit [48]. The prevalence of ictal or postictal bradycardia or asystole in the epilepsy population is not known. The prevalence of ictal asystole determined in patients with intractable epilepsy during video-EEG monitoring is about 5 in 1,200 patients [43]. Implanted loop recordings of ECG over 220,000 h in 19 patients with intractable epilepsy detected severe ictal bradycardia or asystole that required permanent cardiac pacing in 3 (16 %) of the patients [45]. However, only 2.1 % of all recorded seizures were associated with bradycardia or asystole.

Other studies observed ST-segment depression on ECG during or after seizures [49] and prolongation of the QT interval with epileptiform EEG discharges [50]. This QT prolongation was noted to be more severe in patients who subsequently had SUDEP than in those who did not.

Animal studies have demonstrated that both ictal and interictal EEG discharges can disrupt autonomic cardiac nerve discharges, consequently predisposing the animal to potentially fatal cardiac arrhythmias [51]. Another study observed that secondarily GTCS is associated with decreased heart rate variability [52]. Also, abnormal shortening of QTc, but not QTc prolongation, occurred significantly more often in secondarily GTCS.

Autopsy series of SUDEP cases have shown that the heart is heavier than expected for body height, but similar observations also have been made for the lungs and the liver [11]. The severity of abnormalities observed in these organs, however, is not sufficient to cause sudden death. Fibrotic changes in the deep and subendocardial myocardium have also been described in persons with SUDEP. In one prospective study, these fibrotic changes were found in 40 % of SUDEP cases versus 6.6 % of control specimens [53]. However, another study found no difference in the rate of morphologic abnormalities in the conduction system between SUDEP and non-SUDEP autopsy specimens [54].

Postmortem cardiac investigations into the cause of SUDEP are hampered by low autopsy rates and also the low rate in diagnosing SUDEP cases, even when clinical SUDEP criteria are fulfilled [55]. The clinician should be aware that syncope and seizures induced by primary cardiac arrhythmia have rarely been misdiagnosed

as epilepsy [56]. The extent to which this situation contributes to the incidence of SUDEP is not known.

Encouraging advances have been made in recent years in the area of cardiac genetics. Epilepsy has recently been observed in mouse lines that have dominant human LQT1 mutations [57]. The cardiac KvLQT1 delayed rectifier channel has been detected in brain regions of these mice, in which a defect in the ability of neurons to repolarize after an action potential can produce seizures and cause autonomic dysregulation of the heart. Therefore, we now have evidence that mutations in the long-QT syndrome gene *KCNQ1* could result in dual expression of channelopathies in the heart and the brain. A related study showed that mice lacking Kv1.1 Shakerlike potassium channels encoded by the *Kcna1* gene exhibit severe seizures and die prematurely [58]. Although the channel is widely expressed in mouse brain but not in myocardium, it is extensively expressed in the juxtaparanodes of the wild-type vagus nerve. Thus, Kv1.1 potassium deficiency could underlie primary neurogenic cardiac dysfunction, which may be a mechanism for SUDEP.

Other Possible Mechanisms in SUDEP

A frequent autopsy finding in SUDEP is increased lung weight or pulmonary edema [59]. In the clinical practice setting, acute pulmonary edema has been observed after multiple convulsive seizures and, rarely, after a self-limited convulsive seizure. There are rare reports of seizure-related pulmonary edema with fatal consequences [60, 61]. Nonconvulsive status epilepticus has also been reported to be associated with adult respiratory distress syndrome [62]. The relevance of pulmonary edema to SUDEP has been doubted because SUDEP is characteristically not preceded by a period of dyspnea. How seizure activity leads to acute pulmonary edema is also undetermined. It has been speculated that seizure induction of adrenergic overdischarge is a link between seizure attacks and acute neurogenic pulmonary edema [63].

Some evidence suggests that respiratory arrest can occur during seizure activity (ictal apnea) or after seizure activity (postictal apnea) and potentially lead to cardiac arrhythmias [64–66]. Video-EEG monitoring at an epilepsy monitoring unit documented a near-SUDEP incident in a 20-year-old patient with postictal apnea [66]. Ongoing ECG recording showed normal rhythm after the seizure, and asystole did not develop until the respiratory arrest became prolonged. Although SUDEP and near-SUDEP incidents are rarely encountered during video-EEG monitoring, seizure-related apnea (of >10 s) was observed in 55 % of monitored patients and oxyhemoglobin desaturation (to <85 %) in 35 % [67]. The longest apnea duration was 63 s and the lowest oxyhemoglobin desaturation was 55 %. Similar phenomena have been observed in children [68]. The phenomenon of ictal hypoxemia could be due to global suppression of cerebral activity by seizure episodes. A recent study retrospectively reviewed generalized convulsive seizures recorded at an epilepsy monitoring unit in ten patients who subsequently had SUDEP [69]. Their seizures had longer postictal generalized EEG suppression than control patients without SUDEP. SUDEP risk was calculated to increase by 1.7 % for every 1-s increase in the duration of the postictal generalized EEG suppression.

Animal studies support the role of respiratory arrest as an important mechanism in SUDEP. Johnston and colleagues [70, 71], using a sheep model of SUDEP, observed that central hypoventilation consistently precedes cardiac arrhythmia. Similar observations were made in 75 % of audiogenic seizure mice (DBA/2 J strain) [72]. Serotonergic mechanisms may have an important role in postictal apnea. Whereas normal saline did not protect the mice from respiratory arrest, increasing doses of a serotonin-reuptake inhibitor, fluoxetine, was associated with a decreased incidence of postictal respiratory arrest [73]. The mice became susceptible again to respiratory arrest after the fluoxetine effect had dissipated. Cyproheptadine, an antiserotonergic agent, had the opposite effect on the mice. Mice that were not susceptible to postictal apnea at baseline became susceptible after cyproheptadine was given, and the susceptibility disappeared with the termination of the drug effect. An earlier study showed that a strain of mice altered genetically to be deficient in serotonin

receptors had development of audiogenic seizures and postictal apnea [74]. A subsequent retrospective study of seizures recorded at an epilepsy monitoring unit showed that complex partial seizures in patients taking selective serotonin-reuptake inhibitors were less likely to be associated with ictal hypoxemia than seizures in patients not taking them. However, no difference was noted for generalized convulsive seizures, which is the type of seizures most likely to be associated with SUDEP [75].

Small studies have noted some differences in baseline measures of autonomic function between patients with epilepsy and control subjects. Some of the differences noted were a higher heart rate at rest and a hypersympathetic response to the Valsalva maneuver and tilt-table test [76]. Temporal lobectomy has also been reported to decrease sympathetic cardiovascular modulation and baroreflex sensitivity [77]. The relevance of these observations to SUDEP is still unknown.

Possible Approaches to SUDEP

Because the focus of this book is on sudden cardiac death, the foregoing discussion of the potential mechanisms underlying SUDEP was divided into cardiac and noncardiac mechanisms. It should not be assumed that one mechanism operates in all SUDEP cases. The current state of knowledge is insufficient for us to discount the possibility of the co-occurrence of more than one mechanism in some, if not all, patients. Such a possibility can arise if seizure activity suppresses brainstem centers for cardiac and for respiratory activities.

The current knowledge regarding SUDEP risk factors and mechanisms is insufficient for developing preventive measures that are practical and reliable for decreasing the incidence of SUDEP. Nonetheless, given the strong relationship between seizure control and SUDEP occurrence, a major preventive measure against SUDEP is improvement of seizure control. Compliance with AED intake should be emphasized to patients, and they should be encouraged to strive for the best seizure control possible. When seizures are refractory to AED therapy, patients should be evaluated for epilepsy surgery. Those who become seizure free after epilepsy surgery have a lower risk of SUDEP than those in whom the surgery failed [28].

Some investigators have suggested that increased nighttime supervision of patients with poorly controlled epilepsy could potentially prevent SUDEP [22]. The odds ratio for SUDEP in supervised patients was 0.4 when compared with patients who had no supervision [34]. SUDEP often occurs at night without witnesses. The rate of SUDEP in children with poorly controlled epilepsy is low, possibly because they are less likely than adults to be in unsupervised settings. Supervision may permit timely detection of seizure occurrence and prompt intervention to interrupt the phenomenon of seizure-related apnea. Anecdotal experience shows that stimulation of the patient, such as repositioning or patting the patient, often induces the resumption of breathing. Provision of oxygen may be needed in some patients. Oxygenation remarkably decreases the risk of death in the audiogenic seizure mouse model of SUDEP [72].

In one study, 71 % of SUDEP patients were found in a prone position [78]. This would be another argument for more rigorous supervision of patients. However, constant supervision of patients with intractable epilepsy cannot be reasonably expected of family members or caregivers.

Sudden Cardiac Death in Other Neurologic Conditions

Sudden death associated with acute neurologic disorders such as severe strokes and head trauma has been referred to as *neurogenic* or *cerebrogenic* sudden death. Rapid and severe increased intracranial pressure is a frequently suspected event underlying sudden neurogenic death [79].

Intracranial pressure can be increased by lesions outside the cerebral ventricles or by processes occurring within the ventricular system. An example of the latter is increased intracranial pressure from acute obstruction of the third ventricle by a colloid cyst, which is associated with sudden death in 10 % of cases [80]. Severe

increased intracranial pressure can have lethal neuroanatomical and neurochemical consequences. Tentorial and tonsillar herniations directly damage brainstem structures. Extreme increased intracranial pressure may increase autonomic discharges, which leads to blood pressure instability and cardiac arrhythmia. Cardiac arrhythmias and ECG repolarization abnormalities occur not infrequently in acute brain disorders, especially in subarachnoid hemorrhage [81]. More common ECG alterations are large, peaked T waves ("cerebral T waves"), QT interval prolongation, and U waves. Most ECG alterations are transient and unrelated to neurogenic sudden death.

Sudden death also occurs in strokes that are not sufficiently extensive to produce increased intracranial pressure. Animal and clinical evidence shows that injury to the insula in these cases is an important factor in the occurrence of potentially lethal cardiovascular instability [82, 83]. Intracerebral hemorrhage is also associated with increased cardiac troponin levels, which independently predict in-hospital mortality [84]. Less well understood is the rare occurrence of sudden death in patients with lateral medullary infarction [85]. It is possible that respiratory arrest is the primary complication of this disorder, which then leads to cardiac arrhythmia.

Many patients with myotonic dystrophy or certain forms of mitochondrial encephalomyopathies eventually have development of cardiac conduction defects, and sudden cardiac death is not uncommon in those whose illness is moderately or well advanced [86, 87]. First-degree heart block is the most common cardiac conduction defect in myotonic dystrophy, and it may precede the presentation of the clinical illness. Conduction abnormalities affecting the His bundle are also common, even in patients without cardiac symptoms. Goodwin and Muntoni [88] reviewed the risk of cardiac involvement in different types of muscular dystrophies. Periodic assessment with ambulatory ECG may benefit patients who have types of muscle dystrophies that are highly associated with potentially fatal cardiac arrhythmias [89]. Such assessments must be initiated before skeletal muscle involvement becomes severe, because cardiac involvement may occur early in some patients.

Metabolic diseases such as those that affect glycogen storage and lipid metabolism can have associated cardiomyopathies. The topic has been extensively reviewed by Gilbert-Barness [90]. Some mutations, such as those that affect troponin T and B-myosin genes, may carry a higher risk of sudden cardiac death due to conduction defects.

A rare potassium channelopathy, Andersen-Tawil syndrome, which may be seen in the neurologic practice as periodic paralysis, has cardiac conduction defects as one of its features. Sudden cardiac death can occur in those with ventricular arrhythmias or long-QT syndrome [91].

Some patients with the neurodegenerative syndrome of multiple system atrophy die unexpectedly at night during sleep. The death is likely due to central respiratory insufficiency. Central respiratory insufficiency with central sleep apnea, and bilateral vocal cord paralysis causing stridor, have on occasions been presenting symptoms of multiple system atrophy [92]. Tracheostomy can be considered when these symptoms appear during the course of the illness. Unexpected death due to respiratory insufficiency during sleep also occurs in some patients with amyotrophic lateral sclerosis [93].

Conclusions

The fact that sudden or rapid death occurs in neurologic diseases is well known. The cardiac role in causing rapid death is intuitively accepted to be secondary in situations such as massive subarachnoid hemorrhage or stroke, but the exact cardiologic mechanisms underlying these rapid neurogenic or cerebrogenic deaths have not been fully elucidated. More intriguing is the phenomenon of SUDEP, a sudden catastrophic condition in which cardiologic causative mechanisms have long been suspected but are still unproved. The abruptness of death during normal activities in otherwise healthy individuals compels the consideration of cardiac arrhythmia as the most critical mechanism that leads inexorably to death in SUDEP. The understanding and prevention of SUDEP will continue to be hampered by the relatively low incidence of the condition and the decreasing rate of autopsy

investigation of epilepsy-related deaths. Large multicenter studies must continue to vigorously investigate potential SUDEP cases with gross anatomical studies and perhaps with the emerging molecular or genetic markers of sudden cardiac deaths [94].

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27
Sudden Cardiac Death and Alcohol

Vincent M. Figueredo and Bhaskar Purushottam

Abstract

Alcohol is a well-recognized risk factor for sudden death. Alcohol abuse may contribute to a significant proportion of non-coronary sudden deaths. There are several mechanisms through which alcohol abuse could increase sudden death risk, including increasing the QT interval, decreasing vagal input, sympathoadrenal stimulation, electrolyte abnormalities and cardiomyopathy. Ventricular arrhythmias are the most common mode of alcohol-related sudden death, including automaticity, triggering and re-entry mechanisms. Other less common causes of alcohol-related sudden death including intracranial bleeds, heart blocks, metabolic acidosis with cardiac standstill, and exsanguinating gastrointestinal bleed, should be borne in mind, when evaluating an alcoholic patient who has been resuscitated.

Keywords

Alcohol • Alcohol abuse • Ethanol • Sudden death • Sudden cardiac death • Cardiomyopathy • Ventricular tachycardia • Withdrawal • Intoxication

Introduction

The consumption of alcoholic beverages has been documented as early as 10,000 BC [1]. Alcohol (French alcool/; Arabic al-kuhl) refers to the intoxicating constituent of wine, beer, spirits, or any of numerous beverages consumed in almost all societies; that is ethanol or ethyl alcohol (C2H5OH) [2]. As most cultures throughout history have consumed alcohol, either for social, religious or medicinal reasons, the potential abuse of and addiction to alcohol have long been recognized. Alcohol abuse contributes to 4 % of the global burden of disease [3].

In the United States, regardless of sex or race, long-term heavy alcohol consumption is the leading cause of non-ischemic cardiomyopathy [4]. There are approximately 79,000 deaths attributable to excessive alcohol use each year in the United States (US) [5]. This makes alcohol abuse the third leading lifestyle-related cause of death [6]. Alcohol abuse is responsible for 2.3 million years of potential life lost annually [7]. In the single year 2005, there were more than 1.6 million hospitalizations [7] and more than four million emergency room visits

V.M. Figueredo, MD (✉) • B. Purushottam, MD
Cardiovascular Medicine Department,
Institute for Heart and Vascular Health, Einstein Medical Center, 5501 Old York Road, Levy 3232, Philadelphia, PA 19141, USA
e-mail: figueredov@einstein.edu; bpurushottam@gmail.com, purushob@einstein.edu

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[8] for alcohol-related conditions. According to the Behavioral Risk Factor Surveillance System (BRFSS) survey, more than half of the adult US population drank alcohol in the past 30 days. Approximately 5 % drank heavily, and 15 % binge drank [9].

Each year, 300,000 cases of out-of-hospital cardiac arrest occur in the US [10]. Among the non-coronary causes of sudden cardiac death (SCD), alcohol is an important etiology. There are no consistent data on the proportion of SCD related to alcohol. One study postulated that as many as 5–50 % of SCD were attributable to alcohol [11]. Due to the limited data on alcohol consumption in most patients suffering cardiac pathologies, the role of alcohol as a cofactor in SCD may be underestimated.

Metabolism

Following oral administration, ethanol is absorbed rapidly into the bloodstream from the stomach and small intestine. Peak alcohol blood levels occur approximately 30 min after ingestion [12]. Gastric metabolism of ethanol is lower in women than in men, which may contribute to the greater susceptibility of women to ethanol [13, 14].

Ethanol is metabolized largely by sequential hepatic oxidation, first to acetaldehyde by alcohol dehydrogenase (ADH) and then to acetic acid by aldehyde dehydrogenase (ALDH) [12]. The hepatic cytochrome P450 isozyme CYP2E1, can also contribute to ethanol metabolism, especially at higher ethanol concentrations and under conditions such as alcohol abuse, where its activity may be induced. Although CYP2E1 is not a major factor in ethanol metabolism, it can be an important site of interaction between ethanol and other drugs. During acute alcohol consumption there can be decreased clearance of CYP2E1 substrates that ethanol competes with for oxidation by the enzyme system (e.g., phenytoin and warfarin) [12]. The complex metabolism of ethanol along with genetic polymorphisms (e.g., ADH) may contribute towards differential susceptibility to SCD related to alcohol.

Effects of Alcohol on the Cardiovascular System

Cardioprotective Effects

In most countries, the risk of mortality due to coronary heart disease (CHD) is correlated with high dietary intake of saturated fat and elevated serum cholesterol levels. France is an exception to this rule, with relatively low mortality from CHD despite the consumption of high quantities of saturated fats; the "French paradox". Epidemiological studies suggest that widespread wine consumption may confer a cardioprotective effect, with one to three drinks per day resulting in a 10–40 % decrease in the risk of CHD events, compared to no alcohol consumption. In contrast, daily consumption of greater amounts of alcohol leads to an increased incidence of non-coronary causes of cardiovascular events, such as arrhythmias, cardiomyopathy and hemorrhagic stroke, offsetting the beneficial effects of alcohol on CHD; that is, alcohol has a J-shaped dose-mortality curve. Reduced risks for CHD are seen at average intakes as low as two to seven drinks per week [15]. Data based on a number of prospective, cohort, cross-cultural, and case–control studies in diverse populations consistently reveal lower rates of angina pectoris, myocardial infarction, and peripheral artery disease in those consuming light (1–20 g/day) to moderate (21–40 g/day) amounts of alcohol [12].

One possible mechanism by which alcohol could reduce the risk of CHD is through its effects on cholesterol. Changes in plasma lipoprotein levels, particularly increases in high-density lipoprotein (HDL) and decreases in low-density lipoprotein (LDL), have been associated with the protective effects of ethanol, regardless of the type of alcoholic beverage. Flavonoids found in red wine (and purple grape juice) may have an additional antiatherogenic role by protecting LDL from oxidative damage.

Another way in which alcohol consumption conceivably could play a cardioprotective role is by altering factors involved in clotting. Alcohol consumption elevates levels of tissue plasminogen activator, decreasing clot formation.

Decreased fibrinogen concentrations observed following ethanol consumption may also be cardioprotective [16]. Epidemiological studies have linked moderate consumption of ethanol to inhibition of platelet activation [17].

Pathological Effects of Alcohol on the Cardiovascular System

Hypertension

Consumption of greater than 30 g alcohol per day (more than two standard drinks) is associated with a 1.5–2.3 mm Hg rise in diastolic and systolic blood pressures [12]. Studies demonstrate a positive, nonlinear association between alcohol and hypertension [12]. The prevalence of hypertension attributable to excess alcohol consumption is not known, but studies suggest 5–11 % [12].

Cardiac Arrhythmias

Alcohol has pharmacological effects on cardiac conduction, including prolongation of the QT interval, prolongation of ventricular repolarization, and sympathetic stimulation [12]. Ventricular tachycardia may be responsible for the increased risk of unexplained SCD that has been observed in persons who are alcohol-dependent [18]. Atrial arrhythmias associated with chronic alcohol use include atrial fibrillation, atrial flutter, and supraventricular tachycardias. Fifteen to twenty percent of idiopathic cases of atrial fibrillation may be related to alcohol [19]. During continued alcohol use, treatment of these arrhythmias may be more resistant to cardioversion or medical therapy. Patients with recurrent or refractory atrial arrhythmias should be questioned carefully about alcohol use.

Cardiomyopathy

Alcohol has dose-related toxic effects on both skeletal and cardiac muscle. Numerous studies have shown that alcohol depresses cardiac contractility and can lead to cardiomyopathy [12]. Approximately half of patients with idiopathic cardiomyopathy in developed countries are thought to be alcohol-related. Although the clinical signs and symptoms of idiopathic and alcohol-induced cardiomyopathy are similar, alcohol-induced cardiomyopathy may have a better prognosis if patients are able to stop drinking [12]. As 40–50 % of persons with alcohol-induced cardiomyopathy who continue to drink die within 3–5 years, abstinence remains the primary treatment.

Stroke

Clinical studies indicate an increased incidence of hemorrhagic and ischemic stroke in persons who drink more than 40–60 g alcohol per day [20]. Many cases of alcohol-related stroke follow binge drinking episodes, especially when stroke occur in younger patients.

Epidemiological Data Regarding Alcohol Consumption and SCD

It is now well-known that alcohol consumption is one of the major modifiable risk factors in SCD – be it coronary or non-coronary in origin. One of the first studies to demonstrate an association between heavy alcohol use and SCD was published in 1977 by Dyer et al. [21]. In their study, 'problem drinkers' from the Chicago Peoples Gas Company had significantly higher 15-year mortality rates from all causes, cardiovascular diseases, coronary heart disease, and sudden death. These differences could not be entirely explained by their blood pressure, smoking, and relative weight status.

Wannamethee and Shaper [22] conducted a prospective cohort study (British Regional Heart Study) on 7,735 men, aged between 40 and 59 years, across 24 towns in England, Wales and Scotland in 1992. They found a positive association between drinking and the risk of SCD. As shown in Fig. 27.1, heavy drinkers had a nearly twofold increase in risk when compared to non-drinkers, even after adjusting for multiple confounding factors. Also noted in the study was that death from ischemic heart disease was more likely to be sudden in heavy drinkers.

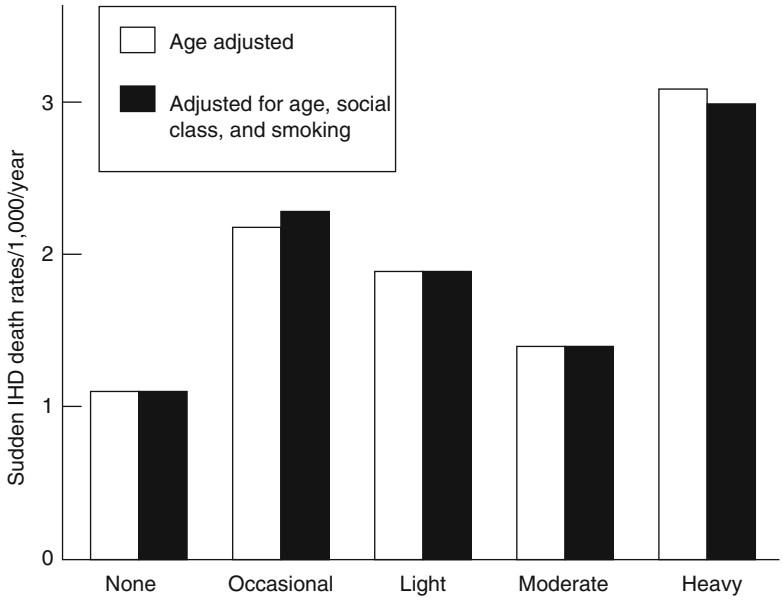

Figure 27–1. Alcohol intake and sudden death rates/1,000/year adjusted for age and in addition for social class and smoking (From Wannamethee and Shaper [22]. Reprinted with permission from BMJ Publishing Group)

Lithell et al. [23] prospectively followed 2,322 participants and 454 non-participants (50 year old men) for 10 years after a health screening examination in Uppsala, Sweden. Among the participants, 26 suffered sudden death and of those 46 % were registered with the Swedish temperance board (persons with heavy alcohol abuse, drinking offence or driving under the influence). In logistic analysis, persons registered with the temperance board had a significant high risk for SCD (odds ratio of 2.43).

Fraser and Upsdell [24], in the Auckland Study, compared definite myocardial infarction patients not dying suddenly with cases of SCD. They found that heavy drinkers had a higher proportion of coronary events presenting as SCD. The Framingham Study [25] found that sudden death, in the absence of clinical evidence of coronary heart disease, was more common among men drinking more than 90 oz of ethanol per month.

Given the association between heavy alcohol consumption and SCD, additional studies examined the question as to whether light-moderate alcohol consumption had an impact on SCD. Albert et al. [26] prospectively followed 22,071 apparently healthy male physicians in the Physicians Health Study, who were 40–84 years old and had no history of myocardial infarction, stroke, transient ischemic attacks or cancer. At baseline and at 84 months of follow-up, seven possible response categories of alcohol consumption were recorded. Over 12 years of follow-up they found that men who consumed two to four drinks per week or five to six drinks per week at baseline had significantly reduced risks of SCD of 60 and 79 %, respectively, compared with those who rarely or never consumed alcohol. The relationship between alcohol consumption and SCD was U-shaped, with the risk approaching unity at approximately two drinks per day. On the contrary, one prospective study from Finland [27] reported a positive association between moderate alcohol intake (≥200 g/month, equivalent to three to five drinks/week) and SCD. Albert et al. [26] suspected that the pattern of drinking, heavy consumption at less frequent settings per week, which was probably uncommon in the Physicians Health Study, could explain these discrepant results.

Recently, Chiuve et al. [28] conducted a prospective cohort study with 87,067 women from the Nurses' Health Study, who were free of chronic disease, to assess the association between alcohol intake and risk of SCD. After 26 years of follow-up they found a U-shaped association between alcohol consumption and risk of SCD in age- and calorie-adjusted, as well as multivariate-adjusted, models (Fig. 27.2). The lowest risk of SCD occurred among women who consumed

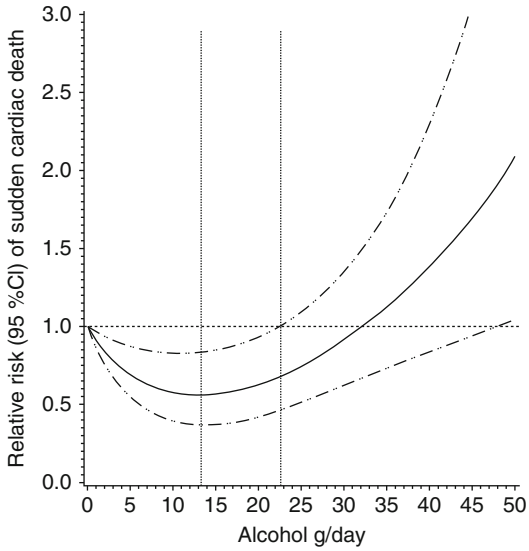

Figure 27–2. Multivariate relative risk of SCD as a function of alcohol intake data were fitted by a restricted cubic spline Cox proportional hazards model. The 95 % confidence intervals are indicated by the *dashed lines*. Models adjusted for age, calories, smoking, BMI, parental history of MI, menopausal status, use of postmenopausal hormones, aspirin use, multivitamin and vitamin E supplements, physical activity and intake of omega-3 fatty acid, alpha-linolenic fatty acid, *trans*-fatty acid, ratio of polyunsaturated to saturated fatty acids, diagnosis of CHD, stroke, diabetes, high blood pressure and high cholesterol. The spline was based on 247 cases after the exclusion of former drinkers and women with intake >50 g/day (From Chiuve et al [28]. Reprinted with permission from Elsevier Limited)

5–14.9 g/day of alcohol (0.5–1 drink/day) when compared to abstainers (multivariate RR = 0.64). In women with the highest consumption of alcohol (>30 g/day) the multivariate RR was 1.15 when compared to the abstainers. Thus, epidemiological data from numerous studies suggest the risk of SCD to be lower in individuals with low to moderate alcohol intake (two to six drinks/week) compared with those who rarely or never consume alcohol or those with high intake (three to five drinks/day) and binge drinkers [2, 29].

Mechanisms of Sudden Cardiac Death Related to Alcohol

Evidence suggests a proarrhythmic milieu can develop in the settings of acute alcohol intoxication, alcohol withdrawal, and chronic alcohol abuse. Potential mechanisms of alcohol-induced arrhythmias are discussed below and are shown in Fig. 27.3.

Acute Alcohol Intoxication

Acute alcohol intoxication presents with central nervous system symptoms and signs after two to three drinks in most people (serum ethanol >50 mg/dL). Symptoms can range from euphoria to coma, depending on the alcohol level and associated drug use.

Alcohol ingestion causes an increase in the release of catecholamines [30, 31]. Perman [30] suggested that increased adrenaline excretion is due to adrenal medullary stimulation by ethanol. Howes et al. [31] demonstrated the dual effect of ethanol on increasing noradrenaline levels, as well as decreasing its clearance (the rise in noradrenaline commences 30 min after drinking and lasts for about 4 h). James and Bear [32] showed in anesthetized dogs that direct perfusion of the sinus node with acetaldehyde (metabolite of ethanol) produced significant stimulation of norepinephrine concentrations similar, to those occurring when humans consume alcohol.

Koskinen et al. [33] studied the acute effects of ethanol (dose of 1 g/kg body weight) on heart rate, blood pressure variability and baroreflex sensitivity in 12 healthy male subjects. They found a significant decrease in heart rate variability owing to diminished vagal modulation of the heart rate, reflecting reduced baroreflex sensitivity. Weise et al. [34] studied eight healthy volunteers and found that their blood pressure and heart rate remained unaltered during intoxication, but their heart rate variability was significantly reduced immediately after ingestion. Similarly, Rossinen et al. [35] demonstrated that in patients with coronary artery disease, acute ethanol intake elevated heart rate and reduced heart rate variability.

Aasebo et al. [36] studied 84 patients who were hospitalized with acute ethanol intoxication and found that P wave and QTc intervals were prolonged compared with sober subjects. Also, they found that P wave, PR, QRS and QTc intervals were longer when the subjects had high blood ethanol levels at admission than at discharge.

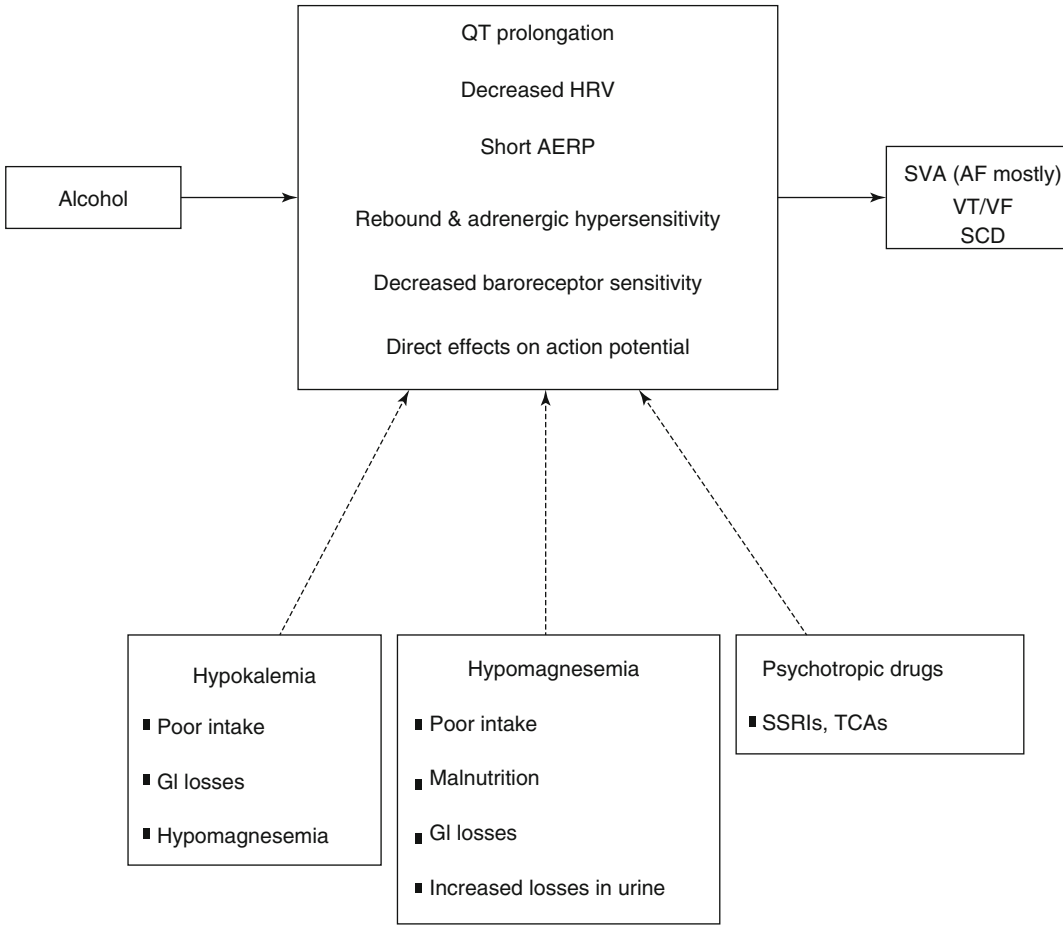

Figure 27–3. Potential mediators of alcohol-induced cardiac arrhythmias. *AERP* atrial effective refractory period, *AF* atrial fibrillation, *GI* gastrointestinal, *HRV* heart rate variability, *SCD* sudden cardiac death, *SSRI* selective serotonin reuptake inhibitor, *SVA* supraventricular arrythmia, *TCA* tricyclic antidepressant, *VF* ventricular fibrillation, *VT* ventricular tachycardia (From George and Figueredo [2]. Reprinted with permission from Lippincott Williams & Wilkins)

Further studies are needed to examine the role of QRS duration in alcohol-related SCD.

Buckingham et al. [37] studied 38 patients admitted to an acute community alcoholic detoxification center with 24-h ambulatory electrocardiograms and serum ethanol levels. They found a correlation between serum ethanol level and the mean rate of ventricular ectopic beats/h. Nonsustained ventricular tachycardia was more common in patients with previous underlying heart disease.

Animal experiments [38] have shown that high concentrations of ethanol produce concentration-dependent coronary vasospasm, which were not prevented by several antagonists. This could be another potential mechanism through which binge drinkers may develop SCD.

As delineated above, multiple potential mechanisms can predispose those with acute alcohol intoxication to life-threatening arrhythmias, including QT prolongation and increases in catecholamine levels.

Acute Alcohol Withdrawal

Acute alcohol withdrawal syndrome consists of symptoms and signs that include tremor, agitation, anxiety, and autonomic nervous system overactivity, manifested by increases in heart rate, respiratory rate, and body temperature.

Withdrawal usually begins 5–10 h after ethanol intake, peaks on day 2 or 3, and improves by day 4 or 5, although mild levels of these problems may persist for 4–6 months as a protracted abstinence syndrome. Approximately 2–5 % of alcoholics experience delirium tremens, where the withdrawal includes delirium (mental confusion, agitation, and fluctuating levels of consciousness) associated with a tremor and autonomic overactivity [39]. In this state of heightened activity, patients are at an increased risk for SCD.

Maki et al. [40] studied ten male subjects attending a withdrawal clinic after prolonged alcohol abuse. One day into withdrawal, there was a significant elevation of beta-adrenoceptor levels, which was accompanied by a parallel activation of the beta-adrenoceptor-mediated cAMP production of lymphocytes. There were no major changes in beta-adrenoceptor levels or cAMP production during the next 7 days. Interestingly, on admission the mean beta-adrenoceptor density was approximately 60 % of the mean level of healthy control subjects. Plasma catecholamine levels were elevated at arrival and decreased steadily during the withdrawal period. They concluded that chronic alcoholism is associated with a reduction of lymphocytic beta-adrenoceptor density and functioning, which is followed by a rapid reversal during withdrawal. Further, this is responsible for the accelerated heightened responsiveness to catecholamines during the first ethanol-free day of chronic alcoholics.

Bar et al. [41] investigated baroreflex sensitivity, heart rate variability, blood pressure variability, cardiac index, left ventricular work index and total peripheral resistance in 20 patients undergoing acute alcohol withdrawal, compared with matched controls. They found a marked down-regulation of baroreflex sensitivity during acute alcohol withdrawal. Non-linear parameters of heart rate variability and baroreflex sensitivity correlated with the severity of the acute alcohol withdrawal syndrome. Interestingly, they also found a milder down-regulation of baroreflex sensitivity in 15 abstaining alcoholics.

The QT interval reflects the most critical phase for the generation of reentry and ventricular arrhythmia generation [42]. Berger et al. [43] established a index normalizing QT variability to heart rate variability. Beat-to-beat QT interval variability reflects the temporal fluctuation in ventricular repolarization and provides a window into repolarization abnormalities [44]. Abnormal QT variability is associated with ventricular arrhythmias and SCD [45–47]. Bar et al., studied high resolution electrocardiographic recordings from 18 patients suffering from acute alcohol withdrawal, 18 matched controls and 15 abstaining alcoholics. They found that the heart rate and QT variability index were significantly increased in acute alcohol withdrawal. In contrast, abstained alcoholics did not significantly differ from controls.

Otero-Antón et al. [48] studied QT intervals in 62 patients (52 male; 10 female) who were admitted with acute alcohol abstinence syndrome. They found that 47 % had a prolonged QTc interval of more than 440 milliseconds on their admission ECG. In 27 patients, who had a second ECG during the hospital stay, the QTc interval had significantly shortened. Eight patients found to have prolonged QTc on admission had a second ECG performed on them after complete recovery from withdrawal symptoms and in all cases the QTc interval had returned to normal.

Cuculi et al. [49] performed a retrospective analysis on 49 patients (38 males, 11 females) with a diagnosis of delirium tremens or alcohol withdrawal seizures. The QTc interval was prolonged in 63 %, with 10 % developing tachyarrhythmias (two torsade de pointes, one sustained ventricular tachycardia, two supraventricular tachycardias, and one atrial fibrillation).

Electrolyte abnormalities are commonly present during withdrawal in chronic alcohol abusers [50–53], which can increase arrhythmia risk [54]. Stasiukyniene [55] studied 114 chronic alcoholics during withdrawal. Hypokalemia was observed in 29 %, hypomagnesemia in 30 %, and hyponatremia in 73 %. Potential causes include: poor nutritional intake and malabsorption; increased excretion during vomiting, diarrhea and diuresis; decreased renal tubular reabsorption; altered ionic permeability of cells; elevated plasma catecholamines and respiratory alkalosis (from hyperventilation) which cause an intracellular shift of potassium and magnesium [56]. The more pronounced the alcohol withdrawal syndrome, the sharper the decline in potassium

and magnesium levels [51], which in turn increases the risk for arrhythmias and SCD.

Animal experiments [57] have demonstrated that abrupt termination of an ethanol regimen provokes ventricular arrhythmias and enhances susceptibility to the arrhythmogenic effects of epinephrine. In summary, heightened catecholamine activity and effects on heart rate variability and baroreflex sensitivity, along with QT prolongation, may contribute towards SCD in acute alcohol withdrawal.

Chronic Alcohol Abuse

Alcohol dependence is defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) as repeated alcohol-related difficulties in at least three of seven life areas that cluster together at about the same time. Alcohol abuse is defined as repetitive problems with alcohol in any one of four life areas—social, interpersonal, legal, and occupational—or repeated use in hazardous situations such as driving while intoxicated. In the US, in both sexes and all races, chronic alcohol abuse is the leading cause of non-ischemic cardiomyopathy [4]. There are several changes at the gross, histological and molecular levels that may contribute to increased SCD. To follow are studies which examine the association of chronic alcohol abuse and SCD, as well as the possible alcohol-related mechanisms of SCD.

Vikhert et al. [58] studied 752 SCD cases. Alcoholic cardiomyopathy was found in 17 %; predominantly in men under age the 50 (73 %). Gross morphology, light microscopy, electron microscopy and enzyme histochemistry findings were similar to other forms of dilated cardiomyopathy.

Kino et al. [59] found the most frequent cardiovascular finding in 145 asymptomatic male chronic alcoholics admitted to Ranryoen Hospital, Japan (alcohol detoxification centre) was a prolonged QTc interval of more than 440 milliseconds (43 %), unrelated to serum electrolyte abnormalities. Day et al. [60] prospectively followed 69 patients with histologically proven alcoholic liver disease (without evidence of structural heart disease, abstinent from alcohol for at least 7 days before investigation) and 40 healthy non-drinking controls, matched for age and sex. They found that QT intervals recorded at the start of the study were longer in alcoholics than in controls (unrelated to electrolyte abnormalities). Also, the QT intervals were prolonged in the 14 patients who died compared with survivors, mainly due to long QT intervals in the 6 patients with SCD (Fig. 27.4). Borini et al. [56] in a study from Brazil, found that 55 % of their 44 female alcoholics had a prolonged QTc interval.

Milovanovic et al. [61] studied 25 patients with alcoholic liver cirrhosis to analyze the risk predictors for SCD related to autonomic dysfunction. As shown in Fig. 27.5, based on autonomic reflex tests, these subjects had a high incidence (56 %) of severe autonomic dysfunction, manifested as pronounced vagal impairment. The presence of vagal neuropathy in liver cirrhosis is an independent predictor of mortality [62]. Other studies have shown that chronic alcohol ingestion is associated with autonomic neuropathy, predominately of vagal origin [63–65], potentially contributing to the increased incidence of SCD in alcoholics [66, 67]. Genovesi et al. [68] showed that the QT/RR slope was steeper in 48 cirrhotic patients with an alcoholic etiology when compared to those with a viral etiology.

Malpas et al. [69] performed autonomic function testing in 23 alcohol dependent men (changes in heart rate, RR interval and blood pressure with deep breathing, standing, Valsalva maneuver, neck suction) and measurement of 24 h heart rate variability, and compared them with 11 healthy men. Sixteen alcohol dependent men (group 1) had normal standard autonomic function tests and seven had vagal neuropathy (group 2). As shown in Fig. 27.6, the 24 h heart rate variability was significantly lower in both alcohol dependent groups than in controls, while the two alcohol dependent groups were not significantly different from each other. This could suggest that 24 h heart rate variability was more sensitive in detecting changes in autonomic integrity than the standard tests of autonomic function [69]. A similar pattern was seen in a previous study of diabetic patients [70].

Sakagami et al. [71], studied patients with alcoholic pancreatitis (n = 36) and alcoholic dependence (n = 37), and compared them to healthy control subjects (n = 36). They found that

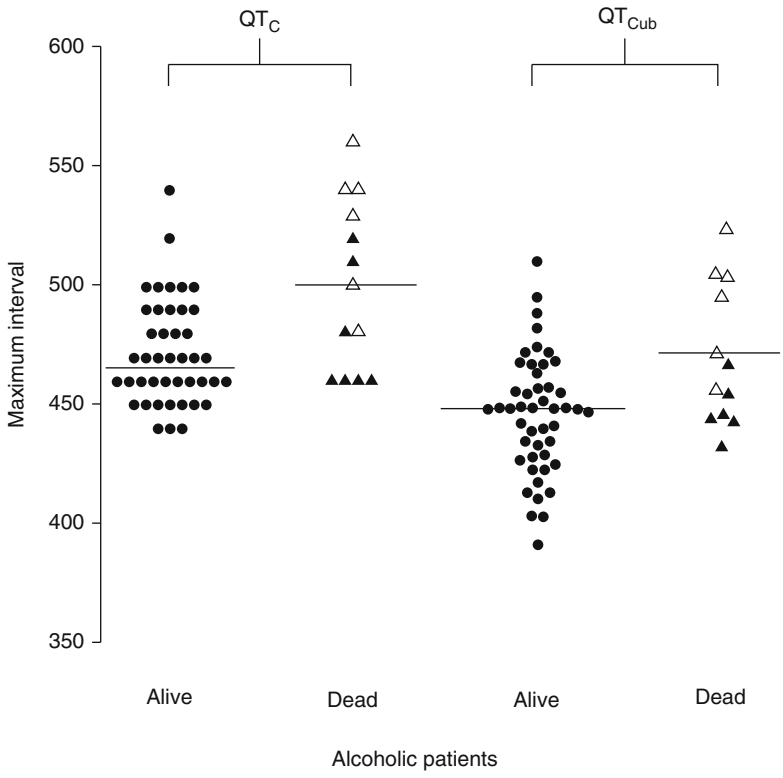

Figure 27–4. Corrected QT intervals in alcoholic patients and survival. *Open triangle* cardiac sudden death, *solid triangle* non-cardiac cause of death. *Horizontal lines* represent means (From Day et al. [60]. Reprinted with permission from Elsevier Limited)

patients with alcoholic pancreatitis and alcohol dependence had a longer QT and increased QTc dispersion compared to control subjects. Interestingly patients with alcoholic pancreatitis had a longer QT and increased QTc dispersion than those with alcoholic dependence only. Often, patients with alcoholic pancreatitis also have secondary diabetes and therefore a greater risk for autonomic dysfunction, which could explain the increased QT and QTc dispersion [63, 72, 73]. Whether this translates into a higher risk of SCD in the patients with alcoholic pancreatitis requires further study.

Chronic alcohol abuse can cause dilated cardiomyopathy with a dose-dependent decrease in left ventricular ejection fraction. Fauchier et al. [74, 75] studied 194 patients with non-ischemic dilated cardiomyopathy. When they compared 28 patients with alcoholic cardiomyopathy without abstinence with 119 patients with idiopathic cardiomyopathy, they found a similar event rate in SCD, sustained ventricular tachycardia and ventricular fibrillation during a mean follow-up of 51 months (Fig. 27.7). In contrast, patients with alcoholic cardiomyopathy who abstained (n = 47) had a significantly lower number of events when compared to the other groups, highlighting the importance of abstinence in alcohol-related cardiomyopathy.

In chronic alcohol abuse, the mode of SCD appears multifactorial. In addition to cardiomyopathy, prolonged QTc, increased QTc dispersion, steeper QT/RR slope and autonomic dysfunction with vagal impairment can all be contributing factors to SCD.

Electrophysiological Effects of Alcohol

One of the most quoted studies regarding the electrophysiological effects of alcohol in alcoholics is by Greenspon and Schal [76]. Fourteen patients with a history of rhythm disturbances, heart disease and alcohol abuse underwent electrophysiological testing at baseline (non-sedated state) and after 90 mL of 80-proof whiskey. One patient developed nonsustained ventricular tachycardia and another had paired ventricular

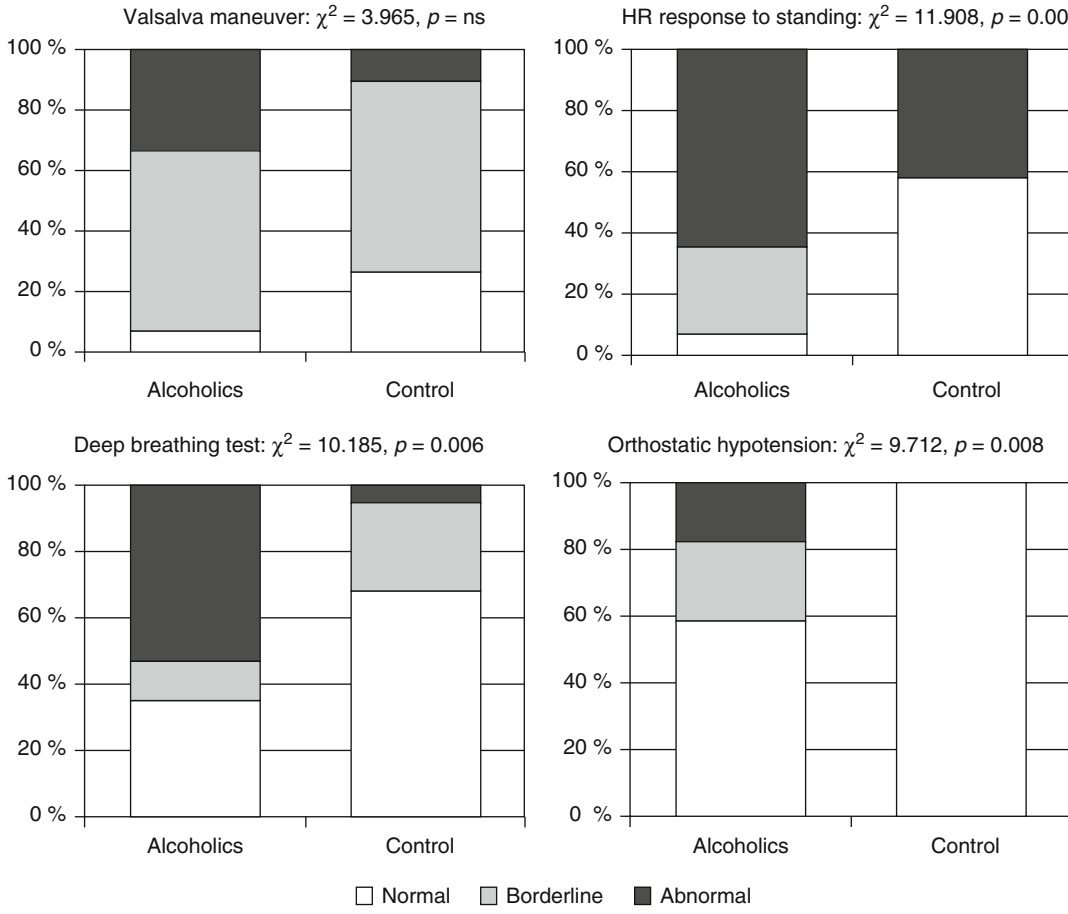

Figure 27–5. Cardiovascular reflex tests (From Milovanovic et al. [61]. Reprinted with permission from Institute of Molecular Physiology and Genetics)

responses. Post alcohol administration, one patient developed sustained ventricular tachycardia and four developed non-sustained ventricular tachycardia. The His-ventricle interval was observed to be increased post alcohol administration. One patient was admitted to the hospital with a Mobitz II block post alcohol administration.

Panos et al. [77] reported on a case of a binge drinker, who had been resuscitated from a cardiac arrest, and had normal baseline electrophysiological testing. Following intravenous alcohol administration, paired ventricular extrastimuli from a right ventricle pacing catheter induced a rapid polymorphic ventricular tachycardia requiring cardioversion. Repeat electrophysiological testing 24 h later in the absence of alcohol was again normal. Another study by Gould et al. [78, 79] found that ethanol alters conduction velocity and action potential duration, which can facilitate ventricular re-entry.

In vitro studies [80–82] suggest that high concentrations of alcohol can shorten the atrial and ventricular action potential durations. Studies in animal models [83] have demonstrated prolonged atrioventricular and intraventricular conduction times. Ettinger et al. [84] reported a decreased ventricular fibrillation threshold in chronic alcohol fed animals, which were given alcohol acutely. Similarly, Guideri et al. [85] found an increased sensitivity during withdrawal to ventricular arrhythmias and sudden death in animals that were pretreated with alcohol for 7 weeks.

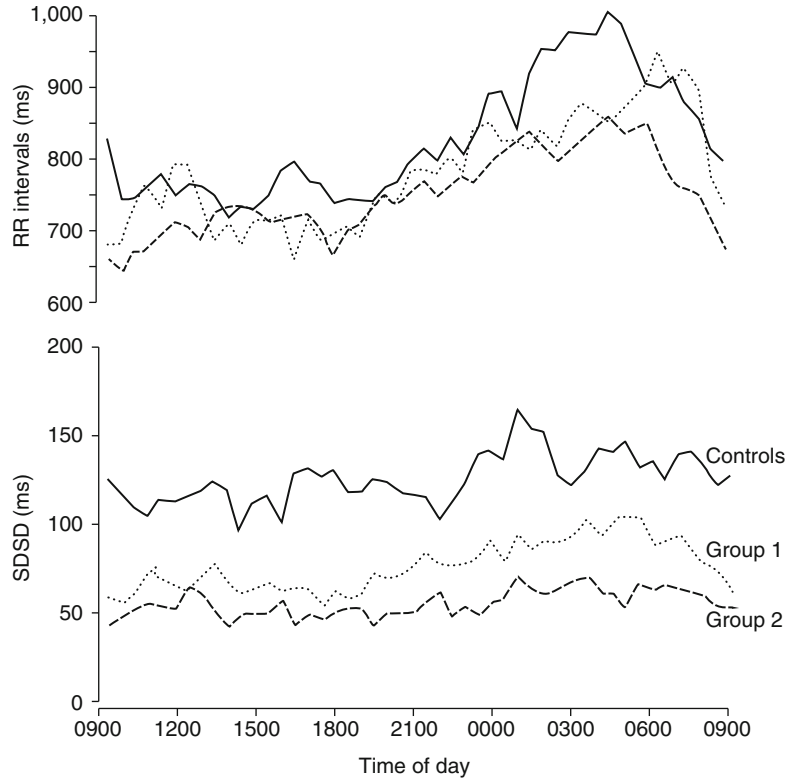

Figure 27–6. Individual mean heart rate variability (SDSD) in the three groups for the whole 24 h period. The *solid line* indicates the mean value in each group. There was a significant difference between controls and both alcohol dependent groups that the standard tests of autonomic function did not identify (From Malpas et al. [69]. Reprinted with permission from BMJ Publishing Group Ltd)

Klein et al. [86] were the first to show the acute inhibitory effects of alcohol on single cardiac sodium channel gating. Reduction of sodium channel activity can lead to an increased sodium-calcium-exchanger activity in the myocardium, which then prolongs the action potential; thus making the myocardium vulnerable to afterdepolarizations which can trigger ventricular arrhythmias [87]. This may be the mechanism through which QT interval is prolonged. However, additional studies are needed to establish this relationship.

Genetic Factors in Alcohol and Sudden Cardiac Death

Several genetic polymorphisms controlling alcohol metabolism have been identified [88]. These include ADH isoforms (ADH1A, 1B, and 1C), ADH1B gene polymorphisms, gamma-1 and gamma-2 forms of ADH1C, CYP2E1, CYPs1A2, CYP3A4, and ALDH2*2 [12]. A recent study demonstrating variations in susceptibility genes and their relation to dilated cardiomyopathy in chronic alcoholics found that only a fraction of patients actually develop dilated cardiomyopathy, which suggests a genetic vulnerability [89]. Similarly, there could be genetic factors which could influence inter-individual variation in myocardial electrophysiological responses to alcohol. This will require further study.

Other Things to Consider

As discussed earlier, electrolyte abnormalities during the acute alcohol withdrawal stage, such as hypokalemia and hypomagnesemia, can set up the substrate for life threatening

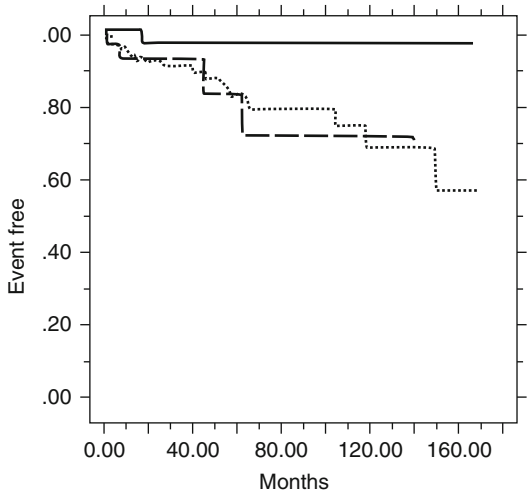

Figure 27–7. Survival curves of sudden deaths and major arrhythmic events (sustained VT, VF) in patients with ACM and IDCM. The *solid line* indicates patients with ACM and alcohol abstinence, the *small dashed line* indicates IDCM, and the *large dashed line* indicates patients with ACM without abstinence. Compared to patients with ACM and alcohol abstinence, relative risk of events was 8.0 for patients with ACM without abstinence (log-rank test, $p = 0.01$) and 7.3 for patients with IDCM (log-rank test, $p = 0.03$) (From Fauchier [74]. Reprinted with permission from American College of Chest Physicians)

ventricular arrhythmias. Alcoholic ketoacidosis occurs following prolonged excessive alcohol consumption, mainly due to starvation and glycogen depletion, fluid volume depletion and an elevated NADH/NAD rate secondary to alcohol metabolism, which in turn causes ketoacid generation. A severe form of this process results in severe metabolic acidosis, which can result in pulseless electrical activity. Yanagawa et al. [90] reported six cases of cardiac arrest in alcoholic ketoacidosis. All six exhibited pulseless electrical activity upon sudden cardiac arrest. Coronary thrombosis, pulmonary thrombosis, tension pneumothorax and cardiac tamponade were excluded. They concluded that severe metabolic acidosis with respiratory acidosis, hypoxia, hypothermia and hemorrhage contributed to the cardiac arrests.

Abusers of alcohol are more likely to abuse non-prescription drugs such as cocaine and amphetamines, which can result in life threatening arrhythmias and SCD (see Chap. 28). Alcoholics tend to have a higher incidence of psychiatric morbidity, often requiring medications such as tricyclic antidepressants, selective serotonin reuptake inhibitors and lithium, which can prolong the QT interval. Alcohol can be a strong contributing factor in hemorrhagic strokes [11, 91, 92], which can be fatal if they are large in size or involve the brainstem region causing cerebral edema, herniation, ventricular arrhythmias, sudden vagotonic stimulation with bradycardia and cardiac standstill [93–96]. There have been a few case reports of alcohol induced sinus bradycardia [97] and Mobitz II block [77], which can cause syncope and may have the potential to cause sudden death. The probability of alcohol causing coronary vasospasm as suggested in one animal experiment [38] remains controversial.

Excessive alcohol consumption can cause severe, poorly controlled hypertension, a main cause of aortic dissection, which can lead to sudden death. While the etiologic link between excessive alcohol consumption and aortic dissection is highly plausible, it remains to be confirmed in large registries and studies [98]. Alcohol intoxication or withdrawal can result in status epilepticus [99–101], which has the potential to culminate into sudden death [102]. Finally, alcoholism is associated with trauma and exsanguinating gastrointestinal bleeding, both of which can lead to sudden death.

Management

Clearly, prevention is the best treatment. Patients should be educated about the hazards of excessive drinking. The judicious use of beta blockers, for antihypertensive and anti-catecholamine actions, fluids, benzodiazepines and correction of metabolic and electrolyte abnormalities in monitored settings are very important during acute intoxication and withdrawal stages. In alcoholic cardiomyopathy, treatment should follow the standard guidelines as advised for non-ischemic cardiomyopathy, with abstention.

As per the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines, complete abstinence from alcohol is recommended [29] (class

I recommendation with level of evidence C) in cases where there is a suspected correlation between alcohol intake and ventricular arrhythmias. It is a class I recommendation for implantable cardioverter-defibrillator (ICD) therapy in patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia after evaluation to define the cause of the event and to exclude any completely reversible causes. Given the strong addiction with alcohol and the complex interactive mechanisms in SCD, it becomes an individualized decision in ICD therapy. Such matters require detailed discussions with the patient (and the family) with the single most important intervention being to avoid the offending agent. There is no data on the preemptive or prophylactic use of antiarrhythmic medications. Their use should be guided as per the clinical situation.

Conclusions

Alcohol is a well-recognized risk factor for SCD. Alcohol abuse may contribute to a significant proportion of non-coronary sudden deaths. There are several mechanisms through which alcohol abuse could increase SCD risk, including increasing the QT interval, decreasing vagal input, sympathoadrenal stimulation, electrolyte abnormalities and cardiomyopathy. Ventricular arrhythmias are the most common mode of alcohol-related SCD, including automaticity, triggering and re-entry mechanisms. Other less common causes of alcohol-related sudden death including intracranial bleeds, heart blocks, metabolic acidosis with cardiac standstill, and exsanguinating gastrointestinal bleed should be borne in mind, when evaluating an alcoholic patient who has been resuscitated. The current recommendations on alcohol intake are not to exceed >2 drinks/day for men and 1 drink/day for women with no underlying heart disease. It is advised to abstain from alcohol if a patient has cardiomyopathy. Despite the pervasive use of alcohol in most societies, much remains unknown regarding its electrophysiological effects of the myocardium and its influence on SCD.

Conflicts of Interests **None**

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28
Sudden Cardiac Death and Addictive Chemical Substances

Bhaskar Purushottam and Vincent M. Figueredo

Abstract

Over the last century, an epidemic of substance abuse in the United Sates has resulted in significant mortality and morbidity. Drug abuse is now a major problem in many societies, though the pattern of drug abuse differs from country to country and even from one province to another. The most common illicit drugs abused worldwide include cannabis, cocaine, amphetamines, and opiates such as heroin. In this chapter, we discuss the role of addictive substances in sudden death.

Keywords

Cannabis • Marijuana • Cocaine • Amphetamines • Opiates • Heroin • Methadone • Benzodiazepines • Propofol • Androgenic anabolic steroids • Caffeine • Sudden death • Sudden cardiac death

Introduction

Over the last century, an epidemic of substance abuse in the United States (US) has resulted in significant mortality and morbidity. Drug abuse is now a major problem in many societies [1], though the pattern of drug abuse differs from country to country and even from one province to another [2]. The most common drugs abused worldwide include alcohol, cannabis, cocaine, amphetamines, and opiates such as heroin [2–4]. The role of alcohol in sudden death is reviewed in the previous chapter. In this chapter, we discuss the role of other addictive substances in sudden death.

B. Purushottam (✉) • V.M. Figueredo
Cardiovascular Medicine Department,
Institute for Heart and Vascular Health,
Einstein Medical Center, 5501 Old York Road,
Levy, 3232, Philadelphia, PA 19141, USA
e-mail: bpurushottam@gmail.com,
purushob@einstein.edu; figueredov@einstein.edu

Cocaine

Cocaine is the second most commonly used [5] and widely trafficked illicit drug [6] in the world, only trailing cannabis. Among the illicit drugs leading to emergency department visits in the US, cocaine is responsible for the majority [7]. Cocaine is one of the most frequent causes of drug-related death reported by forensic pathologists [8]. In the US, the lifetime prevalence of recreational cocaine use is currently estimated to be greater than 14 %. Cocaine use is predominantly in individuals between 18 and 25 years of age, with males using more than twice as much as females. Usage rates according to race are 1.1 % for blacks, 0.9 % for Hispanics, 0.5 % for whites, and 0.1 % for Asians [9]. As its use has increased, the number of cocaine-related

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cardiovascular events, including angina pectoris, myocardial infarction, cardiomyopathy, and sudden death, have increased commensurately. Cocaine related deaths are predominantly seen in males in their mid 30s, with death occurring at home and predominately on weekends [10–13].

Cocaine (benzoylmethylecgonine, $C_{17}H_{21}No_4$) is an alkaloid extracted from the leaves of the Erythroxylon coca (a plant native to South America; contains 0.5–1 % cocaine), which was first used as a local anesthetic for ophthalmological procedures in 1884 and, interestingly, as an ingredient in a popular cola beverage in the early twentieth century. Freebase cocaine is the alkaloid in a basic non-salt form, prepared from cocaine hydrochloride by an organic extraction from a basic solution with ether. When heated, it makes a crackling sound, hence its street name, "crack". Cocaine is well absorbed through all body mucous membranes and can be administered by nasal, sublingual, intramuscular, intravenous, and respiratory routes. The onset of action varies from 3 s to 5 min depending on the route of administration. Also dependent on the route of administration are peak effects and duration of action, which vary from 1 to 90 min. In humans, cocaine has an elimination half-life of 30–60 min and is metabolized by plasma and hepatic cholinesterases to benzoylecgonine and ethyl methylecgonine, which are excreted in the urine. Unmetabolized cocaine is usually not present in serum after 6 h, but the metabolites can be detected for up to 48 h. Benzoylecgonine has been detected in urine as long as 22 days after the last dose of cocaine in asymptomatic patients who have a history of chronic cocaine abuse.

Pharmacological Actions of Cocaine

Sympathomimetic Actions

Cocaine increases the release and reduces the reuptake of serotonin and dopamine in the brain. It blocks reuptake of norepinephrine and dopamine at presynaptic adrenergic terminals, causing an accumulation of catecholamines at postsynaptic receptors (Fig. 28.1) and enhancing the effect of norepinephrine [14, 15]. In addition, cocaine also causes release of norepinephrine and epinephrine from the adrenal medulla [15]. Therefore, it acts at multiple levels of catecholamine release, making it a powerful sympathomimetic agent [10].

Anesthetic Actions

Cocaine inhibits sodium channels during depolarization, hence blocking the initiation and transmission of electrical signals that account for its anesthetic effects [16]. Currently, cocaine is used primarily for topical anesthesia of the upper respiratory tract, where its combination of both vasoconstrictor and local anesthetic properties provide anesthesia and shrinking of the mucosa [17]. The sympathomimetic effects occur at one tenth the concentrations needed for the anesthetic action [18]. These sodium channel blocking actions may be important in the arrhythmogenic properties of cocaine.

Vascular Effects

Cocaine increases endothelin-1 levels, a powerful vasoconstrictor, and decreases production of the vasodilator nitric oxide [19, 20]. Cocaine increases plasminogen-activator inhibitor levels [21]. Also, it has been associated with an increase in platelet count, increased platelet activation and platelet hyperaggregability [22–24]. Cocaine users have been found to have elevated levels of C-reactive protein, von Willebrand factor, and fibrinogen [25]. These actions may make cocaine prothrombotic.

Cardiovascular Effects of Cocaine

Cardiac Ergonomics

Cocaine increases the heart rate and blood pressure in a dose-dependent fashion [26]. The chronotropic effects of cocaine are amplified with concomitant alcohol use [27]. Many cocaine users tend to be young men who also smoke cigarettes [28, 29]. The combination of cocaine and cigarette use results in greater increases in heart rate and vasoconstriction than either cocaine use or cigarette smoking alone [30]. Coronary vasoconstriction in the setting of cocaine use is most likely secondary to stimulation of the

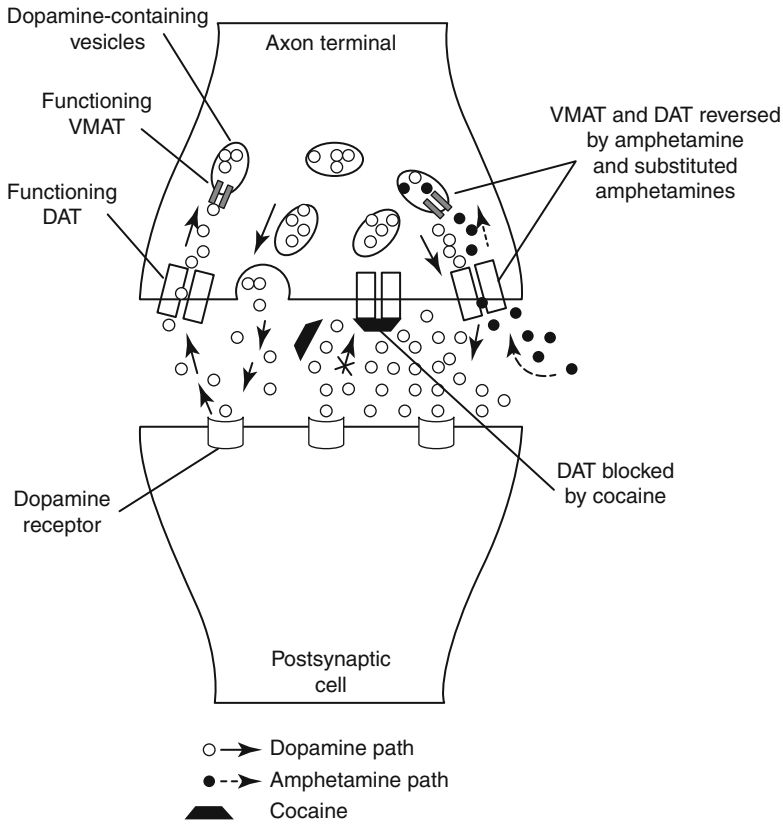

Figure 28–1. Effects of various drugs on the presynaptic axon terminal and postsynaptic cells in the heart. *Left:* normal functioning dopamine transporter (and norepinephrine and serotonin transporters) and vesicular monoamine transporter in the presynaptic axon terminal, and dopamine uptake in the postsynaptic cell. *Center:* Cocaine, a transporter antagonist, increases extracellular dopamine (and neuroepinephrine) by binding to dopamine transporter and blocking neurotransmitter uptake. *Right:* amphetamine and substituted amphetamines, including methamphetamine, methylphenidate (Ritalin, Novartis Pharmaceuticals Corporation, East Hanover, NJ), methylenedioxymethamphetamine (ecstasy), and ephedra (ma huang), reverse the action of the dopamine transporter and vesicular monoamine transporter, increasing neurotransmitter available in the synapse. *DAT*_dopamine transporter, *VMAT*_vesicular monoamine transporter (From Figueredo [72]. Reprinted with permission from Elsevier Limited)

alpha-adrenergic receptors [20]. By increasing heart rate, blood pressure, and contractility, cocaine leads to increased myocardial demand, which predisposes towards myocardial ischemia and fatal ventricular arrhythmias.

Electrophysiological Effects

Prolonged cardiac conduction times have been seen with high doses of intravenous cocaine in both anesthetized [31] and conscious [32] dogs. One minute into cocaine infusion,transient increases in heart rate, QRS duration and QTc intervals occur. Parker et al. [33] showed that cocaine significantly prolonged the PR, QRS, QTc, AH, and HV intervals in another canine model. Sherief and Carpentier [34] demonstrated that rapid increases in extracellular cocaine in vitro produced a decrease in the amplitude of action potentials and a fall in resting potentials of atrial and ventricular fibers, leading to a blockade of action potential propagation. Studies have shown cocaine to depress sinus node automaticity and block conduction at the AV node [35], prolonging AH and HV intervals [36]. Kanani et al. [37] found that cocaine reduced the ventricular fibrillation threshold in anesthetized dogs.

Epidemiological Data on Cocaine and Sudden Death

In 1895, Garland first reported a series of six deaths from cocaine [38]. More recently, Lucena et al. [39] conducted a prospective case control study of 2,477 forensic autopsies, with a reference population of 1,875,462 subjects. Six hundred and sixty eight (60 % of the 1,114 natural deaths) fulfilled the criteria of sudden death. Based on toxicological analysis, 3.1 % of the sudden deaths were cocaine related.

Surveys have shown that the combined use of alcohol and cocaine (seen in 3 of every 4 cocaine abusers) increases the risk of sudden death by as much as 18 to 25 fold [40]. Darke et al. [41] studied 146 cases of cocaine-related fatalities from the coronial records in New South Wales, Australia. Cocaine toxicity was thought to be the direct cause of death in 86 % of cases with 81 % thought to be due to combined drug toxicity (opiates, alcohol, and benzodiazepines). This study demonstrates that polysubstance abuse is commonly seen in cocaine-related fatalities.

Potential Cardiac Mechanisms of Sudden Death with Cocaine

Myocardial Ischemia

Cardiac disease was the most frequent cause (62 %) of cocaine-related sudden death in the study reported above by Lucena et al. [39]. Coronary arterial thrombosis was the predominant cause of cocaine-related cardiac death. Cocaine use has been associated with accelerated coronary atherosclerosis in individuals devoid of traditional atherosclerotic risk factors; in fact, it was present in 76 % of the sudden death victims in the study by Lucena et al. Most subjects who abused cocaine also smoked cigarettes; in the Lucena study, 81 % of the sudden death victims reportedly smoked cigarettes concomitant with cocaine use.

The combination of cocaine and cigarette smoking was studied in humans during cardiac catheterization. Concomitant cigarette smoking substantially exacerbated the deleterious effects of cocaine on myocardial oxygen supply (e.g. potentiated cocaine-induced coronary arterial vasoconstriction) and demand (e.g. dramatically potentiated the cocaine-induced increase in rate–pressure product) [30]. Even small doses of cocaine taken intranasally have been associated with vasoconstriction of coronary arteries [42]. Coronary vasoconstriction may be more accentuated in patients with preexisting coronary artery disease [43]. Acute thrombosis of coronary arteries shortly after cocaine use has been described [44]. Autopsy studies demonstrated the presence of coronary atherosclerosis in young cocaine users along with associated thrombus formation [45].

Thus, cocaine can cause myocardial ischemia by increasing myocardial oxygen demand through increasing heart rate, blood pressure and contractility, decreasing oxygen supply through vasoconstriction, inducing a prothrombotic state by stimulating platelet activation and altering the balance between procoagulant and anticoagulant factors, and finally by accelerating atherosclerosis [10, 46].

Arrhythmogenesis

Ventricular arrhythmias occurring in the setting of cocaine abuse can be categorized into two types, based on temporal resolution and mechanism of action. Ventricular arrhythmias occurring immediately after cocaine use are more likely to result from sympathomimetic and local anesthetic actions (effects on ion channels) on the myocardium, rather than late onset arrhythmias which are generally secondary to myocardial ischemia [10]. One report found that approximately 65 % of deaths related to cocaine overdose occurred within 5 h after cocaine administration, with approximately 30 % occurring between 2 and 5 h [47].

Perera et al. [48] and Gamouras et al. [49] demonstrated that cocaine abuse is associated with cardiac repolarization abnormalities on the ECG. These include prolonged QTc interval, increased QTc dispersion and the appearance of abnormal U waves. Cocaine blocks the rapid component of the delayed rectifier potassium current (IKr), causing a prolongation of the action potential duration [50, 51] as well as the induction of early afterdepolarizations in ventricular myocytes. O'Leary [52] demonstrated

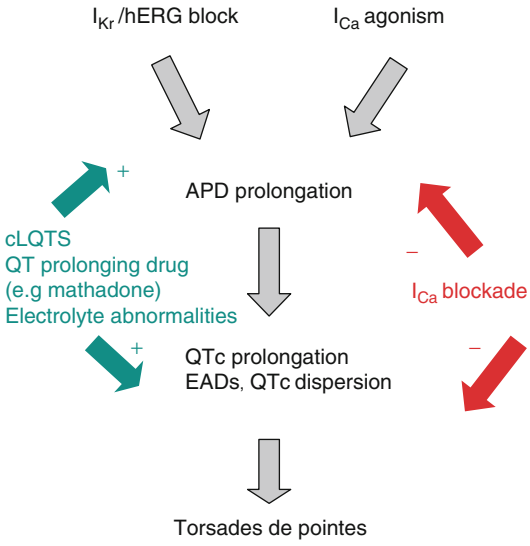

Figure 28–2. Schematic diagram showing links between hERG, L-type Ca current and cocaine-induced arrhythmia. Vertical 'information flow' (*downward arrows*) shows consequences of IKr/IhERG inhibition, namely prolongation of ventricular action potential duration (APD) and consequent QTc prolongation and QTc dispersion at the intact tissue/heart level. Delayed repolarization (especially at low rates) predisposes to early after depolarisations (EADs). EADs and enhanced dispersion of repolarization (QTc dispersion) would be anticipated to combine to lead to TdP arrhythmia. At low cocaine concentrations ICa agonism may exacerbate effects of hERG inhibition. '+' on *left hand side* of diagram indicate conditions that exacerbate repolarization-delay/TdP risk. '—'on *right hand side* of diagram indicate where L-type Ca channel inhibition could offset consequences of IhERG inhibition (From O'Leary [53]. Reprinted with permission from John Wiley and Sons)

that cocaine inhibits the cloned human ether-ago-go-related gene (HERG) channel and the IKr current, which could explain the cocaine's role in prolonging the action potential duration and QT interval, potentially inducing arrhythmias (Fig. 28.2) [53].

Gamouras et al. showed that maximal QT prolongation did not occur for up to 24 h after admission, which cannot be explained by cocaine itself as its half-life is approximately 48 min [54]. Therefore, the possibility of cocaine metabolites contributing to such effects must be considered. The potential role of cocaine metabolites in cocaine-related deaths is supported by the work of Ferriera et al. [55] who studied the effects of cocaine and its metabolites on HERG-encoded potassium channels. They found that cocaethylene is slightly more potent than cocaine as a blocker of HERG, whereas methylecgonidine has much lower potency, and both benzoylecgonine and ecgonine methyl ester were essentially inactive at clinically relevant concentrations. Hence, the metabolites of cocaine could play a role in the arrhythmogenic pathway leading to sudden cardiac death.

Cocaine users often ingest ethanol or other illicit drugs concurrently. Of the cocaine-related sudden death victims reported by Lucena et al., concomitant ethanol use was documented in 76 % [56]. This combination is associated with myocardial depression, decreased coronary blood flow, dysrhythmias, and sudden death, all of which may be due, in part, to cocaethylene, a pharmacologically active metabolite of cocaine that is synthesized by the liver if ethanol is present. In fact, in studies in experimental animals, cocaethylene is more toxic and arrhythmogenic than either substance alone, with a longer elimination half-life and larger volume of distribution [6].

Cocaine has a sodium channel blocking effect resembling that of flecainide [57]. This sodium channel blocking property of cocaine is now thought to be an important mechanism in cocaine-related sudden cardiac death (Fig. 28.3) [53, 58]. It is interesting to note that class IB antiarrhythmic drugs, such as lidocaine, inhibit the voltage-gated cardiac sodium channels and have an antiarrhythmic effect, whereas cocaine may be pro-arrhythmic. Lidocaine produces a strong voltage dependent inhibition of the fast sodium inward current (INa); resulting in a significant leftward shift of the steady-state inactivation to hyperpolarized potentials, thus preventing fatal arrhythmias [59]. However, the voltage-dependent inhibition of the INa current by cocaine is far weaker in comparison; hence producing only a very small leftward shift of the voltage-dependent inactivation. This would result in sufficient INa current to elicit an action potential, which could propagate throughout the myocardium, and in the presence of the nonhomogeneous conduction rates of action potentials through ischemic tissue, induce fatal ventricular arrhythmias [51]. Also, the blockage of INa current itself impairs impulse conduction and can create a substrate for reentrant circuits [60].

Littman et al. [61] found that in a healthy young man, a transient Brugada pattern was

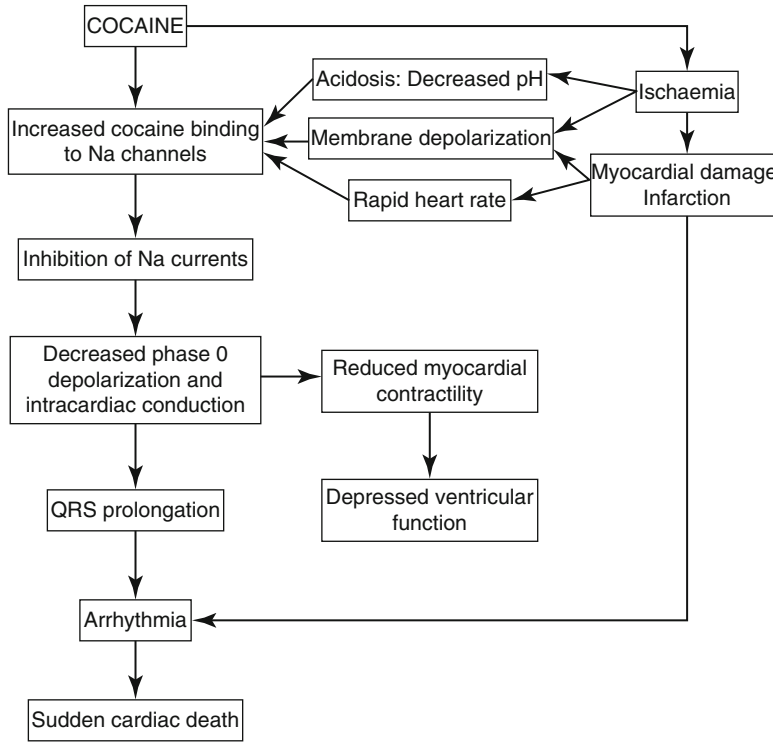

Figure 28–3. Schematic of cocaine-induced cardiotoxicity related to Na channel inhibition. Cocaine stabilizes Na channels in inactivated states that do not conduct Na current. Na channel inhibition slows the rapid upstroke of the AP (Phase 0 depolarization), an important determinant of intracardiac conduction. Slowed conduction decreases myocardial contractility leading to depressed left ventricular function and hemodynamic impairment. Prolongation of ventricular depolarization (QRS interval) exposes the myocardium to potentially lethal re-entrant arrhythmias. Combining Na channel inhibition with other proarrhythmic electrical disturbances, such as the inhibition of delayed rectifier hERG (long QT intervals) or L-type calcium channels, further increases the likelihood of arrhythmias and sudden cardiac death. Cocaine-induced ischemia caused by enhanced sympathomimetic stimulation of coronary vasculature can lead to myocardial damage that further potentiates Na channel inhibition and cardiac arrhythmias. Cocaine binding is enhanced at rapid heart rates due use-dependent inhibition, under conditions where the resting membrane potential is depolarized due to high-affinity binding to inactivated states and during episodes of acidosis, which stabilizes cocaine in its more potent positively charged form (From O'Leary and Hancox [53]. Reprinted with permission from John Wiley and Sons)

provoked repeatedly after recreational cocaine use from a baseline normal ECG and interestingly, not so by pharmacological provocation. Several similar cases of drug-induced Brugada syndrome following cocaine overdose have also been reported [62–64].

Cocaine increases intracellular calcium concentrations, which can produce afterdepolarizations, potentially triggering ventricular arrhythmias [65]. Cocaine reduces vagal tone, decreasing heart rate variability, thus potentiating cocaine's sympathomimetic effects [66]. Cocaine induces repolarization and depolarization abnormalities by blocking potassium channels, increasing L-type calcium channel current and inhibiting sodium influx, making the myocardium more susceptible to arrhythmias [67–69]. Through these electrophysiological mechanisms, cocaine abuse has been associated with QT interval prolongation, torsades de pointes, Brugada pattern, ventricular tachycardia, ventricular fibrillation, and asystole [70].

Pre-mortem imaging and histological studies have shown that left ventricular hypertrophy, myocardial fibrosis, and small vessel coronary arterial disease are common in cocaine users [31, 71]. These conditions may predispose to development of arrhythmias following cocaine ingestion, especially if a metabolic abnormality (e.g. acidosis or hypoxemia) is also present.

Despite several proposed mechanisms which can lead to fatal arrhythmias, the overall percentage of cocaine abusers that actually experience significant arrhythmias and sudden death is small and highly unpredictable [39, 57]. Cocaine has been reported as a rare cause of dilated cardiomyopathy which can increase risk for sudden cardiac death [72].

Cocaine can also cause bradyarrhythmias [35, 36,73,74]. Proposed mechanisms include localized spasm involving the sinoatrial artery, inferior myocardial infarction, vagal stimulation during nasal inhalation, overdrive suppression after supraventricular tachycardia and finally a direct toxic effect [75]. As discussed earlier, Sherief and Carpentier [34] demonstrated in a rat that under high concentrations of cocaine (similar to the levels found in fatal acute intoxication), there is a block of the propagation of action potentials, while the sinus node is still generating action potentials at a rate compatible with life. Further studies will need to determine whether acute cocaine intoxication can cause cardiac arrest in the absence of sinus node arrest, even if latent ectopic pacemaker fibers are firing, due to blocked propagation of the action potentials through the myocardium.

Potential Non-cardiac Mechanisms of Sudden Death with Cocaine

Aortic dissection or rupture has been shown to occur with cocaine abuse [76–78] likely secondary to abrupt increases in systemic arterial pressure. In addition to aortic rupture, cocaine can cause rupture of mycotic and intracerebral aneurysms [79–81], and cause hemorrhagic strokes [82–84]. Cocaine abuse has been associated with status epilepticus [85, 86] which can result in sudden death [87].

Management

Cocaine induced chest pain should be managed promptly with the standard therapy comprising of benzodiazepines, aspirin, nitroglycerin, calcium channel blocker and phenotolamine as suggested in the scientific statement from the "American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology" [10]. If clinically indicated, the patient should undergo immediate coronary angiography and possible percutaneous intervention. Beta-blockers should be avoided in patients presenting with cocaine-related cardiovascular events. However, at discharge, beta-blockers should be considered for patients with coronary artery disease or left ventricular dysfunction if abstinence is likely. Metabolic and electrolyte abnormalities should be corrected promptly and aggressively.

Ventricular arrhythmias that occur immediately after cocaine use may respond to the administration of sodium bicarbonate. Sodium bicarbonate has been used successfully to reverse the conduction defects and arrhythmias associated with intoxication from type IA and IC antiarrhythmics [88, 89], and other drugs with sodium channel blocking properties. In a study using sodium bicarbonate as an antidote in dogs infused with cocaine, it promptly decreased the cocaine-induced QRS prolongation [89].

The use of lidocaine has been controversial. One animal model suggested that lidocaine exacerbated cocaine-associated seizures and arrhythmias, as they have similar effects on sodium channels [90]. Lidocaine may potentiate the central nervous system effects of cocaine and be proconvulsant [88, 91, 92]. In contrast, other animal studies [93], and one retrospective clinical study [94], demonstrated no adverse outcomes in patients treated with lidocaine in the setting of cocaine associated myocardial infarction. No data exist concerning the efficacy of amiodarone in cocaine intoxication. Also there is no data supporting the prophylactic use of antiarrhythmics during cocaine intoxication to prevent sudden cardiac death.

Given the strong addiction cocaine causes and the complex mechanisms of cocaine-related sudden cardiac death, defibrillator implantation becomes a case by case decision. However, in patients with systolic dysfunction who meet the criteria should be offered defibrillator therapy for primary prevention of sudden cardiac death as per the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines [95].

Cocaine and Sudden Death Conclusions

There is a clear association between cocaine use and sudden death. The most common mechanism is likely acute coronary thrombosis, which

is due to a combination of factors; coronary vasospasm, increased myocardial oxygen demand, prothrombotic milieu and accelerated coronary atherosclerosis. Cocaine inhibits sodium influx, blocks potassium channels and increases L-type calcium channel current, which are associated with action potential and QTc interval prolongation, afterdepolarizations, Brugada pattern, and bradyarrhythmias. Cocaine can decrease heart rate variability, which potentiates its sympathomimetic effects. Other less common causes of cocaine-induced sudden death include aortic dissection, intracranial hemorrhage and status epilepticus. Intravenous sodium bicarbonate is advised in the treatment of ventricular arrhythmias induced by cocaine intoxication and if needed lidocaine may be used for persistent or recurrent ventricular arrhythmias.

Amphetamines

Amphetamines are synthetic stimulants first synthesized in the 1920s and introduced into medical practice in 1936 [96]. Amphetamines belong to the phenylethylamine family. Numerous substitutions of the phenylethylamine structure are possible, resulting in different amphetamine compounds. Commonly abused forms include methamphetamine ("speed"), used in oral or intravenous forms, or synthesized into a crystalline, smokable form ("ice"), and MDMA (3,4-methylene-dioxymethamphetamine, "ecstasy") and its legal counterpart MDEA (3,4-methylenedioxyethamphetamine, "eve"), which are analogs of MDA (3,4-methylenedioxyamphetamine), a drug originally used for appetite suppression.

Amphetamines are broken down metabolically, mainly by liver CYP2D6 [97]. However, several additional enzymes are involved in their degradation [98], and some of these appear to be saturated at relatively low drug concentrations. Consequently, as the dose is increased and the higher-affinity enzymes are saturated, disproportionately large increases in blood and brain concentrations occur [99]. Elimination from the body is moderately slow, with the half-life for MDMA disappearance from the blood on the order of 8 h [100–102]. Because it takes about five half-lives (i.e., about 40 h for MDMA) for over 95 % of the drug to be cleared from the body, this may explain the persistence of troublesome after-effects for 1–2 days after use. Some MDMA metabolites are pharmacologically active, especially its first metabolite MDA.

Pharmacological Actions of Amphetamines

As shown in Fig. 28.1, amphetamines potentiate the effects of catecholamines. They cause the direct release of stored catecholamines from the presynaptic membrane and function as a weak inhibitor of monoamine oxidase, the enzyme that functions to inactivate neurotransmitter molecules such as norepinephrine and dopamine [96]. Their actions mimic cocaine to a certain extent.

Cardiovascular Effects of Amphetamines

Unlike cocaine, the effects of amphetamines on the cardiovascular system are less well described. Amphetamines elevate blood pressure and can cause tachycardia, palpitations, and sweating. At high doses, arrhythmias can occur [103, 104]. Cardiovascular effects can divided into two types [105]: hypertension, with a consequent risk of ruptured blood vessels and hemorrhage, and tachycardia, with resulting increased cardiac workload, and risk of heart failure. Of note, the most commonly reported vascular complication of amphetamine abuse is intracerebral hemorrhage [106].

Epidemiological Data on Amphetamines and Sudden Death

The incidence of sudden death among amphetamine users is rare. Pilgrim et al. [107] reviewed 169 cases reported to the Victorian coroner (Australia) from 2001 to 2005 for sudden and unexpected death, where a forensic autopsy detected amphetamines in the blood. They found 6 cases in which a cerebral hemorrhage caused death, 3 cases in which serotonin syndrome was established, 19 cases in which long-term use of amphetamines was associated with heart disease, and 3 cases where amphetamine-class drugs alone were regarded as the cause of death. Gould et al. [108] found an increased association of stimulant

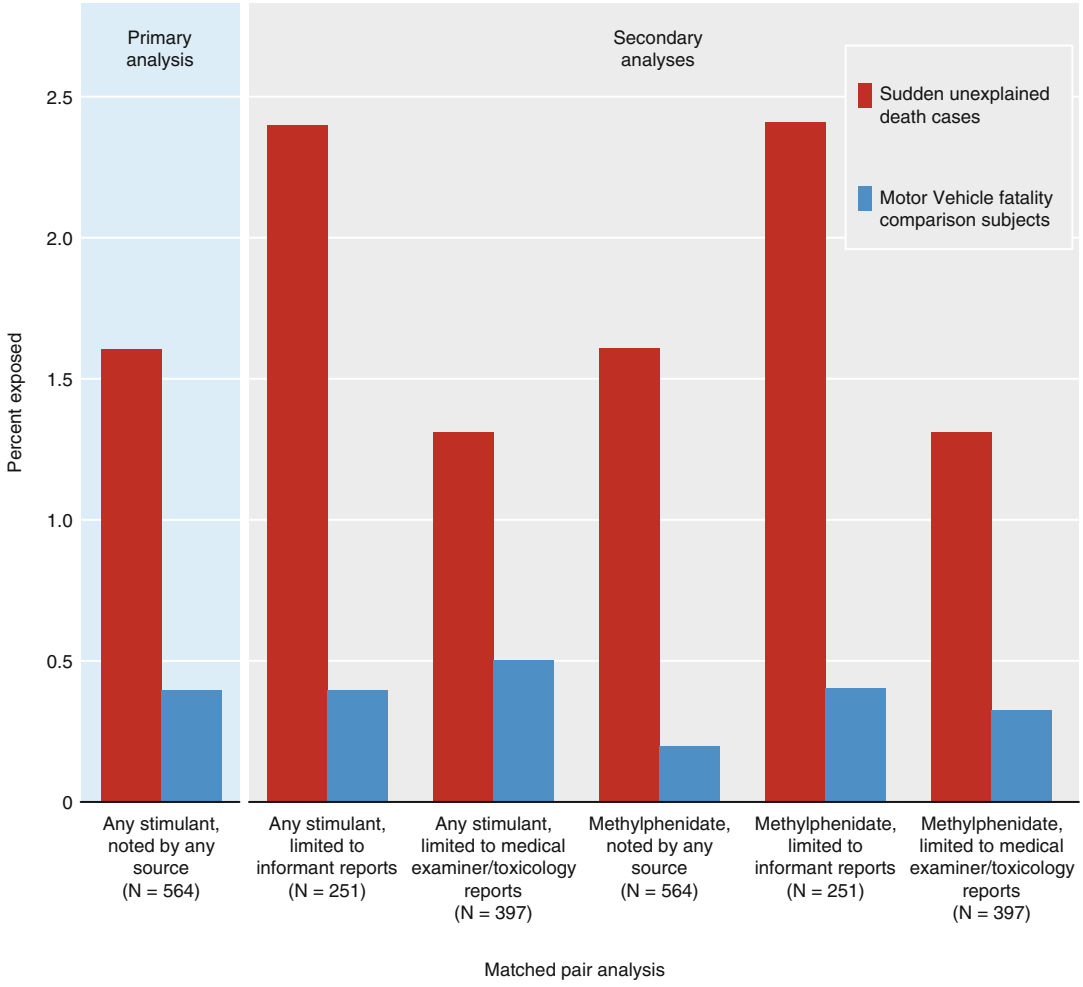

Figure 28–4. Rate of stimulant exposure among sudden unexplained death cases and a matched comparison group of motor vehicle passenger fatalities (From Gould et al. [108]. Reprinted with permission from American Psychiatric Publishing)

use and sudden unexplained death among young people in a matched case–control study on 564 sudden death cases occurring between the ages 7 and 19 years compared with a matched group of 564 young people who died as passengers in motor vehicle traffic accidents (Fig. 28.4).

Potential Cardiac Mechanisms of Sudden Death with Amphetamines

Myocardial Ischemia

Myocardial infarction has been directly linked to the use of amphetamines [105, 109]. Hong et al. [106] reported a case of a young woman presenting with diffuse arterial vasospasm manifesting as an acute myocardial infarction, pulseless and painful right index finger and a high blood pressure after smoking crystal methamphetamine. The patient eventually died of cardiogenic shock. Packe et al. [110] reported a case of a 25-year-old man who suffered myocardial infarction and subsequent ventricular fibrillation. Ragland et al. [109] reported a case of a lateral wall myocardial infarction in a young woman with normal coronaries on angiography. Further, they reported exacerbation of ischemic symptoms in this amphetamine abusing patient after receiving propranolol. As with cocaine, beta-adrenergic agents should not be used alone

in patients with amphetamine-induced myocardial ischemia due to the risk of unopposed alpha-adrenergic activity and potential for coronary vasospasm [111].

Bashour [112] reported a case of amphetamine associated myocardial infarction in a young woman with filling defects in the proximal left anterior descending coronary artery, which resolved after 3 days treatment with intravenous heparin. This suggests amphetamines may be prothrombotic, like cocaine. Thus, it appears that amphetamine-related myocardial infarction can be multifactorial, with contributing factors including vasospasm, a prothrombotic milieu, and increased myocardial workload.

Arrhythmogenesis

Cardiac arrhythmias are a well-recognized cause of sudden death in amphetamine abuse [113–116]. Gallardo-Carpentier et al. [117] demonstrated that in a rat model, overdrives consistently induced delayed afterdepolarizations and triggered activity in the presence of amphetamines.

Dowling et al. [118] described a case involving an 18-year-old woman who presented to the emergency room in ventricular fibrillation after ingesting MDMA (ecstasy). Jacobs [119] reported six cases of young patients who died unexpectedly after chronic abuse of amphetamines. They found that death was not attributed to a lethal intoxication but to acute myocardial necrosis, right ventricle rupture, cardiomyopathy, or arrhythmias.

There are a few reports [120, 121] which suggest amphetamines can increase the QTc interval. However, there is growing evidence to suggest that amphetamines do not cause statistically or clinically significant increases in QTc interval [122].

A number of congenital cardiac conduction abnormalities may go undiagnosed in young people, such as Wolff–Parkinson–White, Romano–Ward, Brugada, Jervell and Lange–Nielsen Syndromes. These individuals are at risk of sudden death from excessive sympathetic stimulation when using amphetamines [123].

Cardiomyopathy

Cardiomyopathy can develop in patients who have abused the oral [118, 124, 125], intravenous [126, 127], and smoked [114] forms of chronic amphetamine use.

Potential Non-cardiac Mechanisms of Sudden Death with Amphetamine

The most commonly reported vascular complication of amphetamine abuse is intracerebral hemorrhage [106]. Specifically, MDMA has been associated with intracranial hemorrhages [128– 131]. It has been proposed that these result from rupture of vessels already weakened by congenital anomalies or pre-existing disease, when the added burden of drug-induced hypertension is imposed upon them [107]. Aortic dissection has been reported [132].

Management

The initial treatment and management of amphetamine toxicity is similar to that of cocaine treatment. Beta-blockers should be avoided as they can precipitate severe coronary spasm. Dilated cardiomyopathy with systolic dysfunction should be managed as per standard of care. The decision for defibrillator therapy in the setting of secondary prevention of sudden death should be individualized. There is no data on the use antiarrhythmics in amphetamine toxicity.

Amphetamines and Sudden Death Conclusions

Amphetamine abuse has exponentially grown over the last few decades [133]. Amphetamine use can result in sudden death through various mechanisms: coronary vasospasm and increased sympathomimetic effects causing myocardial ischemia/infarction, arrhythmogenesis, and cardiomyopathy.

Heroin and Methadone

Heroin (3,6-diacetylmorphine), is a semi-synthetic narcotic first synthesized in 1874 and marketed as a safer, less addictive substitute for morphine [134]. It is the most frequently abused opiate [135]. Methadone is a long-acting mu opioid receptor agonist with pharmacological properties qualitatively similar to those of morphine.

The cardiovascular effects of heroin are not extensively described in the literature. Brashear et al. [136] studied effects of intravenous heroin on mongrel dogs and found that heroin resulted in a significant decrease in systemic blood pressure, cardiac output, and heart rate. This decrease in heart rate may reflect a vagal influence. Interestingly, when morphine was given to 18 mongrel dogs there was a significant, but transient, rise in blood pressure and heart rate [137]. These effects have been attributed to release of histamine.

Paterna et al. [138] studied the effects of heroin on isolated, perfused rabbit hearts and did not find significant change in cardiac enzymes, heart rate, contractility, or coronary blood flow. They concluded that the cardiovascular effects of heroin were based on systemic rather than direct cardiac effects.

Heroin can cause a syndrome that simulates acute myocardial failure with non-cardiogenic pulmonary edema [139, 140]. This syndrome can result in sudden death within 12–24 h. Peon and Ruiz-Gonzalez [141] reported myocardial failure in the setting of heroin abuse. However, direct cardiovascular effects produced by heroin remain unclear [111].

Zunkler and Wos-Maganga [142] studied the effects of methadone and heroin on hERG currents. Both methadone and heroin inhibited hERG currents in a concentration-dependent manner. The potency for inhibiting hERG currents is 100-fold lower for heroin than for methadone.

Glauser et al. [143] studied admission ECG of 25 acutely overdosed heroin addicts. The most common findings were nonspecific ST-T changes in 17 patients, sinus tachycardia in 11, and left or right atrial enlargement in 8. Five patients had more serious arrhythmias; four had atrial fibrillation and one had ventricular tachycardia. They felt that the electrocardiographic abnormalities were probably related to hypoxemia, but also suggested that the abnormal cardiac rhythms may be due to the direct effects of heroin or its metabolites.

Several studies demonstrate that methadone prolongs the QTc interval in a dose dependent fashion [144–147], and increases the risk of torsade de pointes and sudden death [145]. Butler et al. [148] identified 51 deaths occurring during methadone treatment. There were two cases in which arrhythmia appeared to be the cause of death, and ten cases in which arrhythmia could not be excluded as a cause. The authors concluded that the risk of fatal cardiac arrhythmia in methadone maintenance patients appears to be low and the major risk factor for death was use of prescription drugs and methamphetamine, in addition to methadone. The combination of methadone and benzodiazepines causes a statistically significant increase in action potential duration, potentially increasing the risk for sudden death [149].

Chugh et al. [150] prospectively evaluated sudden cardiac deaths investigated by the Portland, Oregon medical examiner. Twenty-two sudden cardiac death cases with therapeutic levels of methadone were compared with 106 consecutive sudden cardiac death cases without evidence of methadone on toxicologic screen. Among cases with methadone, a cardiac cause of sudden death was identified in only 23 %, with no clear cause of sudden death in the remaining 77 %. Among cases without methadone, however, an attributable cardiac cause of sudden death was identified in 60 %. The low prevalence of identifiable cardiac disease or structural abnormalities in the methadone cases suggests a causative role for methadone in the pathogenesis of sudden death.

Lipski et al. [151] studied the ECG of 75 asymptomatic individuals in a methadone program, including 34 patients using heroin within 24 h, and 41 having used heroin and other drugs along with methadone within 3 days. They found ECG abnormalities in 61 %, the most common being QTc prolongation, as well as prominent U waves and bradyarrhythmias.

When on methadone, a QTc >500 ms is associated with a 'clinically significant' risk for developing arrhythmia and torsade de pointes [152, 153]. Mayet et al. [154] in a cross-sectional study of 155 opioid-dependent patients prescribed methadone prior to referral for an ECG, found methadone dose was predictive of QTc length in a multivariate analysis (Fig. 28.5). Of note, Levo-alpha acetyl methadol, another treatment for opioid dependence, was withdrawn from the European market following cases of sudden cardiac death [155].

There are no consensus guidelines for ECG screening in patients on methadone maintenance treatment (MMT) programs. An expert

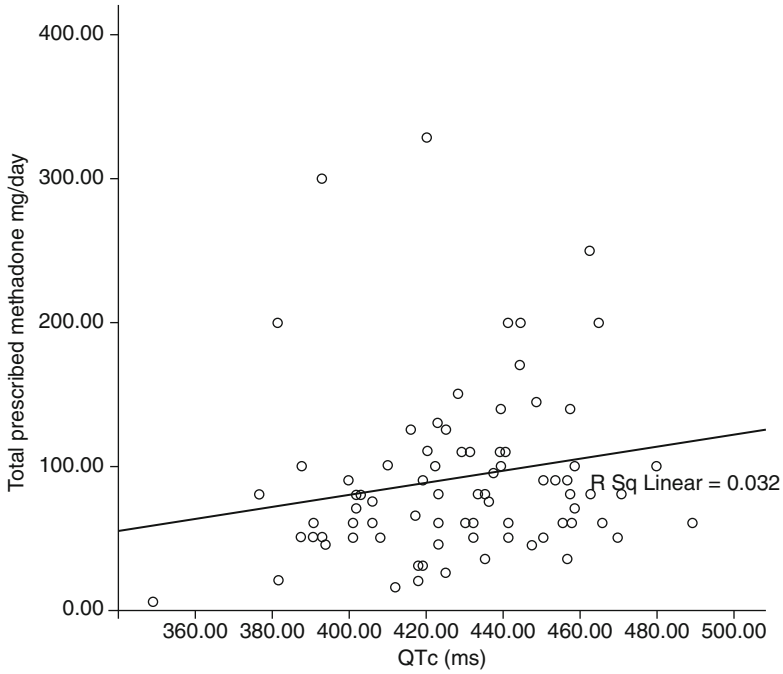

Figure 28–5. Methadone (mg/day) versus QTc interval (ms) (From Mayet et al. [154]. Reprinted with permission from Taylor & Francis Ltd.)

panel for ECG screening and monitoring for patients in MMT recommended obtaining a pretreatment ECG for all patients to measure the QTc interval and a follow-up ECG within 30 days, and annually thereafter (Table 28.1) [156]. Additional ECGs are recommended if the methadone dosage exceeds 100 mg/day or if patients have unexplained syncope or seizures. If the QTc interval is greater than 450 ms but less than 500 ms, the clinician needs to discuss the potential risks and benefits with patients and monitor them more frequently [155, 157]. If the QTc interval exceeds 500 ms, the clinician needs to consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia. Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone [155]. ECG are advised for patients on methadone with heart or liver disease, electrolyte abnormalities, concomitant QT prolonging medications/CYP3A4 inhibitors or are prescribed methadone >100 mg daily [147].

In conclusion, heroin abuse can result in sudden death, especially if large doses are administered intravenously. It appears that the predominant mechanism(s) are pulmonary in etiology, such as non-cardiogenic pulmonary edema. However, cardiac mechanism(s) cannot be ruled out entirely. Given this day and age of polysubstance abuse, the mechanisms for sudden death become multifactorial.

Table 28–1. QTca interval screening in methadone treatment

QTca interval screening in methadone treatment
Recommendation 1 (*Disclosure*): Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
Recommendation 2 (*Clinical History*): Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.
Recommendation 3 (*Screening*): Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and then a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.
Recommendation 4 (*Risk Stratification*): If the QTc interval is greater than 450 ms but less than 500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
Recommendation 5 (*Drug Interactions*): Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone.

From Krantz et al. [156]. Reprinted with permission from American College of Physicians
[a]QTc = rate-corrected QT

Patients on methadone with a prolonged QTc interval are at increased risk for sudden death. These patients should be followed up with serial ECG and dosing of methadone should be adjusted along with detailed discussions with the patient. Once again, the decision of defibrillator therapy should be individualized.

Cannabis

Marijuana (Cannabis) remains the most commonly used illicit drug in the US. Coronary and cerebral ischemia are known complications of combined cannabis and cocaine intake [158, 159]. Gupta et al. [160] report the sudden death of a 25-year old man after consuming a glass of cannabis sativa. Marijuana has been recognized as a possible trigger for acute myocardial infarction [161–163]. Guidelines published on autopsy practice by the Royal College of Pathologists have now listed marijuana as a potential cause for sudden death [164, 165].

Benzodiazepines

Benzodiazepines are often part of the polypharmacy or polysubstance abuse leading to sudden death. As mentioned earlier, the combination with methadone increases the action potential duration and therefore the risk of sudden death by prolonging the QTc interval [149]. Drummer and Ranson [166] studied 16 deaths associated with toxic concentrations of benzodiazepines and found that five cases were solely caused by benzodiazepines. Administration of large doses can result in a fatal respiratory arrest.

Gasoline Fume and Solvent Inhalation

The intentional inhalation of fumes from gasoline or solvents for recreational purposes is commonly known as “huffing”, “sniffing” or “dusting” [167]. Inhalant abuse is known to be cardiotoxic and can potentially cause sudden death and chronic myocardial damage [167, 168]. The most common cause of “sudden sniffing death” is arrhythmia, usually associated with the use of toluene (used in paint thinner) and 1,1,1-tricholoroethane (methyl chloroform) [168, 169]. Apart from ventricular fibrillation, sinus bradycardia and hypoxia-induced heart block have also been implicated as possible mechanisms [168, 170–172].

Reflex vagal inhibition caused by the cool aerosolized propellants stimulating the larynx can also result in sudden death [168]. Alper et al. [173] found that glue abusers with a history of unexplained syncope and those who were asymptomatic had a longer QT interval and corrected QTc dispersion when compared to healthy controls. Also, the symptomatic group had a greater QT interval and corrected QTc dispersion than those in the asymptomatic group.

Propofol

Riezzo et al. [174] reported a case of 26-year-old man, a physician trainee in anesthesiology and propofol abuser, who developed a Brugada pattern ECG on admission to the intensive care unit, which soon progressed into a prolonged QT interval, idioventricular rhythm, ventricular fibrillation and finally death. Similar fatalities have been reported in the past with recreational use of propofol [175, 176]. Vernooy et al. [177] report six of seven patients with propofol infusion syndrome [178, 179], developed coved ST-elevation in lead V1 to V3 and died within hours of irrecoverable electrical storm. This may suggest that the mechanism underlying the arrhythmia is similar to that responsible for ventricular arrhythmias in the Brugada syndrome.

Anabolic Androgenic Steroids

Montisci et al. [180] reported three cases of sudden cardiac death in previously healthy athletes who were anabolic androgenic steroid (AAS) users. The most typical cardiac abnormality in AAS abusers is left ventricular hypertrophy, associated with fibrosis and myocytolysis. There is a growing body of evidence that chronic AAS abuse may be associated with an increased risk of sudden death, myocardial infarction, and cardiomyopathy [72, 181, 182]. These AAS-related

cardiovascular abnormalities may predispose to sudden death.

Caffeine

Caffeine is the most commonly consumed stimulant in the world and is usually taken in the form of coffee (75 % of all use) [183]. An alkaloid, caffeine (l,3,7-trimethylxanthine), has a powerful cardiac stimulatory effect [111]. Caffeine in high concentrations can provoke arrhythmias, which can be harmful in individuals with ischemic heart disease and preexisting ventricular arrhythmias [184]. Fatal intoxications with caffeine, including sudden death, have been described, but are rare [111, 185]. Toxic doses are usually in the 5–10 g range, but fatalities have been described with as little as 1 g (15 mg/kg) [111].

Summary

There is fair evidence in the literature, highlighting the association of the above mentioned addictive substances with sudden death. Complicating this association when drug abusers present to the hospital, is the fact that they are often on multiple prescribed and non-prescribed drugs which result in a multifactorial mechanistic pathway to sudden death. Therefore, it is important to keep an open and intrusive approach, when assessing these patients in the emergency room during, or after, cardiac arrest. Post resuscitation, the duration of monitoring will depend on the offending drug(s), half-life of the drug(s), active metabolites and co-morbid conditions. One should also be very cautious and mindful about using pharmacological interventions, as drug interactions can play a significant role in altering the homeostasis; for example, beta-blockers in the setting of cocaine or amphetamine abuse. Once the patient has recovered, the issue of defibrillator therapy in secondary prevention is controversial. Often, drug abusing patients relapse, increasing their risk for sudden death. Clearly, the most important intervention is to help them recover and abstain.

Conflicts of Interests **None**

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29
Obstructive Sleep Apnea and Sudden Death

Apoor S. Gami and Virend K. Somers

Abstract

Obstructive sleep apnea (OSA) is a prevalent condition associated with several cardiovascular diseases. This article reviews the epidemiology of OSA, the physiology of normal sleep, the pathophysiology of sleep in patients with OSA, and the mechanisms by which OSA may increase the risk of sudden death. The available epidemiological data to support such a relationship are reviewed.

Keywords

Sleep apnea • Obesity • Sudden death • Cardiac arrest • Cardiovascular disease

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent condition that is associated with a broad range of cardiovascular disease conditions. The pathophysiological events during apneas in patients with OSA cause acute and often profound autonomic, cardiac and vascular changes during sleep, and may also result in daytime abnormalities of neural circulatory control and cardiovascular structure and function. These changes may contribute to sudden death during sleep and may increase the risk of sudden death during the day. We will review the epidemiology of OSA, the physiology of normal sleep, the distinctive pathophysiology of sleep in patients with OSA, the mechanisms by which OSA may increase the risk of sudden death, and available population data that support such a relationship.

Epidemiology of OSA

A synthesis of findings from large population-based studies in racially and geographically diverse populations reveals that about 20 % of middle-aged adults have at least mild OSA. The OSA syndrome, which consists of not only the physiology but also the symptoms of OSA, is present in about 5 % of these populations [1]. The prevalence of OSA increases through the late adult years and plateaus at 20–41 % after age 65 [1, 2]. Men are two to three times more likely to have OSA than are women [1]. The condition

A.S. Gami, MD, M.Sc (✉)
Section of Electrophysiology,
Midwest Heart Specialists,
133 E. Brush Hill Rd., Suite 202,
Elmhurst, IL, 60126, USA
e-mail: doctorgami@gmail.com

V.K. Somers, MD, Ph.D.
Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic College of Medicine,
Rochester, MN, USA

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most strongly associated with and causally related to OSA is obesity [3]. Total body weight, body-mass index, and fat distribution all correlate with the presence of OSA, and 40–60 % of obese adults have OSA [1, 3]. The majority of individuals with OSA are undiagnosed [4], likely due to the lack of symptoms in people with mild OSA, the ubiquity of its cardinal symptom of sleepiness in others, and the general lack of access to polysomnography to establish the diagnosis. By conservative estimates, over 25 million American adults have OSA.

Physiology of Normal Sleep

Sleep comprises one-fourth to one-third of our lives and generally has been considered a physiologically restorative period. The fact is that sleep consists of dynamic and elaborate physiological processes, many of which impact cardiovascular regulation and function.

A night of sleep usually consists of four or five cycles of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep stages, with REM stages getting progressively longer in later cycles [5]. During NREM sleep, sympathetic neural activity decreases and parasympathetic tone predominates. During REM sleep, a tonic state alternates with multiple periods of phasic activity. REM and its baseline tonic state are periods of high parasympathetic tone, whereas during phasic REM bursts of sympathetic neural activity occur (Fig. 29.1) [6]. As a result, REM sleep is associated with dynamic fluctuation in autonomic balance. Superimposed upon these changes related to sleep stage, autonomic balance also exhibits a diurnal rhythm. Sympathetic

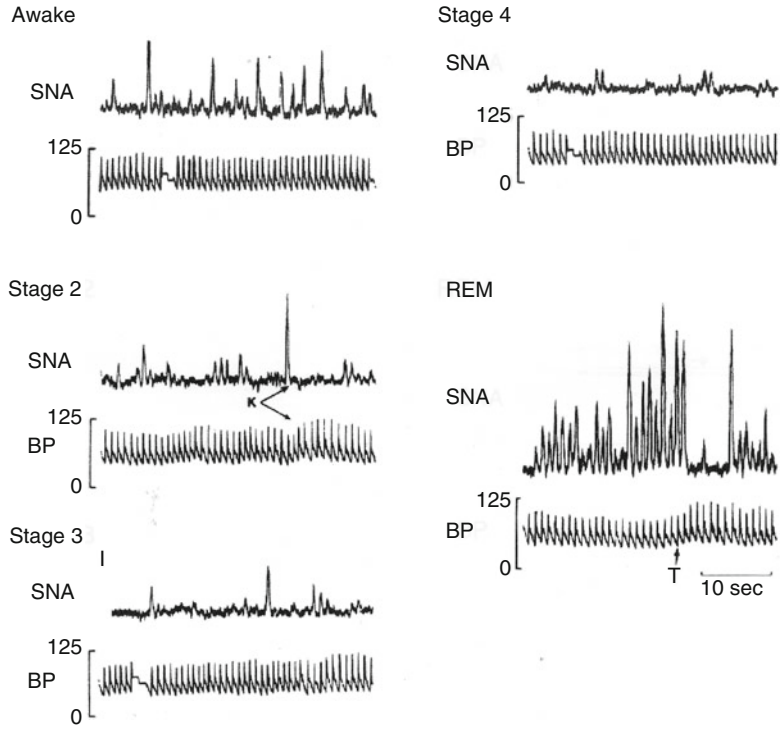

Figure 29–1. Recordings of sympathetic nerve activity (SNA) and mean blood pressure (BP) in an individual while awake and during Stages 2, 3, 4, and rapid-eye-movement (REM) sleep. As non-REM sleep deepens (stages 2 through 4), SNA gradually decreases and BP and variability in BP are gradually reduced. Arousal stimuli elicited K complexes on the electroencephalogram (not shown), which were accompanied by increases in SNA and BP (indicated by the *arrows*, stage 2 sleep). In contrast to the changes during non-REM sleep, heart rate, BP, and BP variability increased during REM sleep, together with a profound increase in both the frequency and the amplitude of SNA. There was a frequent association between REM twitches (momentary periods of restoration of muscle tone, shown by *T* on the tracing) and abrupt inhibition of SNA and increases in BP (Somers et al. [6]. Reprinted with permission from the Massachusetts Medical Society)

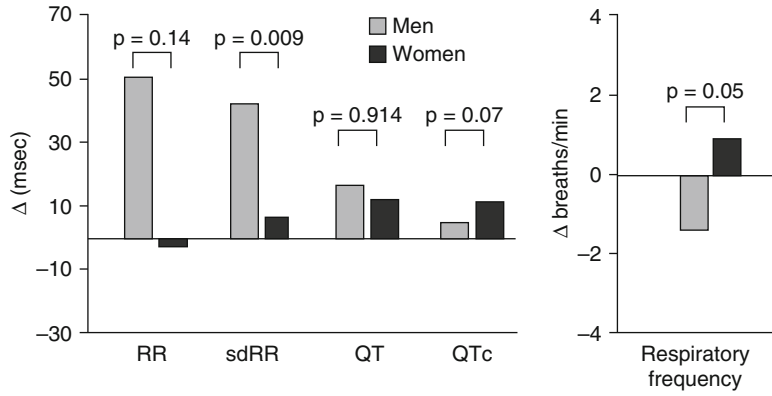

Figure 29–2. Electrocardiographic measurements and breathing frequency during wakefulness and rapid-eye-movement (REM) sleep in men and women. RR interval and RR variability (sdRR) from wakefulness to REM sleep significantly increase in men and remain stable in women. In both men and women, the QT interval increases. The corrected QT interval (QTc) remains stable through sleep in men while it increases significantly during REM sleep in women. Breathing frequency decreases in men and increases in women. Δ = REM – wakefulness. * = significant difference between REM and wakefulness within subjects (Modified from Lanfranchi et al. [11], with permission from Lippincott Williams & Wilkins)

activity is highest during the day and peaks in mid-morning, and parasympathetic activity is highest during the night [7].

The general effect of normal sleep on cardiac electrophysiology is due to the predominance of parasympathetic tone. As a result, normal sleep is associated with decreases in the arterial baroreceptor set point, heart rate, blood pressure, cardiac output, and systemic vascular resistance. This overall cardiovascular "quiescence" during sleep is punctuated by REM sleep-related surges in heart rate and blood pressure to levels similar to wakefulness [6]. Thus, in healthy people, benign nocturnal arrhythmias and conduction disturbances occur due to relative vagotonia. These include sinus bradycardia, marked sinus arrhythmia, sinus pauses, and first-degree and type I second-degree atrioventricular block [8]. Normal sleep is also associated with delayed cardiac repolarization, as reflected by a prolonged corrected QT interval (QT_c) during sleep in healthy individuals [9, 10]. Some data suggest that this may be most evident during REM sleep stages in women (Fig. 29.2) [11].

Normal sleep is associated with variations in coagulability and vascular function that are also possibly due in part to the predominance of parasympathetic tone during sleep. Compared to the morning awake state, sleep is associated with increased fibrinolytic activity, increased levels of tissue plasminogen activator, decreased blood viscosity, and decreased platelet aggregation – all changes that mitigate pathologic coagulation [12–16]. Interestingly, the association of sleep with reduced platelet aggregation seems to be related specifically to the supine position, as the attenuation of platelet aggregation ceases not with awakening but rather with upright posture in the morning [17, 18]. Arterial endothelial function in healthy adults also appears to have a day-night pattern, with better arterial flow-mediated endothelium-dependent vasodilation during the evening compared to the morning [19]. Similarly, in patients with coronary artery disease, both coronary vascular tone and peripheral arterial function have a diurnal variation, with better vascular function evident during the afternoon [20].

Pathophysiology of Sleep in OSA

Sleep in individuals with OSA is characterized by transient occlusions of the upper airway, which result in episodes of partial cessation (hypopnea) or complete cessation (apnea) of airflow

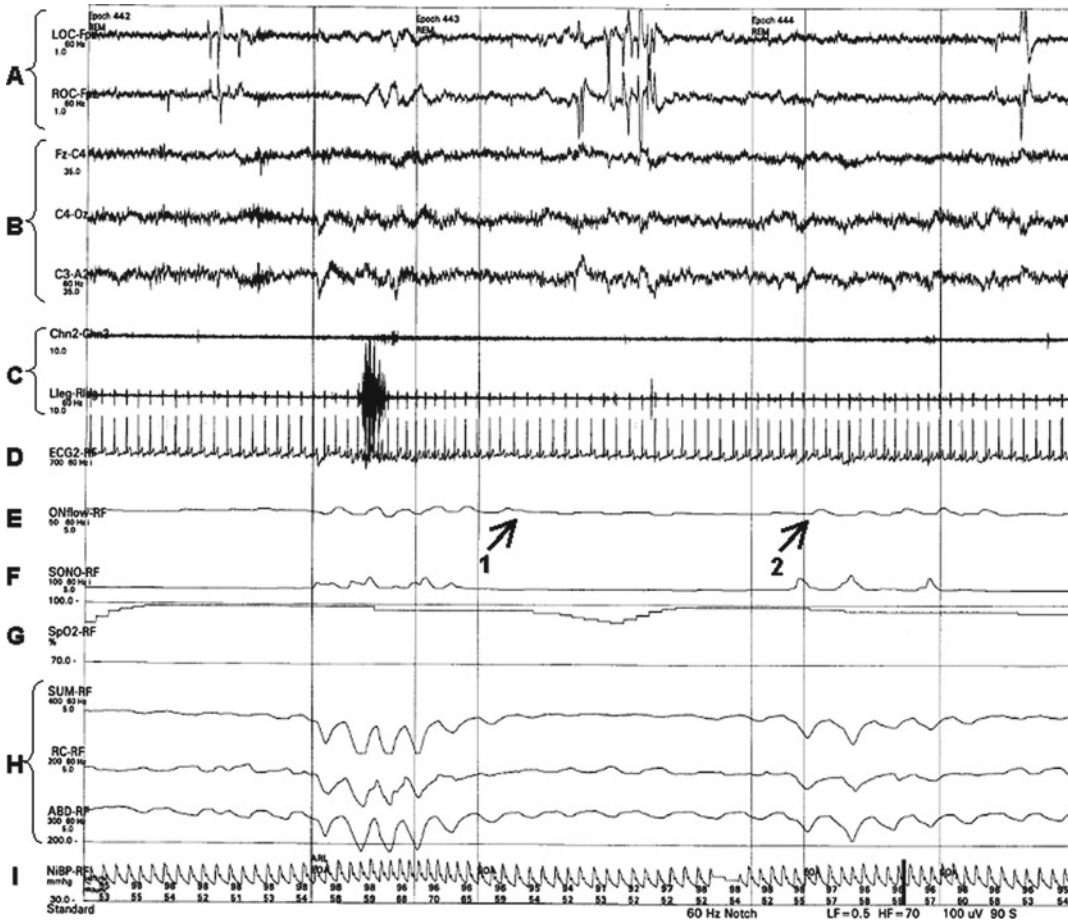

Figure 29–3. Polysomnography recording from a patient with obstructive sleep apnea. The tracing shows the (*A*) electrooculogram, (*B*) electroencephalogram, (*C*) electromyogram, (*D*) electrocardiogram, (*E*) measures of airflow, (*F*) sonogram, (*G*) oximetry, (*H*) measures of thoracoabdominal movements, and (*I*) blood pressure during 90 s of rapid-eye-movement (REM) sleep in a subject undergoing an overnight sleep study. *Arrow 1* identifies initiation of an obstructive apnea, and *Arrow 2* identifies its termination (From Gami et al. [3]. Reprinted with permission from Elsevier)

(Fig. 29.3) [21]. The patency of the upper airway during inspiration is determined by competition between negative transmural pharyngeal pressures and pharyngeal dilator and abductor muscle tone [22, 23]. Dominance of the former results in posterior movement of the tongue and soft palate against the posterior pharyngeal wall, which obstructs airflow [24]. Central nervous system modulation during sleep decreases pharyngeal muscle activity and destabilizes the airway musculature, especially during REM sleep when there is loss of muscle tone, making airway obstruction more likely [22, 25, 26]. These apneas and hypopneas result in hypoxemia and futile ventilatory efforts, which ultimately activate the central nervous system and produce a transient but usually subconscious arousal to a lighter stage of sleep that allows restoration of airway patency and airflow. Hyperventilation occurs after apneas due to activation of peripheral and central chemoreceptors by the episodic hypoxemia and hypercapnia [27, 28]. These series of events can recur up to hundreds of times during each hour of sleep [29]. The most common measure of the severity of OSA is the apnea-hypopnea index (AHI), which is the average number of obstructive apneic and hypopneic events per hour of sleep. An AHI <5 is

considered normal, and an AHI ≥5 is consistent with at least mild OSA physiology and has been associated with the development and progression of cardiovascular diseases [30, 31]. Other indices of the severity of OSA that are relevant to cardiovascular outcomes include measures related to the severity or duration of oxygen desaturations during sleep.

OSA and Potential Mechanisms of Sudden Death

In contrast to the physiology of normal sleep described earlier, individuals with OSA experience severe perturbations of cardiac regulation *during* sleep, which individually or in concert may increase the risk of sudden death. Obstructive apneic events cause reductions in oxygen saturation and systemic hypoxemia, and in some individuals oxygen desaturation can be prolonged and fall below technically measurable levels. It has been shown that these repetitive oxygen desaturations are directly linked to ventricular ectopy in patients with OSA [32], and this may represent a direct dysrhythmic mechanism linking OSA to nocturnal sudden death.

Hypoxemia, with associated hypercapnia, also causes activation of the chemoreflex [33, 34], which results in marked increases in nocturnal sympathetic drive reflected by vascular sympathetic nerve activity and serum catecholamines [33, 35]. This causes repetitive fluctuations and surges in heart rate and blood pressure during sleep [33]. Although the primary cardiac response to hypoxia and apnea is bradycardia (see later), tachycardia is evident at the end of apnea when breathing resumes. This is also the time when the blood pressure peaks are highest. Apneic episodes are thus marked by the simultaneous occurrence of hypoxemia and increased myocardial oxygen demand, due to the increased heart rate and blood pressure caused by sympathetic overdrive. Predictably, this situation can cause nocturnal myocardial ischemia [36–40], which may induce ventricular dysrhythmias and sudden death in these patients.

Another mechanism for ischemic events and sudden death in patients with OSA may be a paradoxical nocturnal increase in coagulability. Platelet activation and aggregation are increased during sleep in patients with OSA [41–46]. Furthermore, fibrinogen levels are increased [47, 48] and fibrinolytic activity is decreased [42].

Cardiac electrophysiology during sleep in patients with OSA is distinct from that of normal sleep, mostly due to marked nocturnal cardiac autonomic abnormalities. Heart rate variability and the day-night parasympathetic modulation of sinus node activity are attenuated in patients with OSA [49–53]. OSA impacts the main autonomic mechanisms mediating heart rate variability, including medullary coupling between respiratory and cardiac vagal neurons, input from the arterial baroreflex, and vagal feedback from pulmonary stretch receptors [54–56]. The latter may be affected by marked fluctuations in negative intrathoracic pressure during obstructive apneas. The duration of ventricular repolarization, represented by the QT_c, and the heterogeneity of repolarization, reflected by QT_c interval dispersion, are abnormal in patients with OSA (Fig. 29.4) [57–61]. The increase in QT_c dispersion correlates with the severity of OSA, measured by both the AHI and the duration of significant nocturnal hypoxemia [61].

Significant arrhythmias and conduction abnormalities occur during sleep in OSA patients [8, 32, 62–71]. A controlled, multicenter study showed that during sleep nonsustained ventricular tachycardia occurred in 5.3 % and complex ventricular ectopy occurred in 25 % of patients with sleep-disordered breathing (which included OSA as well as central sleep apnea) [72]. After adjustment for comorbidities, patients with sleep-disordered breathing had a 3.4-fold risk of non-sustained ventricular tachycardia and a 1.7-fold risk of complex ventricular activity compared to patients with normal sleep. Type 2 second degree AV block occurred in 2.2 % and intraventricular conduction delays occurred in 8.9 % of patients with sleep-disordered breathing [72]. Electrophysiology studies in patients with OSA and severe sinus bradycardia or advanced atrioventricular block during sleep demonstrated nearly normal sinus node and atrioventricular nodal function [70], which highlights the profound influence of autonomic modulation in these patients.

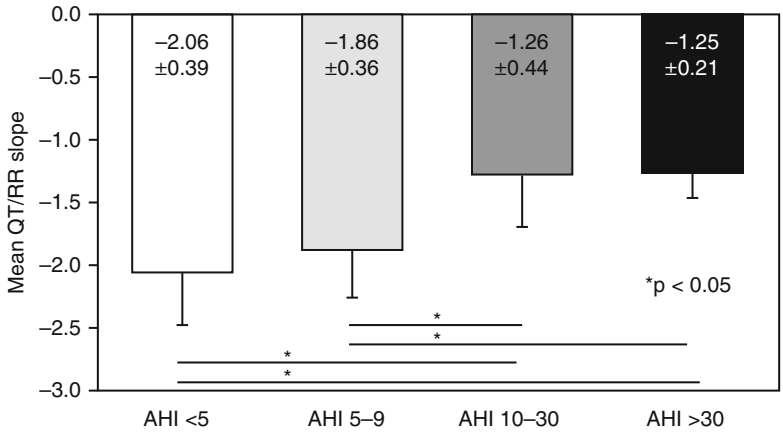

Figure 29–4. Alteration of the QT/RR slopes according to the severity of obstructive sleep apnea (OSA). OSA leads to abnormal beat-to-beat changes in ventricular repolarization, characterized by a flattened relationship between QT duration and RR intervals at heart rates less than 70 beats per minute. The relationship correlates with the severity of OSA, based on the apnea-hypopnea index (AHI) (Modified from Roche et al. [59], with permission from John Wiley and Sons)

In addition to ischemia and ventricular tachyarrhythmias, sudden death in patients with OSA may due to severe bradyarrhythmias. The cessation of airflow and hypoxemia can activate the diving reflex, which simultaneously causes cardiac parasympathetic overdrive and peripheral vasoconstriction in all vascular territories except the brain and heart. The resultant bradyarrhythmias are most frequent during REM sleep, may be severe, and as mentioned above may include sinus arrest and high-degree AV block [69, 72, 73]. In a series of 239 consecutive patients diagnosed with OSA at one hospital, 7 % had profound sinus bradycardia (<30 beats per minute) or advanced atrioventricular block with asystole >2 s [71]. These severe bradyarrhythmias were limited to patients with an AHI ≥60, representing severe OSA. Sudden deaths due to bradyarrhythmias are well documented [74–76], including in patients with heart failure [74], and it is conceivable that severe bradyarrhythmias may be causally related to sudden death in patients with OSA.

OSA is strongly associated with the occurrence of stroke [77, 78], and stroke itself acutely increases the risk of cardiac dysrhythmias [79, 80]. Most patients with strokes are not monitored for cardiac arrhythmias, and it is possible that some sudden deaths in OSA patients are related to strokes that result in malignant arrhythmias.

Other less recognized but potentially important causes of sudden death in patients with OSA are profound cerebral hypoxemia and ineffective arousals due to impaired chemosensitivity. Three illustrative cases of sudden death, one resuscitated and the others fatal, were recently described [81, 82]. These patients had polysomnographic monitoring during severe obstructive apneic events that led to profound systemic hypoxemia (oxygen saturation as low as 12 %), lack of arousal, and sudden death, evidenced by encephalographic inactivity and cardiopulmonary arrest (Fig. 29.5). Electrocardiographic monitoring did not reveal dysrhythmias preceding these events, and autopsy in one patient revealed no significant cardiac structural abnormalities or occlusive coronary artery disease [81]. These cases suggest that OSA may be a direct cause of sudden death. The mechanisms may include severe cerebral and systemic hypoxemia, and ineffective central arousals during severe apneas due to deranged chemosensitivity [34, 83, 84]. It is possible that sudden unexplained deaths that historically have been presumptively attributed to cardiac dysrhythmias (due to the lack of structural abnormalities) may be in fact due to the direct effects of OSA in some individuals, with severe sustained hypoxemia leading to death by way of depression of central activity.

In addition to the acute mechanisms discussed above, OSA has multiple effects on chronic cardiovascular function that may increase the risk of sudden death [85]. A wealth of cross-sectional data have demonstrated a strong association between OSA and chronic systemic hypertension, and prospective epidemiological studies have implicated OSA as an independent risk factor for incident hypertension [30, 31, 86, 87]. OSA is now broadly accepted as a secondary cause of

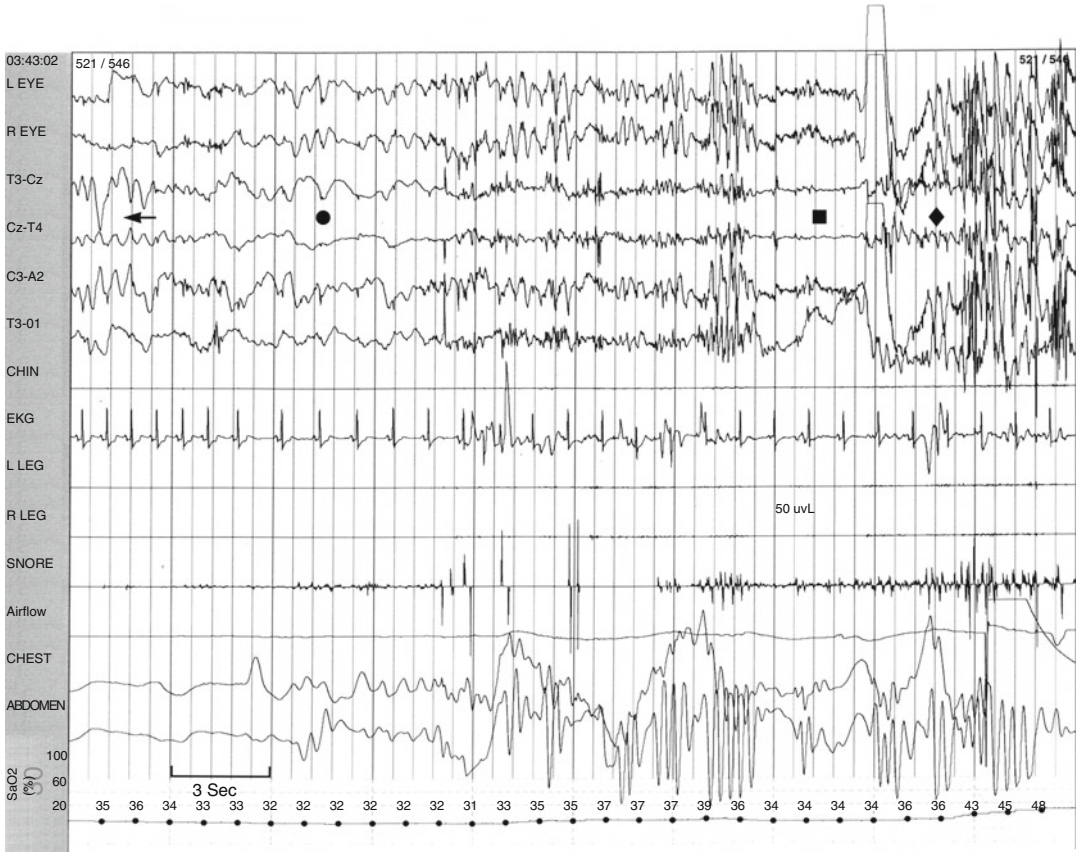

Figure 29–5. Resuscitated sudden death during an obstructive apnea. This patient had a prolonged obstructive apnea, which resulted in a sudden EEG change from a classic REM saw tooth pattern (see *arrow*) to a poorly organized, diffuse delta slow-wave pattern (see *closed circle*). This was followed by a general flattening of all activity (see *square*) that led to attempts to arouse the patient (as evidenced by diffuse movement artifact; see *diamond*). Nevertheless, persistent obstruction necessitated emergent rescue breathing maneuvers. Persistent EEG flattening followed by slowing and eventual recovery of normal waking patterns occurred later (not shown). *L* left, *R* right, *T* temporal, *C* central, *O* occipital, *CHIN* mentalis EMG, *L LEG* left anterior tibialis EMG, *R LEG* right anterior tibialis EMG, *SNORE* snoring microphone, *Airflow* nasal airflow, *CHEST* thoracic respiratory effort, *ABDOMEN* abdominal respiratory effort, SaO_2 (%) oxygen saturation (From Dyken et al. [82]. Reprinted with permission from Wolters Kluwer Health)

chronic systemic hypertension [88]. In addition, OSA is strongly associated with coronary artery disease. While this might be expected due to the multiple coronary risk factors often present in these patients, cross-sectional and prospective epidemiological studies have shown that the relationship between OSA and coronary artery disease, including incident ischemic events, is independent of major comorbidities such as obesity, diabetes, hypertension, and hyperlipidemia [89–92]. The strong and independent association of OSA with coronary artery disease would be expected to correlate also with a heightened risk of sudden death.

The chronic effects of OSA are also evident in daytime autonomic nervous system activity. Individuals with OSA have significantly increased sympathetic drive during the awake daytime period, reflected by increased catecholamines and sympathetic nerve activity, which is independent of other comorbid conditions, including obesity [33, 54, 93–95]. This may be due to a carryover from nocturnal autonomic abnormalities and to chronic dysfunction of the peripheral chemoreceptor reflex [34, 96]. While the precise interactions between the autonomic nervous system and arrhythmic sudden death remain largely unknown [97], chronic sympathetic

overdrive has been identified as a risk marker for sudden death [98].

Lastly, OSA is present in a large proportion of patients with heart failure, and it has been implicated in chronic left ventricular dysfunction [99–103]. The treatment of OSA by continuous positive airway pressure causes acute and lasting improvements in ventricular systolic function [99, 101], in one study resulting in an absolute increase of the left ventricular ejection fraction of 9 % after 1 month [103]. The contribution of OSA to ventricular dysfunction may be an important contributor to the neurohumoral response and remodeling that produce the myocardial substrate for sudden death, particularly in patients who are already at higher risk, such as those with ischemic or preexisting structural heart disease.

Associations Between OSA and Sudden Death

Not only is OSA associated, sometimes causally, with a number of mechanisms of cardiovascular disease [85], but OSA is also associated with a heightened risk of cardiovascular disease outcomes. While a number of longitudinal studies assessed the occurrence of cardiac events and mortality in cohorts of patients diagnosed with OSA, most of these studies did not have control groups of patients without OSA for comparison [104–108].

Three *controlled* longitudinal studies ascertained the occurrence of sudden death in patients with OSA [109–111]. Doherty et al. followed 168 patients with OSA for an average of 7.5 years [109]. They compared cardiovascular outcomes, including sudden death, in the 107 OSA patients who had continued OSA treatment (with continuous positive airway pressure) with the 61 OSA patients who had discontinued OSA treatment. Sudden unexpected death occurred in four patients (7 %) with untreated OSA and in no patients (0 %) with treated OSA (there was one arrhythmic death in a treated patient during coronary bypass surgery) [109].

Gami et al. assessed the incidence of sudden cardiac death over a course of 15 years in 10,701 patients undergoing sleep studies at the Mayo Clinic [110]. During an average follow-up of 5.3 years, 142 patients had resuscitated or fatal sudden cardiac death (annual rate 0.27 %). Independent risk factors included age and traditional comorbidities, as well as the lowest nocturnal oxygen saturation during the sleep study (per −10 %, HR 1.14). Sudden cardiac death was predicted by several indices of OSA severity, including an apnea-hypopnea index greater than 20 (HR 1.60), mean nocturnal oxygen saturation less than 93 % (HR 2.93), and lowest nocturnal oxygen saturation less than 78 % (HR 2.60) [110].

Bitter et al. used appropriate implantable cardioverter-defibrillator therapies as a surrogate for sudden cardiac death in a study of 472 heart failure patients who were screened for OSA at the time of their device implant [111]. The time to first appropriate device therapy, representing a sustained ventricular dysrhythmia, was significantly shorter in untreated OSA patients compared to treated OSA patients (HR 2.07) [111].

Additional observations supporting the influence of OSA on the occurrence of sudden death are the strikingly different day-night patterns of sudden death in patients with OSA compared to the general population. In the general population, the risk of sudden death is significantly greater during the second quarter of the day (in the morning hours after waking, i.e. from 6 AM to noon). There is also a significant decrease in the risk of sudden death during the night time hours (from midnight to 6 AM). This pattern is likely due to the day-night variation and sleep/wake-related changes in sympathetic activity, baroreflex function, coagulability, vascular function, and cardiac electrophysiology described earlier.

Since many of the putative mechanisms that may link OSA and sudden death occur acutely during sleep, it is intuitive that sudden deaths would be more likely to occur at night in patients with OSA. A Finnish study of 321 men with sudden death provided the first suggestion that this may be true [112]. In the study, Seppala et al. obtained snoring histories (as surrogates of OSA) from the cohabitants of the deceased men and found that habitual snorers were more

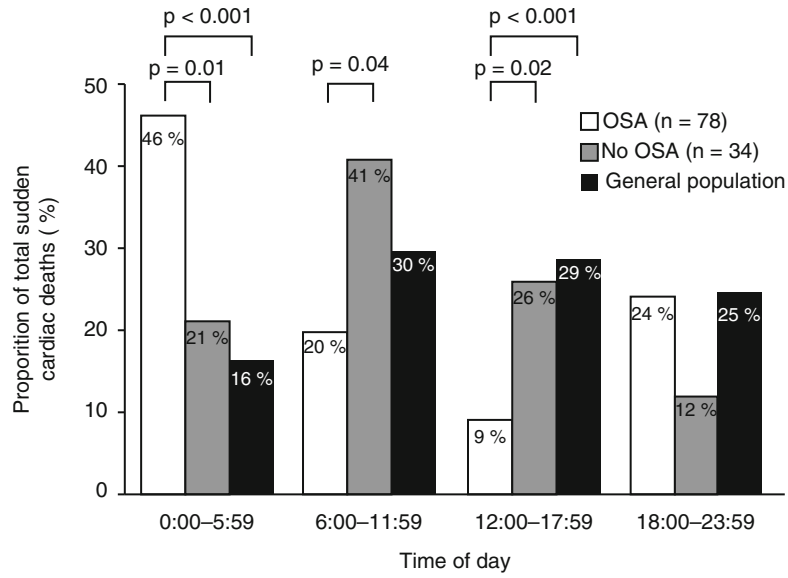

Figure 29–6. Day-night pattern of sudden death. The frequency of sudden death from midnight to 6 AM in individuals with obstructive sleep apnea (OSA) (47 %) was significantly higher than that in individuals without OSA (19 %, $p = 0.009$) and the general population (16 %, $p < 0.001$). The frequency of sudden death from 6 AM to noon in individuals with OSA (20 %) was significantly lower than that in individuals without OSA (42 %, $p = 0.029$) and nonsignificantly lower than that in the general population (30 %, $p = 0.157$). The frequency of sudden death from noon to 6 PM in individuals with OSA (9 %) was significantly lower than that in individuals without OSA (26 %, $p = 0.035$) and the general population (29 %, $p = 0.002$). The frequency of sudden death from 6 PM to midnight was not significantly different between individual with OSA (24 %) and those without OSA (13 %, $p = 0.293$) or the general population (25 %, $p = 0.887$). * = $p < 0.05$, ** = $p < 0.001$, both compared to individuals with OSA (From Gami et al. [113]. Reprinted with permission from the Massachusetts Medical Society)

likely to have sudden death in the early morning hours compared to non-snorers and occasional snorers.

This phenomenon was clarified by Gami et al. in a recent study of 112 patients who had polysomnography to diagnose or exclude OSA prior to experiencing sudden cardiac death [113]. Patients with OSA had a significantly increased risk of sudden death during the sleeping hours, from 10 PM to 6 AM, and patients without OSA had a diurnal pattern of sudden death that was similar to that expected in the general population (Fig. 29.6). Patients with OSA had a 2.6-fold risk of nocturnal sudden death, and the severity of OSA correlated with the magnitude of this risk [113]. These findings were mirrored in a recent prospective study by Zeidan-Shwiri et al., who described the rate and timing of ICD therapies for ventricular dysrhythmias in 45 patients who had undergone overnight sleep studies [114]. The patients with sleep disordered breathing (not just OSA) had an over fivefold risk of ICD therapies between midnight and 6 AM compared to patients without sleep disordered breathing. These observational studies suggest that OSA is a risk factor for sudden death, particularly at night. Whether OSA is also associated with an increase in sudden death during the daytime, or whether sudden death risk in the daytime is relatively decreased, remains to be determined. There is a paucity of data on OSA and sudden death, and definitive longitudinal studies and clinical trials are necessary to clarify this relationship.

Conclusion

OSA is a common condition, particularly in individuals with obesity or cardiovascular diseases, and may represent an important modifiable risk factor for sudden death. The unique pathophysiology of OSA creates a nocturnal milieu of mechanisms that may lead to sudden death. These

include the effects of hypoxemia, sympathetic drive and autonomic imbalance, baroreflex dysfunction, impaired chemosensitivity, hypercoagulability, and electrophysiologic abnormalities. Sudden deaths associated with OSA may be due to acute ischemic events, ventricular tachyarrhythmias, severe bradycardias, strokes, or profound obstructive apneas with ineffective arousals that lead to catastrophic cerebral and systemic hypoxemia. Observational data suggest that OSA increases the risk of sudden cardiac death, particularly during the night, and randomized controlled trials are necessary to clarify whether treating OSA prevents sudden cardiac death.

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30
Sudden Cardiac Arrest in Chronic Kidney Disease

Rod Passman, Mai Ots-Rosenberg, Ihor Gussak, and Hiie M. Gussak

Abstract

Chronic kidney disease (CKD) is a worldwide health problem with increasing incidence, prevalence, morbidity, and mortality. Death from cardiovascular disease in general and sudden cardiac arrest (SCA) in particular are exponentially proportional to declining renal function and are a major cause of mortality among all those with CKD. The greatest risk however is reserved for patients with end-stage renal disease (ESRD) on chronic dialysis. These individuals have an extraordinarily high mortality with an annual death rate of 221 deaths per 1,000 patient-years. Cardiac disease is the major cause of death in these patients, accounting for 45 % of all-cause mortality regardless of the mode of dialysis. Of these, 60 % appear to be due to SCA, making this single diagnosis responsible for a quarter of all-cause mortality. Once cardiac arrest occurs in this group of patients, survival is poor. Even if the arrest occurred in the controlled setting of a dialysis unit, the majority will have died within 48 h and the 6-month survival rate among those dialysis patients successfully resuscitated is dismal. Thus, reducing mortality from cardiovascular disease among ESRD patients, including those due to SCA from arrhythmic events, is a global health challenge. The main objectives of this chapter are to elucidate the nature of SCA in the kidney diseases population, describe possible mechanisms and risk factors, and discuss options for prevention.

Keywords

Chronic kidney disease • Dialysis • Cardiovascular disease • Sudden cardiac arrest

R. Passman, MD, MSCE (✉)
Medicine Department, Cardiology,
Electrophysiology Section,
Northwestern University Feinberg
School of Medicine,
676 N. St. Clair Street, Suite 600,
Chicago, IL 60611, USA
e-mail: r-passman@northwestern.edu

M. Ots-Rosenberg, MD, PhD
Nephrology Division, Internal Department,
Tartu University, Tartu, Estonia
e-mail: mai.ots@kliinikum.ee

I. Gussak, MD, PhD, FACC
Ono Pharmaceutical USA, Lawrenceville, NJ, USA

Department of Internal Medicine,
University of Medicine and Dentistry of New Jersey,
Robert Wood Johnson Medical School,
New Brunswick, NJ, USA
e-mail: igussak@newcardio.com

H.M. Gussak, MD
Medicine Department, UMDNJ, Newark, NJ, USA

New Jersey Medical School,
Hackensack University Medical Center,
Hackensack, NJ, USA
e-mail: hiiem@hotmail.com

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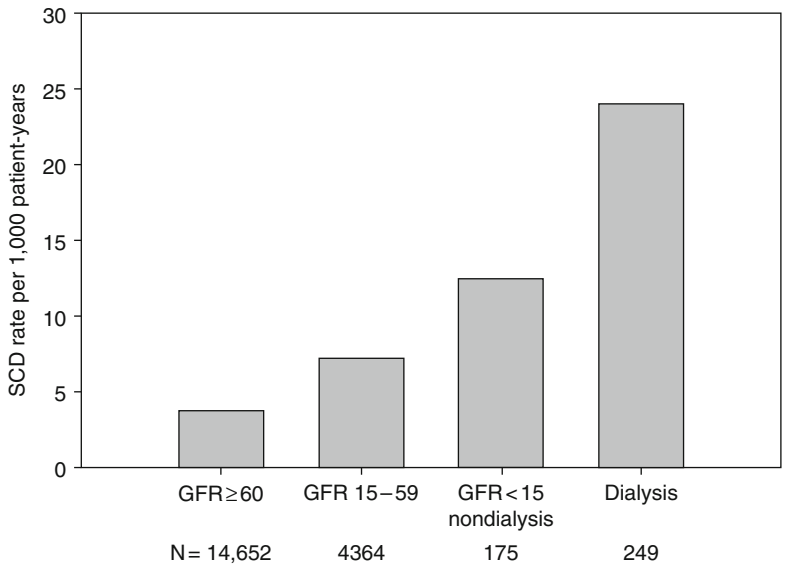

Figure 30–1. The risk of sudden cardiac arrest in various stages of chronic kidney disease (Adapted from: Pun et al. [10] with permission from Nature Publishing Group)

Introduction

Chronic kidney disease (CKD) is a worldwide health problem with increasing incidence, prevalence, morbidity, and mortality. At present 10–16 % of adults worldwide are affected by CKD [1–4]. In the US, mild to moderate kidney dysfunction is present in 34 % of individuals [5]. Fueled in part by the growing epidemics of obesity, diabetes, and hypertension, this number represents a threefold increase over the last decade [6]. Similarly, the number of individuals with end-stage renal disease (ESRD) is also rising. There are currently 600,000 individuals receiving renal replacement therapy in the United States and the increasing incidence is expected to result in 2.2 million such patients by the year 2030 [7].

Cardiovascular mortality is exponentially proportional to declining renal function and is a major cause of death among all patients with renal disease. The presence of even mild renal insufficiency in patients with and without underlying cardiovascular disease is associated with a respective 1.4 to 3-fold increase in the risk of cardiac death and sudden cardiac arrest (SCA) compared to those with normal renal function (Fig. 30.1) [8–10]. The greatest risk of cardiovascular and sudden death however is reserved for those patients on chronic dialysis. Dialysis patients have extraordinarily high mortality with an annual death rate of 221 deaths per 1,000 patient-years [11]. Cardiac disease is the major cause of death, accounting for 45 % of all-cause mortality among patients receiving hemodialysis or peritoneal dialysis. Of these, 60 % appear to be due to SCA, making this single diagnosis responsible for 25 ± 2 % of all-cause mortality [12–14]. The 6–7 % yearly incidence of SCA among dialysis patients exceeds that even of high risk congestive heart failure (CHF) patients. Once cardiac arrest occurs in this group of patients, survival is poor. Even if the arrest occurred in the controlled setting of a dialysis unit, 60 % will have died within 48 h and the 6-month survival rate among those dialysis patients successfully resuscitated is only 3–11 % [15–18]. Thus, reducing mortality from cardiovascular disease among ESRD patients, including those due to sudden cardiac death from arrhythmic events, is a global health challenge. The main objectives of this chapter are to elucidate the nature of SCA in the kidney diseases population, describe possible mechanisms and risk factors, and discuss options for prevention.

Definitions of Sudden Cardiac Death: Do They Apply to the CKD Patient?

Definitions for sudden cardiac death (SCD) describe only the circumstances of death and not the disease process itself. Traditional definitions include either a witnessed cardiac

arrest which occurs suddenly and within an hour of symptom onset or an unwitnessed death which is unexpected, in a patient known to be well in the last 24 h without a clear non-cardiac cause of death. Because oftentimes the suddenness of death and preceding symptoms cannot be determined, more recent operational criteria focus simply on the out-of-hospital occurrence of a presumed sudden pulseless condition and the absence of evidence of a non-cardiac condition as the cause of the event. Whether these definitions apply to patients with CKD, particularly those with advanced disease and specifically those with ESRD who spend a disproportionate amount of time in a hospital setting and have significant competing risks of sudden death from other causes, is a matter of debate.

Arrhythmic mechanisms preceding SCA are difficult to capture, since these events are rarely witnessed. Thus, the window of time to assess the underlying cardiac rhythm prior to death is likely quite small. Retrospective approaches to catalogue SCA arrhythmias from resuscitation accounts are susceptible to bias from data completeness and measurement, and have yielded large variances in the frequencies and types of cardiac arrhythmias recorded. In patients without CKD, the proportion of SCA due to ventricular tachycardia (VT) and ventricular fibrillation (VF) is estimated at 50–75 % [19]. Whether patients with mild to moderate CKD exhibit the same proportion of arrhythmic events during SCA is unknown. However, in the ESRD population there is some evidence to suggest substantial variance from the general population. In a case series of 38 cardiac arrest calls in a single dialysis unit in Montreal, VT/VF was found in only 16 % of at initial evaluation [20]. Autopsy studies, while rare in dialysis patients, have yielded additional important findings. In an autopsy series of 93 chronic dialysis patients in Japan, 35 had cause of death listed as SCA [21]. Of those, the majority of deaths were actually due to vascular events (i.e. stroke, ruptured aneurysms) and not arrhythmic events. Taken together, these findings raise the possibility that the risk of arrhythmic death in patients with CKD, particularly ESRD, may be overestimated in some settings.

Mechanisms and Risk Factors

In the general population, sudden death occurs from a confluence of arrhythmogenic triggers superimposed on a vulnerable substrate. For patients with CKD, both vulnerable substrate and triggers exist in abundance. Underlying structural abnormalities including left ventricular hypertrophy (LVH), systolic dysfunction, atherosclerotic and arteriosclerotic vascular disease provide just some of the anatomic milieu for malignant arrhythmias whereas electrolyte shifts, divalent ion abnormalities, derangements in autonomic function, abnormalities in cardiac repolarization, and the fluctuations imparted by dialysis itself represent just some of the potential triggers (Fig. 30.2) [22].

Cardiac Risk Factors

Ischemic Heart Disease

There is a high prevalence of atherosclerotic heart disease in patients with CKD that increases as renal function declines. The presence of renal dysfunction predisposes the patients to not only the risk of developing atherosclerosis but also acts synergistically to increase the complications of the disease process. Rates of myocardial infarction (MI) and survival post-MI are adversely affected by the presence of renal disease [23–25]. In chronic hemodialysis patients, the presence coronary artery disease (CAD) is associated with a higher burden of ventricular ectopy both during and several hours after dialysis that together play an important role in the initiation of malignant arrhythmias [26]. Atherosclerotic lesions in CKD are characterized by a distinct intima-media thickening and calcification of the coronary arteries. Of the major factors that contribute to accelerated atherosclerosis in CKD, the two most important are chronic inflammation and hyperphosphatemia. Hyperphosphatemia and associated secondary hyperparathyroidism result in noncompliant vessels due to calcium deposition in soft tissues and increased vascular calcification with smooth muscle proliferation. This may partially explain the fact that approximately 20 % of cardiac deaths are attributed to acute myocardial infarction

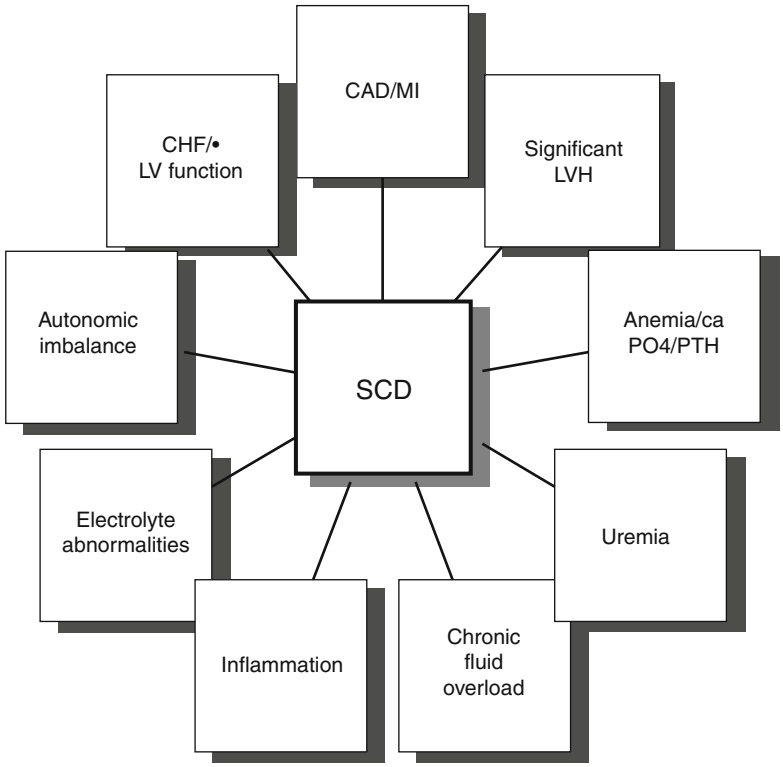

Figure 30–2. Potential causal factors of sudden cardiac arrest (Adapted from: Herzog et al. [22] with permission from Blackwell Publishing)

with the poorest survival occurring in diabetics with ESRD.

Though obstructive CAD is an important contributor to SCA in CKD patients, it is clearly not the only one. Furthermore, traditional CAD-related risk factors are insufficient to explain the markedly increased event rates seen in these individuals. This is supported by retrospective cohort studies that reveal that the SCA risk associated with a decline in renal function cannot be accounted for purely by severity of CAD, CHF, or diabetes [10]. Clinical trial data demonstrate that direct CAD related deaths accounted for only 9 % of all-cause mortality whereas SCA accounted for 26 % [13]. An analysis of data from the USRDS CVSSC found a 2-year mortality of 48 and 43 %, respectively, after nondrug eluting coronary artery stents and coronary artery bypass surgery (CABG) incorporating internal mammary graft use in the dialysis population. The annual mortality attributed to arrhythmic mechanisms was 8.5 and 7 % after stenting and CABG, respectively, which is significantly higher than that observed in the general population. This data imply that while revascularization may have some importance in preventing SCD, the sole reliance on this intervention may be an inadequate clinical strategy for in dialysis patients [27].

Cardiomyopathy

CHF is common in CKD patients, particularly those with ESRD where up to one-third are reported to have CHF at the initiation of dialysis. Three forms of uremic cardiomyopathy are described and include: (1) LVH, (2) dilation, and (3) systolic dysfunction. Left ventricular dysfunction and LVH are far more common in patients with CKD and ESRD than in the general population [28, 29]. Ejection fractions below 35 % are seen in approximately one in seven dialysis patients and LVH present in as much as 80 % [30–32]. The main pathophysiological mechanisms underlying cardiomyopathies are interstitial fibrosis and endothelial dysfunction. Arterial hypertension, one of the most frequent cardiovascular diseases found in CKD patients, is documented in more that 70 % of this population

before the initiation of hemodialysis and is a well-established major risk factor for both renal failure and its association with LVH. Anemia, fluid overload, and the presence of an arteriovenous fistula result in volume overload which may also promote the development of left ventricular dilation and hypertrophy. These structural abnormalities may ultimately lead to diastolic and systolic dysfunctions and their attending risks of heart failure and sudden death. Modern imaging techniques have provided further insights into the mechanisms of uremic cardiomyopathies. MRI evaluation of hemodialysis patients suggest that hypertrophy is the predominant form of uremic cardiomyopathy with left ventricular dilation and systolic dysfunction the result of infarction or diffuse fibrosis, respectively [33]. The presence of LVH in the dialysis cohort carries important prognostic value. Among the many non-traditional non-Framingham cardiac risk factors in ESRD, ventricular hypertrophy has emerged as a powerful predictor of cardiac mortality with a left ventricular mass index of >125 g/m^2 associated with a 30 % increased 5 year mortality [34, 35]. Whether or not this is due to sudden death is uncertain, but an increased rate of arrhythmias can be anticipated due to decreased myocardial reserve and ischemia intolerance, the presence of myocardial scar, and by prolongation in repolarization often associated with increases in left ventricular mass [36]. In fact, observational studies on chronic dialysis patients do demonstrate an association between LVH and QTc prolongation as well as a correlation between hypertrophy and PVC burden during dialysis [36].

CHF due to systolic dysfunction is, not surprisingly, a strong predictor of mortality in patients with CKD. As in nonuremic patients, the severity of heart failure also correlates with survival, but the threshold for increasing risk may be different in patients with more severe forms of CKD [37]. In the non-dialysis population, left ventricular systolic dysfunction of less than 35–40 %, regardless of etiology, is the most potent risk factor for sudden cardiac death. This is not clearly the case however in ESRD patients. For example, dialysis patients who died suddenly but had prior echocardiograms within a short period of time before their deaths showed that the majority of deaths occurred in those with ejection fractions above 35 % [38]. This also appears to hold true for peritoneal dialysis patients. In a prospective cohort study that followed 230 peritoneal dialysis patients for up to 5 years, an EF of ≤48 % was found to be an independent predictor of sudden death, emphasizing that even mild degrees of left ventricular dysfunction may be all that is necessary to precipitate events in the dialysis environment [39, 40].

Electrophysiologic Instability

The propensity for life-threatening arrhythmias in patients with ESRD is linked not only to the high prevalence of structural heart disease but also to underlying perturbations in electrophysiologic properties that likely predispose these individuals to VT/VF. Coronary disease, LVH, and systolic dysfunction are known for their strong remodeling effects of cardiac ion channels resulting in the acquired cardiac channelopathies leading to prolonged (or delayed) ventricular repolarization and increased risk of SCD ["disease-associated" acquired long QT syndrome (LQTS)] [41]. Such an adverse modulation of the cardiac electrophysiological matrix is characterized by a progressive reduction of the naturally redundant K^+ channels (diminished "repolarization reserve") and concomitant increase in sensitivity of the remaining K^+ channels to their inhibition. This results in further prolongation of the electrocardiographic QT interval and elevates the risk for lethal arrhythmias. In addition to the inherent alterations in ion channel modulation, electrolyte disturbances and exposure to multiple proarrhythmic medications and their abnormal excretion or metabolism play important roles in SCA in these patients. Both forms of acquired LQTS ("disease associated" and drug induced) are among the most important and yet preventable mechanisms of SCD in nephrology.

Evidence for proarrhythmia comes from multiple sources. As anticipated, the QTc has been shown to be prolonged in chronic dialysis patients. In a study of studies of 42 such patients, QTc was significantly prolonged compared to age-matched controls [42]. Additionally, dialysis itself appears to increase the QTc. In 68 nondiabetic

ESRD patients without evidence of CAD or LVH, QTc increased from 421 ± 26 ms before hemodialysis to 434 ± 29 ms after hemodialysis [43]. QT dispersion has also been noted to increase following dialysis, though its role in arrhythmogenesis is unclear as present [44, 45].

Other marks of electrical instability have been assessed in the dialysis population. Long-term heart rate variability (HRV) has been used to assess cardiac autonomic tone and is a marker for all-cause mortality in patients with ischemic and non-ischemic cardiomyopathy [46]. End-stage renal disease patients demonstrate a withdrawal in parasympathetic modulation and an increase in the sympathetic input to the sinus node. Alterations in HRV occur more frequently in dialysis patients with LVH and correspond with increased incidences of SCD [47, 48]. In one study of 383 chronic hemodialysis patients, abnormal HRV was independently associated with all-cause and cardiovascular mortality even after adjustment for traditional cardiovascular risk factors [48].

T-wave alternans (TWA), another non-invasive measure of arrhythmogensis, reflects spatiotemporal heterogeneity of repolarization and serves as both a marker and a cause of malignant arrhythmias [49]. In a study of modified moving average TWA in chronic HD patients with normal LV function, 85 % were found to have values at or above the threshold defined as normal in the general population. Using the spectral method of TWA, a study of 200 ESRD patients found abnormal results in 57.5 % compared to 26.7 % of controls with LVH. In the same study, abnormal TWA was significantly associated with uremic cardiomyopathy, atherosclerotic disease, and diabetes [50].

Heart rate turbulence (HRT) is an important predictor of events in heart failure patients and has recently been evaluated in dialysis patients where abnormalities were present in 57 % [51]. It has been postulated that HRT measures vagal responsiveness in a fashion similar to baroreflex sensitivity. Assessment of baroreflex sensitivity in dialysis patients has demonstrated a high prevalence of perturbations and has been shown to predict all-cause and cardiovascular mortality in this population. Data suggest that this measure is a marker for and a result of arterial stiffness due to vascular calcification [52].

Dialysis-Related Risk Factors

Type of Dialysis: Peritoneal Versus Hemodialysis

Data from the USDRS report similar cardiovascular death rates and sudden cardiac death rates between patients treated with peritoneal and hemodialysis. In a 5-year follow up study of 230 peritoneal dialysis patients, 24 % of all deaths were observed to be due to SCA, a number strikingly similar to that observed in clinical trials of hemodialysis patients [39]. This fact underscores the fact that ESRD alone is a primary promoter of an increased risk for SCA regardless of the type of renal replacement therapy. There is an interplay, however, between the type of renal replacement therapy, dialysis vintage, and risk of SCA with the relative hazard of cardiac arrest in hemodialysis compared to peritoneal dialysis varying with time after initiation of renal replacement therapy. The rate of cardiac arrest is about 50 % higher in hemodialysis patients 3 months after dialysis initiation, but they are similar at 2 years [53].

Dialysate

Rapid shifts in electrolyte concentrations can alter the action potential and support proarrhythmia. The use of low potassium dialysate also may be a risk factor for SCD [54]. In a case-control study of 43,200 HD patients, the use of low potassium (<2.0 mEq/L) baths was associated with higher SCA risk, a finding that could not be explained by the pre-dialysis serum potassium levels. Increased ultra-filtration volume and low calcium dialysate were also linked to sudden cardiac arrest in this study. In a separate study comparing 400 reported cardiac arrest cases occurring in dialysis units against a nationally representative cohort of 77,000 hemodialysis patients, those that suffered an arrest were nearly twice as likely to have been dialyzed against a 0 or 1.0 mEq/L potassium dialysate on the day of cardiac arrest (17.1 vs. 8.8 %) [15]. These suggest that avoiding low potassium dialysate prescriptions when possible may reduce the risk of SCA.

Dialytic Intervals

It is interesting to note that the incidence of SCD in hemodialysis patients is heterogeneously dispersed among dialytic intervals and is temporally related to the dialysis procedure. The highest incidence of SCD has been observed to occur during the 2-day interval prior to the first dialysis session of the week. This represents the longest of the interdialytic intervals, with the day of first dialysis and the day after the first dialysis session of the week representing intermediate- and low-risk periods, respectively [38]. In a study of 32,065 participants in the End-Stage Renal Disease Clinical Performance Measures Project, patients receiving hemodialysis three-times weekly were evaluated and the rates of overall and sudden cardiac death on the day after the long (2-day) interdialytic interval with rates on other days were compared. Over a mean follow-up interval of 2.2 years, the rate of all-cause mortality (22.1 vs. 18.0 deaths per 100 person-years, $P < 0.001$), mortality from cardiac causes (10.2 vs. 7.5, $P < 0.001$), mortality from cardiac arrest (1.3 vs. 1.0, $P = 0.004$), mortality from myocardial infarction (6.3 vs. 4.4, $P < 0.001$), and admissions for myocardial infarction (6.3 vs. 3.9, $P < 0.001$), CHF (29.9 vs. 16.9, $P < 0.001$), stroke (4.7 vs. 3.1, $P < 0.001$), dysrhythmia (20.9 vs. 11.0, $P < 0.001$), and any cardiovascular event (44.2 vs. 19.7, $P < 0.001$) were all higher on the day after the long interval than on other days [55]. While it may be assumed that serum potassium plays a role, no such discrepancies were found in those patients with and without SCA [38]. Additionally, no differences in HRV, TWA, or HRT were noted within the same patients between dialytic intervals. Whether daily dialysis can reduce cardiovascular mortality and sudden death risk has yet to be determined [51].

Role of Hyperphosphatemia

Hyperphosphatemia results from diminished phosphate excretion and is seen in nearly half of dialysis patients. In conjunction with hypocalcemia and 1,25 Vitamin D deficiency, hyperphosphatemia leads to secondary hyperparathyroidism which can provoke smooth muscle proliferation, vascular calcification and coronary artherosclerosis [56]. Data from two national random samples of HD patients including 12,833 followed for 2-years showed that hyperphosphatemia, elevated parathyroid hormone levels, and elevations in calcium-phosphate ($Ca\text{-}PO_4$) product were independently associated with death due to CAD and SCA [14, 57, 58]. While the cause of this link is speculative, the data suggest a role for elevated serum PO_4 either in the development, progression, or the rupture of atheromatous plaques in the coronary arteries. Additionally, myocardial fibrosis induced by elevated levels of parathyroid hormone in patients with underlying uremic cardiomyopathy may contribute to arrhythmogenesis while hyperphosphatemia and $Ca\text{-}PO_4$ product are thought to result in myocardial calcification with disruption of the normal conduction system architecture [59, 60].

Prevention of SCD

Medical Therapies

There is little evidence to date that any specific medical therapy has major impact on the prevention of sudden death in the dialysis patient. In a single study of 114 dialysis patients with dilated cardiomyopathy, the use of carvedilol was associated with a decrease in overall mortality and a non-significant 24 % reduction in sudden death risk [61]. An observational report from the US Subset of the Dialysis Outcomes and Practice Patterns Study found that although beta-adrenergic blockers were underutilized in this population, those receiving beta-adrenergic blockers had lower overall mortality [62]. Whether beta-adrenergic blockers reduce the risk of SCD in dialysis patients without heart failure is unknown. Retrospective studies have suggested a survival benefit from the use of angiotensin converting enzyme inhibitors in dialysis patients [63, 64]. In contrast, a randomized placebo controlled trial of fosinopril in dialysis patients with LVH failed to show any reduction in cardiovascular events including cardiac arrest [65]. Similar results were observed in the 4D trial which evaluated the efficacy of atorvastatin in type 2 diabetic dialysis patients. The study, a randomized trial of 178

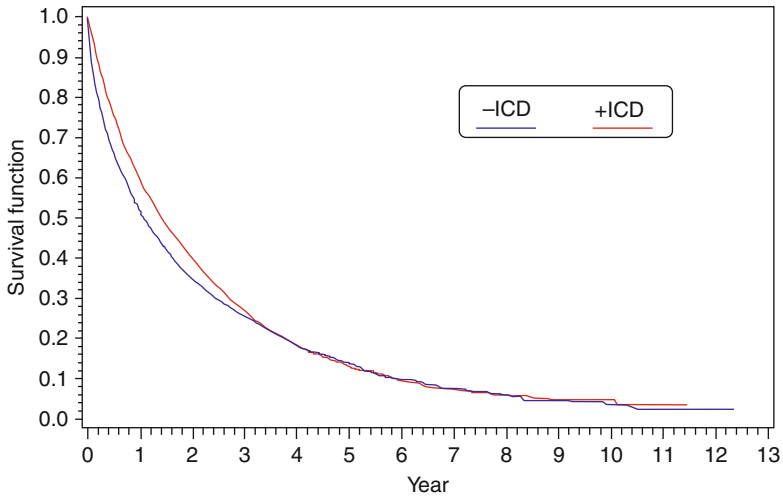

Figure 30–3. Survival of patients who received an implantable cardioverter defibrillator for secondary prevention compared with matched controls (From Charytan et al. [69]. Reprinted with permission from Elsevier Limited)

patients followed for nearly 4 years, showed a nonsignificant 8 % reduction in the composite endpoint of death from cardiac causes, fatal stroke, nonfatal myocardial infarction, or nonfatal stroke [13]. The results can be explained by the fact that deaths due to SCA were nearly three times more prevalent than deaths due to coronary events, suggesting that either CAD is not responsible for sudden death in dialysis patients or it is unresponsive to statin therapy. In a trial of an angiotensin II receptor blocker, however, the results were more encouraging. In one small trial of 80 dialysis patients, those assigned to candesartan demonstrated a significant reduction in cardiovascular events and total mortality and experienced no sudden deaths compared to four in the control arm [66]. However, no firm conclusions on the effects of this therapy on sudden death can be made given the small sample size. Additional studies are necessary before the routine use of angiotensin receptor blockers in dialysis patients without heart failure can be recommended.

ICDs for Sudden Death Prevention

While it may be tempting to assume that a population at high risk for SCD such as those on dialysis would naturally benefit from ICD therapy, this is not clearly the case. The competing risk of death from other causes coupled with the elevated complication rate of ICD implantation likely converges to limit the utility of these devices in the dialysis population.

For nondialysis patients who have survived SCA or who have already manifested potentially life-threatening ventricular arrhythmias, randomized studies have shown that placement of an implantable cardiac defibrillator (ICD) is superior to antiarrhythmic therapy in improving survival [67]. Unfortunately, there are no randomized prospective studies that have examined the outcomes after ICD placement in dialysis patients who have survived SCA and no reports of any dialysis patients included in the randomized trials of ICDs for secondary prevention. Retrospective evidence suggests that ICDs may lower short-term mortality in dialysis patients. A Medicare database analysis compared the survival of dialysis patients who survived cardiac arrest between 1996 and 2001 and either did or did not receive ICD implantation. Of the nearly 6,000 patients, only 8 % received ICD implantation. Using propensity analysis, ICD implantation was independently associated with a 42 % reduction in mortality at 5-years (relative risk 0.58 [95 % CI 0.50, 0.66]) [68]. A more recent analysis using a high-dimensional propensity score analysis, however, demonstrates less of an effect. Analyzing data on 2,232 dialysis patients who received an ICD for secondary prevention between 1994 and 2006 and comparing them to 8,928 otherwise similar patients who did not receive an ICD, the authors found a modest but significant reduction in mortality in years 1 and 2 but a convergence of the curves after 3 or more years (Fig. 30.3) [69]. The USRDS reports median survival of only 18 months in dialysis patients receiving ICDs,

regardless of indication and well below that in non-dialysis ICD recipients [53]. Nonetheless, current guidelines do not distinguish between uremic and non-uremic patients and in the absence of controlled trial data it appears that device implantation for secondary indications is warranted. For primary prevention, the interaction between CKD and ICD-benefit is also poorly delineated. Clinical trials of primary prevention ICDs in patients with ischemic and non-ischemic cardiomyopathy either enrolled no dialysis patients or have not reported on their outcome. In patients even with more mild forms of CKD, the benefit of the ICD for primary prevention of SCD appears to be attenuated [70]. In the randomized MADIT II study of primary prevention ICD in patients with ischemic cardiomyopathy and EF < 30 %, every 10 unit decrease in estimate glomerular filtration rate was associated with a 17 % increase in the risk of sudden cardiac death [70]. In the COMPANION trial, the presence of renal dysfunction was associated with a 1.7-fold increase in the risk of SCD [71].

There are several reasons why ICDs may not prolong the life of the CKD patient. First, defibrillation thresholds are known to be elevated in this population, raising the possibility that the device may be unable to terminate VT/VF should it occur. This may be particularly true in the setting of hyperkalemia [72]. In a study of patients with normal renal function, mild to moderate CKD, and ESRD, a progressive and significant increase in DFTs was noted [73]. Second, complications rates following device implantation are also elevated. Infections, bleeding, and lead dislodgement were all noted to be higher in the ESRD cohort as is compromise of dialysis access [74, 75]. Most concerning, however, is an analysis of the ICD Registry that found that the perioperative mortality was fivefold higher among the 6,851 dialysis patients compared to the 157,218 non dialysis patients (1.9 v 0.4 %) [76]. Lastly, arrhythmic events in this population may simply be an epiphenomenon of impending cardiovascular collapse. Therefore, any device that simply terminates life-threatening arrhythmias may have no impact on long-term mortality. This is supported by a retrospective comparison of dialysis and non-dialysis patients implanted with an ICD showing that dialysis is the strongest predictor of appropriate ICD therapy for VT/VF but also the strongest predictor of mortality [77].

Future Directions

The growing prevalence of CKD and its attendant risk of SCA makes risk stratification and prevention important goals. Unfortunately, the failure to include large numbers of CKD patients, particularly those on dialysis, in most major cardiology trials of the last several decades has limited our ability to better care for these patients. Knowledge gaps and research needs in this area have been identified [5]. Disease-specific, large-scale prospective cohort studies of heterogeneous CKD populations are required to define risk factors for SCA. Evaluated variables should include not only standard cardiovascular measures but additional non-invasive markers of electrical instability (HRV, HRT, TWA) and biomarker studies of apoptosis (cTNT), inflammation (interleukin-6, C-reactive protein, adiponectin), and nutrition (serum albumin, predialysis serum creatinine) [5]. Barriers should be removed to allow data linkage from population-wide cohort and case-control studies. Randomized trials are needed to assess a wide spectrum of interventions as basic as beta-adrenergic blockers and as complicated as ICDs (possibly subcutaneous), sympathetic denervation, and changes in dialysis itself.

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31
Clinical Trials in Sudden Cardiac Death Prevention: Principles and Endpoints

Andrzej S. Kosinski

Abstract

A properly designed and conducted randomized clinical trial is the most objective approach for definitive comparison of medical therapies. However, a clinical trial is a complex collaborative undertaking and requires substantial multidisciplinary planning efforts. This chapter presents the main components of a randomized trial and discusses the essential statistical concepts relevant in a trial design. The primary result and summary of statistical power, analysis, and the follow-up approach of the four recently completed pivotal clinical trials pertinent to the prevention of sudden cardiac death are summarized.

Keywords

Randomized controlled trial • Intention-to-treat principle • Informed consent • Data Safety Monitoring Board • Type I error • Primary endpoint test statistic • Treatment effect • Statistical power • Sample size • Subgroup and interim analyses

Research questions can be approached by means of observational studies, case – control studies, or randomized controlled trials (RCTs). Observational studies are often useful for developing research ideas, but are vulnerable to bias due to an uncontrolled process of treatment assignment. Occasionally, case – control studies may be the only feasible option open to researchers, but such studies are also potentially subject to bias. RCTs are currently recognized as the best tool available for definitive comparison of proposed medical therapies, and are pivotal in the practice of evidence based medicine [1–5]. RCTs involve prospective follow-up of patients and compare in a randomized fashion two or more treatment assignments, one of which is often placebo or a standard treatment. Patients enrolled in a RCT should reflect a well-defined population, selected on the basis of study inclusion and exclusion criteria and enrolled consecutively to avoid the possibility of conscious or unconscious selectiveness in including or excluding patients. The essential feature of RCTs is that they are designed so that treatments are assigned entirely at random, rather than as a result of current standard medical care, as would be the case in a prospective observational study.

Randomization produces treatment groups that are comparable with respect to patient

A.S. Kosinski, Ph.D.
Department of Biostatistics and Bioinformatics,
Duke University School of Medicine,
Duke Clinical Research Institute,
PO Box 17969, Durham, NC 27715, USA
e-mail: andrzej.kosinski@duke.edu

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characteristics, both recorded and unrecorded, and helps avoid patients' self-selection into treatment groups and investigators' tendencies to advocate a particular treatment, thus avoiding possible biases associated with treatment assignment. In other words, random assignment of patients to a treatment provides a proper experiment, because the decision about the treatment assignment is external to the current knowledge of either the patient or the physician.

Ideally, treatment assignment is unknown both to patients enrolled in the study and to the medical professionals administering the treatment. This approach, known as double-blinding or double-masking, is often not feasible for all treatment arms in trials of sudden cardiac death prevention, because medical devices are commonly used as a treatment or component of treatment. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [6], placebo and amiodarone were administered in double-blinded fashion, but assignment to an implantable cardioverter/defibrillator (ICD) obviously could not be blinded. Generally, blinding should be utilized whenever possible in designing a clinical trial, and at minimum preserved when adjudicating study endpoints.

Randomization in multicenter clinical trials should be stratified by center to assure that all treatments are utilized in similar proportions at each center. Randomization sequences should not be known to personnel who recruit patients for a study. A telephone call center can be used to verify patient eligibility and provide treatment assignment. For smaller studies, treatment assignment can be provided by an independent statistical center in sealed envelopes; however, this approach is less reliable than using a central randomization center. Internet based randomization is gaining ground. It is critical that treatment intervention begins as soon as possible after randomization in order to avoid bias that can arise from events occurring between randomization and initiation of assigned therapy. In other words, randomization assignment should be delayed until the last practicable moment before initiation of therapy. For example, patients assigned to the drug therapy (amiodarone or placebo) in the SCD-HeFT study began therapy immediately after the randomization. However, immediate initiation of the ICD therapy was not feasible, but the time from randomization to ICD implantation was short (median duration was 3 days) [6].

Every effort must be undertaken to minimize the number of patients lost to follow-up before the end of a study (if the endpoint is all-cause mortality, national databases such as the National Death Index can be useful for ascertaining vital status) [7]. The potential for biased treatment comparison is substantially greater with increased rates of patient loss to follow-up, because the reason for loss of contact may be related to the outcome under study. Thus, the loss to follow-up of more than a few percent of patients can severely compromise the benefits of randomization. Lack of compliance with a prescribed treatment scheme may also reduce value of randomization, and substantial effort should be expanded to preserve the treatment regimen as described in the protocol. Although every effort should be expanded to minimize the extent of missing values by proactive strategies, inevitably one may need to deal with some missing value problems. A good practice is to follow recommendations of the National Research Council Panel on Handling Missing Data in Clinical Trials [8].

Randomization is often not to a pure form of a particular treatment, but rather to an initial treatment strategy. Patients assigned to the drug arm of a trial comparing drug and device-based interventions may receive a device during the follow-up, if judged absolutely necessary according to current practice standards. The primary analysis of such a study should be performed on the basis of the intention-to-treat (ITT) principle, which states that for purposes of primary analysis, patients are considered according to the treatment arm to which they are randomly assigned, regardless of the treatment they actually receive.

An ethical approach to RCTs is mandatory. Study protocols should include detailed descriptions of the research question and study design, and all investigators participating in a multicenter trial must agree to follow the protocol. Further, researchers participating in a clinical trial can offer patients a randomization only when the relative benefit of a particular treatment is not confirmed. This lack of knowledge,

or *equipoise*, regarding which treatment is preferable has to be present and fully accepted by all investigators before a trial begins. Otherwise, ethical concerns may arise and patient recruitment is likely to suffer. All proposed studies should be reviewed by an Institutional Review Board (IRB) before enrollment begins. Potential subjects need to have an understanding, documented by provision of informed consent, of the nature of the research, including its risks and possible benefits. Patients should also be aware that they have the right to withdraw consent to participate in a study at any time. All RCTs should be overseen by a Data Safety Monitoring Board (DSMB) consisting of experts in the specific field of research and preferably including a biostatistician [9]. DSMBs (also known as Data Safety Monitoring Committees [DSMC], Data Monitoring Boards [DMB], Independent Data Monitoring Committees [IDMC], etc.) must be entirely independent of both trial investigators and sponsors. DSMBs are charged with monitoring the safety of patients and may recommend early stopping of a trial based either on safety concerns or endpoint related information.

The importance of choosing a clinically relevant primary endpoint (outcome measure) cannot be overstated. Surrogate measures are often considered in preliminary studies; however, such measures may prove inadequate in RCTs, as occurred in the Cardiac Arrhythmia Suppression Trial (CAST) [10]. In this trial, drugs providing suppression of ventricular arrhythmias were found to unexpectedly increase risk of death and sudden death. An endpoint of all-cause mortality may be the most appropriate for the purposes of a definitive clinical trial, and most major clinical trials of ICD therapy have considered overall mortality as the primary endpoint [11]. However, overall mortality may be low, requiring large numbers of patients in order to achieve sufficient statistical power and additional components of the endpoint may be considered, if clinically meaningful (e.g., hospitalizations). Smaller trials of cardiac resynchronization therapy (CRT) considered as primary endpoints one or more of the following non-mortality measures: distance walked in 6 min, exercise capacity as measured be peak oxygen consumption, quality of life score, New York Heart Association (NYHA) class, and/or hospitalization for congestive heart failure (CHF) [11]. Choosing the most appropriate primary endpoint is essential for the success and acceptance of a trial, as well as for the progress of clinical practice.

A randomized clinical trial is ultimately a designed statistical experiment. Several key statistical concepts will be reviewed below: type I error, primary endpoint test statistic, treatment effect, statistical power, and sample size.

There is always a possibility that the analysis of study data may show a difference between treatments in a particular trial even when such a difference does not actually exist in the population under study. This mistaken conclusion can result from random variation, because the group of patients enrolled into a particular trial is a random group drawn from the pool of all eligible patients. Such an incorrect conclusion, known as a *type I error*, can have serious consequences, as it may lead to a therapy that in reality is ineffective being mistakenly introduced into medical practice. A 5 % chance of such an error is typically considered as the maximum acceptable. In addition, even though one always hopes that the new treatment will prove beneficial, it is important to consider a two-sided type I error.

The primary analysis compares the occurrence or value of the primary endpoint across treatment arms by means of a statistical test. The form of the suitable *primary endpoint test statistic* depends on the type of primary outcome and the analysis technique. Outcomes can be continuous (e.g., distance walked in 6 min) or binary (e.g., death). Time-to-death can be informative and time-to-event (survival) analysis is often used when the primary endpoint is death or an event that occurs during follow-up. Although the full statistical analysis plan can be prepared separately, the primary endpoint statistical test and the corresponding test statistic need to be specified in the study protocol.

The magnitude of the hypothesized treatment difference (*treatment effect*) needs to be clinically relevant and should be large enough to have an impact on medical practice if observed in a trial. For example, for all-cause mortality, we may consider a 30 % relative reduction in risk of death as the treatment effect we would like to detect. A large treatment effect is easier to detect, and

such a trial requires fewer patients than one attempting to detect a small treatment effect. A trial to detect a very small difference between or among treatments can be designed by considering a sufficiently large number of subjects, but such a difference, even if detected, may not matter in medical practice.

Statistical power is the chance of detecting a prespecified treatment effect if such an effect truly exists. Commonly, a definitive clinical trial requires statistical power to be 90 % or higher. Power of 80 % is occasionally accepted if achieving 90 % power is not feasible. Small underpowered trials may serve for pilot studies, but low statistical power means that researchers cannot have high confidence that a statistically insignifiant result is due to an actual lack of difference between treatments, rather than simply due to a sample size that was insufficient for detection of a clinically meaningful treatment effect.

A sufficient statistical power can be achieved in a trial by considering enough patients or, in other words, considering a large enough *sample size*. Sample size considerations can be contemplated only after the primary endpoint is defined and the method of analysis (primary endpoint test statistic) is chosen. A clinically relevant magnitude of the treatment effect needs to be considered as well. For a chosen treatment effect, the sample size is commonly calculated by accepting a 5 % chance of a type I error (two-sided) and by requiring statistical power to be at least 80 % (but preferably 90 % or higher). Statistical power for trials in which time-to-event analysis is considered depends on the number of events rather than just the number of patients. Various types of follow-up scenarios can be considered in order to accrue the required number of events. Patients can be followed for the same period of time, or until the last enrolled patient has been followed for a minimum reasonable period of time. In the second scheme, all but the last patient are followed for more than such a minimum time, because enrollment is spread over time. Such a design, incorporating a flexible length of follow-up, may need smaller sample size (fewer patients) to achieve the required statistical power.

Sample size can be often computed using a formula that incorporates treatment effect size, type I error, and statistical power. It is also worthwhile to consider simulations as a means of designing clinical trials, especially in nonstandard situations. Simulations consist of repeated random draws of a fixed-size sample from distributions reflecting the standard treatment and experimental arm endpoints. An example of nonstandard situation may be a clinical trial in which subjects assigned to one arm receive a drug and those assigned to the other receive a surgical intervention, and it is possible that patients initially randomly assigned to the drug arm will undergo surgery as a consequence of principles guiding best current medical practice. Such an occurrence sometimes referred to as a "crossover," will lead to departure from the proportional hazards assumption commonly used to compute sample sizes for time-to-event data. The crossover will change event rates in the drug therapy arm when results are analyzed according to the ITT principle, thus affecting the sample size. The timing of such a crossover can also have an impact on the required sample size and can be rather easily explored within the simulations framework. Although formulas for sample size in many nonstandard situations are available under more or less restrictive assumptions, simulations can provide an intuitive and flexible complementary approach to clinical trial design.

It is important to remember that sample size is only an estimate based on best available assumptions about event rates, effect size, or other summary quantities relevant to a particular trial or primary endpoint. Thus, a range of possible design assumptions needs to be considered, and sample size should be chosen conservatively to be the largest feasible within the range of these assumptions.

There are many other issues to be considered when designing a clinical trial. Secondary endpoints may be of interest and should be prespecified. Subgroup analyses may be planned, although subgroup comparisons will likely lack statistical power. Subgroup analyses should be prespecified in the protocol as much as possible, in order to avoid uncontrolled multiplicity of comparisons. Randomization may be stratified not only by center but also by known risk factors. The ability to pool treatment effects over centers

in multicenter clinical trials must be evaluated, especially for trials of medical devices. Adaptive designs for clinical trials are actively investigated [12] but not yet generally accepted. These designs may provide benefits; however, they are considered controversial by some researchers [13]. However, interim statistical analyses are commonly done during the course of a trial; such repeated analyses require proper statistical properties [1, 14]. Use of these methods may provide a statistical argument for stopping a clinical trial early due to observed efficacy or due to a low chance of detecting the predefined treatment effect. The interim results need to be carefully and confidentially reviewed by a Data and Safety Monitoring Board (DSMB).

The main result and summary of statistical power, analysis, and the follow-up approach of selected completed pivotal clinical trials pertinent to the prevention of sudden cardiac death are presented in Table 31.1 and summarized briefly below.

The Multicenter Unsustained Tachycardia Trial (MUSTT) [15] showed that electrophysiologically guided antiarrhythmic therapy with implantable defibrillators, but not with antiarrhythmic drugs, reduces the risk of sudden death in high-risk patients with coronary disease. Study was designed to have 90 % statistical power (with two sided 5 % type I error) to detect reduction in 2-year rate of arrhythmic events by at least 33 % if the no antiarrhytmic therapy group event rate is 20 %. There were 85 enrolling centers. Treatment groups were compared according to the intention-to-treat principle. Time-to-event (survival) analysis was used. All patients were followed until the end of the study. Interim analyses were performed.

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) [16] showed that in patients with a prior myocardial infarction and advanced left ventricular dysfunction, prophylactic implantation of a defibrillator improves survival. Trial was designed to have 95 % statistical power (with two sided 5 % type I error) to detect a 38 % reduction in 2 year mortality rate among the patients in the defibrillator group given a postulated 2-year mortality rate of 19 % among patients assigned to conventional therapy. There were 76 enrolling centers. Treatment groups were compared according to the intention-to-treat principle. All patients were followed until the end of the study and time-to-event analysis was used. Interim

Table 31–1 Selected completed pivotal clinical trials pertinent to the prevention of sudden cardiac death.

Trial	Primary end point	Treatment arms	Population
MUSTT [15] Total n = 704	Cardiac arrest or death from arrhythmia	Antiarrhythmic therapy guided by the results of electrophysiologic testing, including drugs and implantable defibrillators (n = 351) vs. No antiarrhythmic therapy (n = 353).	Patients with CAD, a LVEF of 40 % or less, and asymptomatic unsustained ventricular tachycardia. Randomization only for patients in whom sustained ventricular tachyarrhythmias were induced by programmed stimulation.
MADIT-II [16] Total n = 1232	Death from any cause	Prophylactically implanted defibrillator with no requirement of electrophysiological testing to induce arrhythmias (n = 742) vs. Conventional medical therapy (n = 490).	Patients with a prior myocardial infarction and a LVEF of 30 % or less.
DEFINITE [17] Total n = 458	Death from any cause	Standard oral medical therapy for heart failure (n = 229) vs. Standard oral medical therapy plus a single-chamber ICD (n = 229).	Patients with nonischemic dilated cardiomyopathy, a LVEF of less than 36 %, and premature ventricular complexes or nonsustained ventricular tachycardia.
SCD-HeFT [6] Total n = 2521	Death from any cause	Conventional therapy for CHF with each of the following: Placebo (n = 847) vs. Amiodarone (n = 845) vs. Conservatively programmed, shock-only, single-lead ICD (n = 829). Placebo and amiodarone given in a double-blind fashion.	Patients with mild-to-moderate heart failure with NYHA class II or III CHF and a LVEF of 35 % or less.

CAD coronary artery disease, *LVEF* left ventricular ejection fraction, *CHF* congestive heart failure, *ICD* implantable cardioverter – defibrillator, *NYHA* New York Heart Association

analyses were performed and at the recommendation of the Data and Safety Monitoring Board (DSMB) the trial was stopped early.

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial [17] reported that in patients with severe, nonischemic dilated cardiomyopathy who were treated with ACE inhibitors and beta-blockers, the implantation of a cardioverter – defibrillator significantly reduced the risk of sudden death from arrhythmia and was associated with a nonsignificant reduction in the risk of death from any cause. The primary end point of the study was death from any cause. Sudden death from arrhythmia was a prespecified secondary end point. The trial was initially designed to have 85 % statistical power (with one sided 5 % type I error), assuming 2-year mortality rates of 15 % in the standard-therapy group and 7.5 % in the implantable cardioverter – defibrillator (ICD) group. It was estimated that to observe the required 56 deaths one needs enrollment of 458 patients. In order to report results with the use of two-sided tests and the same statistical power, the follow-up was extended until the 68th death occurred. In retrospect, a two sided type I error should have been used in the initial design of the trial. Randomization was stratified according to center and to the use or nonuse of amiodarone for supraventricular arrhythmias. Treatment groups were compared according to the intention-to-treat principle. All patients were followed until the end of the study and time-to-event analysis was used. Interim analyses were performed.

Mentioned earlier the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [6] showed that in patients with New York Heart Association (NYHA) class II or III congestive heart failure (CHF) and a left ventricular ejection fraction (LVEF) of 35 % or less, amiodarone has no favorable effect on survival, whereas single-lead, shock-only implantable cardioverter – defibrillator (ICD) therapy reduces overall mortality by 23 %. The study was designed to have 90 % power (with the overall two sided 5 % type I error after accounting for two considered comparisons) to detect 25 % reduction in death from any cause by amiodarone or ICD therapy, as compared with placebo. It was assumed that the placebo group has an annual mortality rate of 10 %. Pairwise comparisons of amiodarone with placebo and ICD with placebo were performed according to the intention-to-treat principle. Since two comparisons were considered, each used a two sided 2.5 % type I error. Randomization was stratified by the enrolling center, the cause of CHF (ischemic vs. nonischemic), and NYHA class (II vs. III). All patients were followed until the end of the trial and time-to-event analysis was used. Interim analyses were performed.

Conducting a clinical trial is a complex undertaking, particularly when multiple centers are involved. Managing such complexity requires an established infrastructure. Success depends on many individuals understanding and executing their tasks appropriately and timely, following the study protocol, and focusing on details. Training of trial personnel prior to beginning of a study enrollment is essential, as is accurate evaluation of the timeliness and accuracy of data collection as the trial progresses.

In summary, a properly designed and executed randomized clinical trial requires substantial planning efforts [18], but such efforts will result in a well-run, ethical experiment with a convincing impact on medical practice.

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Part IV
Treatment and Prevention Modalities

Brian D. Powell, Win-Kuang Shen, Michael J. Ackerman, and Ihor Gussak

B.D. Powell, MD
Division of Cardiovascular Diseases,
Sanger Heart & Vascular Institute
Charlotte, NC, USA

W.-K. Shen, MD
Division of Cardiovascular Diseases,
Department of Medicine,
Mayo Clinic College of Medicine,
Mayo Clinic Arizona, Phoenix, AZ, USA
e-mail: wshen@mayo.edu

M.J. Ackerman, MD, PhD, FACC
Department of Medicine, Division of Cardiovascular Diseases, Department of Pediatric and Adolescent Medicine, Division of Pediatric Cardiology,
Department of Molecular Pharmacology and Experimental Therapeutics,
Mayo Clinic, Rochester, MN, USA
e-mail: ackerman.michael@mayo.edu,
haglund.carla@mayo.edu

I. Gussak, MD, PhD, FACC
Ono Pharmaceutical USA,
Lawrenceville, NJ, USA

Department of Internal Medicine,
University of Medicine and Dentistry of New Jersey,
Robert Wood Johnson Medical School,
New Brunswick, NJ, USA
e-mail: igussak@hotmail.com

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Introduction to Part IV: Treatment Modalities

Mark E. Josephson

The field of cardiac electrophysiology has moved from one of diagnosis and understanding of mechanisms to one of pharmacological, electrical, and catheter- or surgical-based ablative therapy to treat arrhythmias. This section, Part IV, edited by Powell, Shen, Ackerman, and Gussak discusses the major therapeutic modalities used to treat bradyarrhythmias and tachyarrhythmias as well as the use of electrical therapies to treat heart failure; most importantly, two chapters discuss the morbidity of implantable defibrillators implantation and how to minimize the morbidity and increase the cost effectiveness of sudden death prevention using these devices.

The role of antiarrhythmic drugs in the prevention of sudden death it is discussed in Chaps. 33 and 34. In the past two decades it has been shown that standard Class I and Class III antiarrhythmic agents are not as effective in preventing sudden cardiac death as implantable cardioverter defibrillators (ICDs). This includes amiodarone, which for many years was touted as being a useful agent to prevent sudden death. Beta blockers remain the one agent that generally impacts cardiac survival. This is no way detracts from the potential ability of antiarrhythmic agents to decrease the incidence as well as the rate of monomorphic ventricular tachycardia, which is not life threatening, but can be hemodynamically debilitating. In addition, antiarrhythmic agents may still be needed to treat other arrhythmias such as atrial fibrillation, which, in and of themselves, may be proarrhytymic. Thus, while the specific use of antiarrhytymic agents for reduction of sudden death has been superseded by the use of ICDs, antiarrhythmic agents still may be necessary to slow or prevent non-life-threatening arrhythmias or make them pace-terminatable or ablatable. Recent information suggests that in certain genetically determined disorders Class I agents may be useful, i.e. long QT3, early repolarization syndromes, catecholaminergic ventricular tachycardia, and idiopathic ventricular fibrillation.

A major advancement in our understanding of pharmacological agents in preventing sudden cardiac death has been the recognition of the potential role of nonantiarrhythmic agents such as angiotensin-converting enzyme inhibitors (ACEI), antialdosterone agents, statins, and polyunsaturated fatty acids, especially fish oils. While there are no prospective randomized trials using these agents primarily for there antiarrhythmic effect, their use in patients with CHF and hypertension is associated with less arrhythmias. The long and established role of beta blockers has been recognized, finally, by the entire cardiology community; they constitute a group of agents that has consistently been of benefit in reducing cardiac sudden death. However, neither the exact

M.E. Josephson, MD
Cardiovascular Medicine Division,
Harvard Medical School, Harvard-Thorndike Electrophysiology Institute and Arrhythmia Service,
Beth Israel Deaconess Medical Center,
185 Pilgrim Rd., Baker 4 West,
Boston, MA 02215, USA
e-mail: mjoseph2@bidmc.harvard.edu

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mechanism by which beta blockers work nor whether all beta blockers are equal has been established. Both ACEIs and angiotensin receptor blockers have been associated with a reduction of sudden death, as have antialdosterone agents. These data are gathered from clinical trials of heart failure and hypertension and as such the specificality of the drugs for prevention of sudden cardiac death is unknown. These drugs may be antifibrotic, but may have other mechanisms of action. Recent experimental evidence has shown that ACEIs can actually improve cell-to-cell coupling, which may in turn facilitate propagation and be antiarrhythmic in that way. The role of the statins is not clear, but is generally believed to be related to anti-inflammatory activity, which may in tern decrease substrate formation. Fish oils appear to reduce sudden cardiac death due to membrane active effects. More work is necessary to understand the mechanisms of these agents before a well-defined role in the specific prevention of sudden cardiac death can be applied. The absolute benefits of all of these drugs are small.

In terms of ICD therapy, it has been established that ICDs prevent sudden death better than drugs. However, there are emerging data that distinguish between patients in whom the device should be implanted and patients who not only will derive no benefit from implantation but for whom there may be excessive morbidity from the device. These are related to age, gender, and a variety of co-morbidities. The technical and clinical issues of ICD therapy implantable defibrillator morbidity is discussed in Chaps. 39 and 40. In my opinion appropriate risk stratification to eliminate those patients who do not need a device is increasingly important. This relates to the cost effectiveness of the devices and the number of devices that need to be implanted to save one life. In my opinion, the Primary Prevention Trials demonstrates a lack of cost effectiveness of the devices. When actually measured, the cost effectiveness is unacceptable to society. Considering that in an SCDHeft population there is only a 1 % per year enhanced survival from sudden cardiac death (1.4 % total mortality per year benefit), the majority of patients in whom a device will be implanted will not obtain a significant benefit and will be subjected to the potential morbidity and mortality associated with implantation. A recent study of a Medicare population found a 0.9 % mortality (30 days) in patients undergoing ICD implantation and a 10.8 % morbidity. It is generally believed that approximately 1 % of the devices will need to be removed because of infection, and that the second and third implants will have two to three times the infection rate. Since many primary prevention devices may lead to repeat implantations, the cost effectiveness will be unacceptable unless patients are risk stratified. Moreover, the morbidity of ICDs will far exceed the benefits. In implantation of a device prevents sudden cardiac death in only a small number of patients, the actual number of people receiving inappropriate therapies due to other arrhythmias, sensing problems, or lead fractures will exceed those receiving appropriate therapies. Moreover, it is unclear s to whether the devices may in fact be proarrhythmic.

In my opinion the primary goal of therapy should be to prevent the arrhythmia in the first place. Catheter and surgical ablation offer that potential. A significant amount of knowledge is available concerning the arrhythmogenic substrate in coronary artery disease with growing information on noncoronary substrates. Since coronary artery disease with prior infarction is the major substrate for ventricular tachycardia as well as fibrillation, understanding that substrate will lead to the ability to reduce or eliminate ventricular tachycardia and fibrillation. Revascularization is always a primary form of therapy, particularly for ventricular fibrillation associated with small scars and ejection fractions exceeding 45 %. In my opinion, surgical intervention for revascularization is probably the best therapy for such patients. When scar formation is extensive, revascularization alone is not useful. However, arrhythmia surgery is extremely valuable in preventing sudden death due to sustained ventricular arrhythmias in patients with prior infarction and ejection fractions less than 40 %. My personal experience with surgery for ventricular tachycardia and fibrillation demonstrated an efficacy exceeding that of ICDs in preventing sudden death or ventricular tachycardia, while at the same time providing revascularization and ventricular remodeling for the patients, resulting in improvement of their heart failure and ischemia. A surgical intervention may provide

the best single approach to preventing malignant ventricular arrhythmias in the setting of coronary artery disease. I believe that we should return to the concept that the primary goal of therapy for arrhythmias is to prevent them in the first place. That can be done by preventing the disease process that causes the substrate (i.e., ischemic heart disease) or by destroying or removing the substrate responsible for the arrhythmia (i.e. surgical resection or catheter ablation). Therefore ICD therapy should be considered a safety valve until we better understand the underlying substrate mechanism of arrhythmias so that we can prevent their occurrence.

Chapter 35 discusses non-surgical treatment of atrial fibrillation including rate vs rhythm control with drugs or ablation. New anticoagulation agents are becoming available and the recognition of the necessity of to anticoagulation no matter what therapeutic course is taken is appropriately stressed. The limitations of AF ablation are recognized.

Chapter 36 describes the surgical treatments for atrial fibrillation. There is a marked discrepancy between results of surgery and catheter ablation most of which is due to the definition of success – actuarial vs Kaplan Meyer analysis of survival, extent of monitoring vs clinical symptoms; inclusion or exclusion of other atrial arrhythmias. My experience suggests a much lower success rate when extensive monitor is used to assess recurrences on a Kaplan Meyer basis. The Mini-Maze is quite useful for patients who have had recent strokes and/or who can't take Coumadin or other anticoagulants. Standardization of follow up methodologies and definitions is required to assess the role of surgery for atrial fibrillation.

Chapters 37 and 38 describe catheter ablation techniques for triggered VT and polymorphic tachycardia and scar dependent VT. While the Haissaquerre group (Chap. 37) has a large experience in ablation VPC triggers the source of these triggers (muscle vs purkinje fibers) need validation. There should be a requirement that the triggering VPC be documented on a 12 lead ECG since multiple VPCs may be present from disparate sites which appear similar in on a holter or ECG. More work is needed to establish the role of this approach which can be successful in treating VT/VF storm in highly selected patients.

Ablation of scar related tachycardia arising on the endocardium and epicardium are beautifully explained in Chap. 38. The variety of mapping techniques and limitations are clearly articulated. There is probably an expanding role for ablation in preventing ICD shocks in patients post infarct. The role of preventative ablation in cardiomyopathy is less certain because we do not understand the pathophysiology as well.

This section provides all of the current available information on modern electrophysiological therapy for arrhythmias and I believe provides a challenge to all of us to seek the ultimate goal of preventing the problem in the first place.

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Clinical Role of Antiarrhythmic Drugs in the Prevention of Sudden Death

Hon-Chi Lee and Kristin T.L. Huang

Abstract

The role of antiarrhythmic drugs for prevention of sudden cardiac death has changed dramatically in the past 20 years. Though antiarrhythmics were once considered first-line therapy for the prevention of sudden death, clinical trials that demonstrated the proarrhythmia effects of Class I antiarrhythmics and others that established the superiority of implantable cardioverter defibrillator (ICD) implantation over amiodarone have driven ICD therapy to supplant antiarrhythmics as the standard of care in patients at high risk for sudden death. Based on current evidence, there is no role for Class I antiarrhythmics as the primary therapy for prevention of sudden death, and most Class III antiarrhythmics, including amiodarone, do not improve survival.

Yet antiarrhythmic drugs remain frequently used. They may be clinically important in specific subsets of patients, such as in those with only moderate reductions in LV function, Brugada Syndrome, LQT Syndrome, or catecholaminergic polymorphic VT. Moreover, due to the negative impact of ICD shocks on quality of life, antiarrhythmics have become an important and widely used adjunctive therapy in patients with ICDs. Amiodarone, d,l-sotalol, and azimilide may help reduce both appropriate and inappropriate ICD therapies, and β-blockers and antiarrhythmics are used to treat electrical storm. Concerns that some antiarrhythmics may increase defibrillation threshold (DFT) and render ICD therapy ineffective may be allayed in light of advancements in ICD technology. Nevertheless, further investigation into this and other potential adverse interactions between antiarrhythmics and ICDs is needed.

Keywords

Sudden death • Antiarrhythmic drugs • ICD • Clinical trials • Primary prevention • Secondary prevention • Appropriate and inappropriate ICD shocks

H.-C. Lee, MD, PhD (✉)
Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Medical School, Mayo Clinic, Rochester, MN, USA
e-mail: lee.honchi@mayo.edu

K.T. L. Huang, MD
Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115
e-mail: kthuang@partners.org

Introduction

The role of antiarrhythmic drugs in the prevention of sudden cardiac death has changed radically in the last 20 years. With the development of intracardiac recordings and programmed electrical stimulation techniques, electrophysiology

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(EP)-guided drug therapy was considered the standard of care in the 1980s. Class I antiarrhythmic drugs were effective in suppressing VT induced by programmed electrical stimulation in many patients in the EP laboratory, yet long-term follow-up demonstrated that these patients continued to have poor outcomes [1]. The results of the Cardiac Arrhythmia Suppression Trial (**CAST**) dealt a death blow to Class I antiarrhythmic drugs and to the hypothesis that suppression of ventricular ectopic activities in post MI patients would reduce the risk of sudden death. The landscape for prevention of sudden cardiac death has since been completely reshaped.

Class I Antiarrhythmic Drug Trials

The International Mexiletine and Placebo Antiarrhythmic Coronary Trial (**IMPACT**) showed that mexiletine was effective in reducing complex and frequent ventricular ectopies in patients with a recent MI, but mortality was higher in the mexiletine group [2, 3]. While the difference in mortality was not statistically significant, these results were a harbinger of what would soon re-define the use of antiarrhythmic drugs in patients at high risk of sudden cardiac death.

CAST was a paradigm-shifting multi-center randomized double-blinded study showing that while the Class IC antiarrhythmic drugs encainide and flecainide were effective in suppressing ventricular ectopies in patients with a history of MI, these drugs were associated with a threefold increase in mortality compared with control, leading to the premature termination of the trial by the Safety Monitoring Board [4].

CAST II evaluated the risk and efficacy of moricizine on survival after MI in patients whose ventricular ectopic activities were adequately or partially suppressed by moricizine. The trial was terminated prematurely because treatment with moricizine was associated with excess mortality in the first 14-day period and lacked long-term efficacy compared to placebo [5].

The findings of the CAST studies were shocking, popularizing the concept of pro-arrhythmia and emphasizing the need to use mortality rather than surrogate markers as the primary end-point in clinical trials. A major consequence of the CAST results was the dramatic curtailing of the use of Class I antiarrhythmic drugs for treating arrhythmias in patients with structural heart disease. A metaanalysis of 61 randomized controlled trials involving 21,486 patients showed increased all-cause mortality with the use of Class I antiarrhythmic drugs [6]. Current evidence indicates that Class I antiarrhythmic drugs are contraindicated in patients with a history of MI and has no role in primary prevention of sudden death in these patients (Table 33.1) [7].

Class II Antiarrhythmic Drug Trials

According to the Vaughan-Williams classification, β-adrenergic blockers are Class II antiarrhythmic drugs, but with the exception of sotalol, β-blockers do not have membrane active properties. Several randomized controlled clinical trials have shown that β-blockers are effective in reducing all-cause mortality in patients after an MI with LV dysfunction, including the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) [8], the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) [9], the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study [10], and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study (Table 33.1) [11].

Besides their beneficial effects in patients with coronary artery disease and congestive heart failure, β-blockers are known to be efficacious in the treatment of idiopathic right ventricular outflow tract VT [12], and catecholaminergic polymorphic VT [13]. In patients with a history of VT/VF, the use of β-blockers is independently associated with improved survival [14]. Indeed, β-blockers are safe and effective in reducing sudden death in patients with cardiac disorders and are considered the mainstay of antiarrhythmic drug therapy [7].

Class III Antiarrhythmic Drug Trials

The Electrophysiology Study Versus Electrocardiographic Monitoring (**ESVEM**) trial randomized patients with a history of VT/VF, cardiac arrest or syncope with inducible sustained VT/VF to serial EP-guided or serial Holter-guided antiarrhythmic drug therapy,

Table 33–1. Antiarrhythmic drug trials in patients at high risk of sudden death

Trial	Number of patients	Patient characteristics	Treatment design	Follow-up duration	Major findings
Class I Antiarrhythmic trials					
IMPACT	630	Recent MI, frequent complex ventricular arrhythmias	Mexiletine vs. placebo	12 months	1. Mexiletine significantly suppressed ventricular arrhythmias 2. Mexiletine trend towards increased mortality (7.6 % vs. 4.8 % in placebo, p = N.S.)
CAST	1,498	6 day to 2 year after MI, PVC >6/h LVEF < 55 % for MI within 90 days, LVEF < 40 % for MI greater than 90 days	Placebo vs. encainide vs. flecainide	10 months	Study was prematurely terminated. 1. Significant increase in mortality in encainide/flecainide group (7.7 %) vs. placebo (3 %), p = 0.0004 2. Significant increase in cardiac arrest in encainide/flecainide group (4.5 %) vs. placebo (1.2 %), p = 0.0004 3. Encainide/flecainide was effective in suppressing PVCs
CAST II	1,155	Same as CAST	Moricizine vs. placebo	14 days, 3 years	1. Exposure phase showed excessive mortality in moricizine group (2.6 % vs. 0.5 % in placebo) 2. Study was prematurely terminated. Long-term phase showed lack of benefit from treatment with moricizine 3. Moricizine was effective in suppressing PVCs
Class II Antiarrhythmic trials					
MERIT-HF	3,991	Class II-IV CHF, LVEF < 40 %	Metoprolol	1 year	1. Metoprolol lowered all-cause mortality by 34 % (7.2 % vs. 11 % in placebo group, p = 0.00009) 2. Sudden death was reduced by 41 % (79 vs. 132 in placebo group, p = 0.0002) 3. Metoprolol reduced deaths from worsening CHF by 49 % (30 vs. 58 in placebo, p = 0.0023)
CIBIS II	2,647	Class III-IV CHF, LVEF ≤ 35 %	Bisoprolol	1.3 years	Bisoprolol showed a mortality benefit 1. All-cause mortality (11.8 % vs. 17.3 % in placebo, p < 0.0001) 2. Sudden death (3.6 % vs. 6.3 % in placebo, p = 0.0011)
COPERNICUS	2,289	Class III-IV CHF, LVEF ≤ 25 %	Carvedilol	10.4 months	Carvedilol reduced: 1. All-cause mortality by 35 % (11.2 % vs. 16.8 % in placebo group, p = 0.0014) 2. The combined risk of death or hospitalization by 24 %
CAPRICORN	1,959	Post-MI, LVEF ≤40 %	Carvedilol	1.3 years	Carvedilol lowered: 1. all-cause mortality by 23 % (12 % vs. 15 % in placebo, p = 0.03) 2. Cardiovascular mortality, non-fatal MI 3. VT/VF (0.9 % vs. 3.9 % in placebo group, p < 0.0001)
Class III Antiarrhythmic trials					
ESVEM	486	h/o VT/VF, cardiac arrest or inducible VT/VF	EP-or Holter-guided anti-arrhythmic drug therapy (sotalol and Class I drugs)	6 years	1. No difference between EP- and Holter-guided therapies in predicting drug efficacy in preventing death or recurrence of arrhythmia 2. Sotalol was superior to Class I drugs 3. High recurrence of arrhythmia (50.7 %) and death (15.5 %) among patients in whom drugs were predicted to be effective

(continued)

Table 33–1. (*continued*)

Trial	Number of patients	Patient characteristics	Treatment design	Follow-up duration	Major findings
SWORD	3,121	LVEF ≤40 %, recent MI or remote MI with CHF	d-sotalol vs. placebo	148 days	1. Increased mortality in d-sotalol group (5 %) vs. placebo (3.1 %) (65 % increase in risk, p = 0.006) 2. d-Sotalol group showed 77 % increase in arrhythmia death (p = 0.008)
DIAMOND	1,510	Within a mean of 3 days of acute MI, LVEF ≤35 %	Dofetilide vs. placebo	15 months	1. No difference in all-cause mortality, cardiac mortality, or total arrhythmic death between the two groups 2. Dofetilide was significantly more effective than placebo in restoring sinus rhythm in patients with AF, p = 0.002
Amiodarone trials					
BASIS	312	h/o MI asymptomatic complex VEA (Lown class 3 or 4b)	Amiodarone vs. individualized antiarrhythmic drugs (mostly quinidine or mexiletine) vs. no anti-arrhythmic drug (control)	1 year	1. Amiodarone group had significantly higher survival rate (p < 0.05) and lower arrhythmia events vs. control (p < 0.01), 2. Individualized antiarrhythmic group not significantly different vs. control
PAT	613	Post acute MI not eligible for β-blocker	Amiodarone vs. placebo	1 year	1. Amiodarone group showed significant reduction in cardiac death (p = 0.048) and in Lown class 4b VEA (p < 0.001) but not in all-cause mortality 2. Thirty percent in amiodarone group developed adverse effects vs. 10 % in placebo group 3. Sub-study showed that amiodarone significantly reduced long-term mortality (9.1 % vs. 16.5 %, p < 0.05) and sudden death (3.4 % vs. 8.2 %, p < 0.05) only in patients with LVEF ≥40 %
SSSD	368	10–60 days after acute MI LVEF 20–45 % ≥3 PVCs/h (pairs or runs)	Amiodarone vs. metoprolol vs. no antiarrhythmic	2.8 years	1. Mortality in amiodarone group (3.5 %) not different from control (7.7 %) but significantly lower than metoprolol group (15.4 %), p = 0.006 2. Amiodarone significantly reduced PVCs
CASCADE	288	Out-of-hospital VF without Q wave MI, >10 PVCs/h, or inducible VT/VF (mean LVEF 35 %, 45 % had CHF, 46 % had ICD)	Amiodarone vs. Holter- or EP-guided antiarrhythmic (conventional) therapy	6 years	1. Amiodarone group had significant reduction in combined end-point of cardiac death, resuscitated VF, or syncopal ICD shocks (47 % vs. 60 % in control, p = 0.007) 2. Amiodarone group had significant reduction in cardiac and sustained ventricular arrhythmias (59 % vs. 80 % in control, p < 0.001) 3. Overall mortality was high and side effects of therapy were common
EMIAT	1,486	5–21 days after MI LVEF <40 %	Amiodarone vs. placebo	21 months	1. No difference in all-cause mortality between two groups 2. Amiodarone group had 35 % risk reduction in arrhythmia deaths
CAMIAT	1,202	6–45 days after MI >10 PVCs/h or NSVT	Amiodarone vs. placebo	1.79 years	1. There was no difference in all-cause mortality between the two groups 2. Amiodarone group had reduced risk of VF or arrhythmic death (3.3 % vs. 6 % in placebo, p = 0.016)

(continued)

Table 33–1. (*continued*)

Trial	Number of patients	Patient characteristics	Treatment design	Follow-up duration	Major findings
GESICA	516	Advanced chronic CHF, NYHA II-IV, LV systolic dysfunction	Amiodarone vs. placebo	13 months	1. Amiodarone reduced totally mortality by 28 % ($p = 0.024$) and hospitalization due to CHF by 31 % ($p = 0.0024$) compared to placebo 2. Sub-study showed that NSVT was an independent risk factor for sudden death ($p < 0.002$) 3. 61 % of the patients had dilated cardiomyopathy and Chagas disease
CHF-STAT	674	NYHA Class II-IV CHF LVEF ≤40 % >10 PVCs/h	Amiodarone vs. placebo	45 months	1. No difference between the two groups in overall mortality and in sudden death 2. Trend favoring amiodarone in reducing mortality in patients with nonischemic cardiomyopathy ($p = 0.07$) 3. Amiodarone significantly improved LV function (LVEF increased by 42 %) compared to placebo 4. A sub-study showed that amiodarone was more effective in controlling ventricular rate in AF and conversion to sinus rhythm

which included Class I antiarrhythmics and sotalol, but not amiodarone [15]. However, over a 6-year follow-up period, 50.7 % of the 296 patients receiving the drugs predicted to be effective experienced recurrence of arrhythmia and 15.5 % died. The high rate of recurrence suggested that the effectiveness of these approaches in the treatment and prevention of sudden cardiac death is limited.

Disappointingly, the Survival With Oral d-Sotalol (**SWORD**) trial found that *d*-sotalol, which lacks β-adrenergic blocking properties, increased both arrhythmic and total mortality in patients with history of MI and left ventricular (LV) dysfunction [16].

The Danish Investigation of Arrhythmia and Mortality on Dofetilide (**DIAMOND-MI**) found that dofetilide did not increase mortality in patients with recent MIs and LV dysfunction [17]. The Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure (**DIAMOND-CHF**) Study similarly found that in patients with reduced LV function and CHF ($n = 1{,}518$), overall mortality was similar between placebo (42 %) and dofetilide (41 %) patients. Dofetilide was effective in converting atrial fibrillation to sinus rhythm, in maintaining sinus rhythm, and in reducing the risk of hospitalization for worsening CHF [18]. These results suggest that dofetilide is safe to use for control of atrial arrhythmias in patients with CHF but does not confer survival benefits. Importantly, the dofetilide group had a 3.3 % incidence of torsade de pointes versus none in the placebo group. Most of these events (76 %) occurred within the first 3 days of drug treatment, underscoring the importance of initiating dofetilide therapy in the hospital.

Azimilide is a Class III antiarrhythmic drug which blocks both the rapid and slow components of the delayed rectifier K^+ currents (I_{Kr} and I_{Ks}). The Azimilide Post Infarct Survival Evaluation (**ALIVE**) study showed no difference in all-cause mortality, in cardiac or arrhythmic mortality between the azimilide and placebo groups [19]. ALIVE subgroup analysis, however, showed that in the azimilide group, fewer patients developed atrial fibrillation, more patients converted to sinus rhythm, and more patients stayed in sinus rhythm than in the placebo group [20].

Dronedarone is a newer Class III antiarrhythmic drug and is a structural analog of amiodarone but without many of the serious adverse effects of amiodarone. Dronedarone has been shown to be effective in treating atrial fibrillation. **ATHENA** was a placebo-controlled, double-blind

study that found that in patients with atrial fibrillation, after a mean follow-up period of 21 ± 5 months, dronedarone did not improve all-cause mortality but significantly reduced cardiovascular mortality, mainly by lowering the rate of death from arrhythmia [21]. Post-hoc analysis showed that dronedarone significantly reduced the risk of stroke by 34 % and is one of the only antiarrhythmic drugs that has demonstrated improved patient outcome in treating patients with arrhythmias [22]. However, results from the **ANDROMEDA** trial showed that dronedarone was associated with excess mortality due to worsening heart failure [23]. Hence, unlike amiodarone, the use of dronedarone is contraindicated in patients with heart failure and reduced systolic LV function.

Amiodarone Trials

The Basal Antiarrhythmic Study of Infarct Survival (**BASIS**) examined the effect of prophylactic antiarrhythmic treatment on patients with persistent asymptomatic complex ventricular arrhythmias after MI [24]. During the 1-year follow-up period, patients receiving low dose amiodarone (200 mg/day) had significant reduction in mortality ($p < 0.05$) and arrhythmia events ($p < 0.01$) compared to the control group, suggesting that amiodarone reduces mortality in the year after MI in patients at high risk for sudden cardiac death. A subsequent report after a mean follow-up of 72 months found that mortality remained significantly lower in the amiodarone group versus the control group [25].

The Polish Amiodarone Trial (**PAT**) studied high-risk post-MI patients ineligible to receive β-blockers who were randomized to receive amiodarone or placebo for 1 year. The results showed significant reductions in the amiodarone group for cardiac mortality ($p = 0.048$) and for Lown class 4 ventricular arrhythmias ($p < 0.001$), but not for all-cause mortality. In addition, 30 % of the patients who received amiodarone experienced adverse effects compared to 10 % of those who received placebo [26].

The Spanish Study of Sudden Death (**SSSD**) enrolled 368 post-MI patients with LVEF of 20–45 % and ≥3 PVC/h in the form of pairs or runs [27]. The patients were randomized to receive amiodarone 200 mg/day, metoprolol 100–200 mg/day, or no antiarrhythmic treatment. After a median follow-up of 2.8 years, mortality in the amiodarone group was not significantly different from that of the untreated control group, but was lower than that in the metoprolol group. Follow-up Holter studies showed that only amiodarone significantly reduced ventricular ectopic activities ($p < 0.0001$).

Amiodarone was the last antiarrhythmic stronghold and was the focus of a number of multi-center clinical trials [28]. The Cardiac Arrest in Seattle: Conventional vs. Amiodarone Drug Evaluation (**CASCADE**) [29] enrolled survivors of out-of-hospital VF not associated with a Q-wave acute MI, who were randomized to empirical amiodarone or Class I antiarrhythmic drugs guided by EP or Holter studies. The combined endpoint of survival free of cardiac death, resuscitated VF, or syncopal defibrillator shocks was significantly better in patients treated with amiodarone than in those treated with other antiarrhythmic drugs (amiodarone 53 % vs. conventional arrhythmic 20 %, $p < 0.001$), but overall mortality was relatively high and side effects were common.

The European Myocardial Infarct Amiodarone Trial (**EMIAT**), a multicenter randomized, double-blind placebo-controlled study, found that in survivors of MI with an LVEF ≤40 % ($n = 1{,}486$), arrhythmia deaths were reduced by 35 % in the amiodarone group ($p = 0.05$ vs. placebo group), but there was no difference in all-cause or cardiac mortality over a mean follow-up of 21 months [30]. Similar to EMIAT, The Canadian Amiodarone MI Arrhythmia Trial (**CAMIAT**) was a multicenter, randomized, double-blind, placebo-controlled trial that found that in survivors of acute MI with frequent or repetitive PVCs ($n = 1{,}201$), resuscitated VF or arrhythmic death was significantly lower in the amiodarone group ($p = 0.016$ vs. placebo group) over a mean follow-up of 1.79 years [31]. However, all-cause mortality was similar between the two groups.

A recent meta-analysis of 15 randomized controlled trials ($n = 8{,}522$ patients) examining the use of amiodarone vs. placebo for the prevention of sudden death showed amiodarone significantly reduced the risk of sudden cardiac death by 29 %

and cardiovascular death by 18 %. However, amiodarone was neutral to all-cause mortality and was associated with a two- and five-fold increased risk of pulmonary and thyroid toxicity [32]. It was suggested that amiodarone can be considered a viable alternative in patients who are not eligible for or who do not have access to ICD therapy for the prevention of sudden cardiac death.

Class IV Antiarrhythmic Drug Trials

Calcium channel antagonists have been used mainly for treatment of hypertension and coronary artery disease. A recent meta-analysis of 15 randomized controlled trials involving 47,694 patients with coronary artery disease showed that treatment with long-acting calcium channel blockers did not change all-cause mortality, cardiovascular mortality, non-fatal MI or heart failure but significantly reduced the risk of stroke and risk of angina pectoris compared with placebo [33]. Similar conclusions were obtained from another meta-analysis of 26 randomized controlled trials involving 21,644 patients who had a previous MI [6]. Calcium antagonists are not considered to be effective for prevention of sudden death but are known to be efficacious in treating specific arrhythmias such as idiopathic ventricular outflow tract VT [34], idiopathic left ventricular fascicular VT [35], and catecholaminergic polymorphic VT [36, 37].

Other Antiarrhythmic Drug Trials

Ranolazine, marketed as an anti-anginal drug, is an inhibitor of the late Na^+ current with antiarrhythmic properties. The MERLIN-TIMI 36 trial randomized 6,560 patients with acute coronary syndrome and showed ranolazine had no effect on cardiovascular death or MI but was associated with a significant reduction in incidence of arrhythmias [38].

Ivabradine is a blocker of the pacemaker current I_f and is a novel medication for treatment of angina. The Systolic Heart Failure treatment with the I_f inhibitor Ivabradine Trial (SHIFT) enrolled 6,558 patients who were in sinus rhythm of ≥70 bpm with symptomatic heart failure and a LVEF ≤35 %. Treatment with ivabradine resulted in reduced hospital admission and death due to heart failure but had no significant effect on all-cause mortality or cardiovascular mortality [39].

Secondary Prevention Trials in Patients with Ischemic Cardiomyopathy – Antiarrhythmic Drugs vs. ICDs

In secondary prevention trials that include treatment with implantable cardioverter-defibrillators (ICDs), antiarrhythmic drugs, including amiodarone, have not measured up to ICDs, which showed a significant improvement in survival for patients at high risk of sudden cardiac death (Table 33.2). The Antiarrhythmic Versus Implantable Defibrillators (**AVID**) trial randomized 1016 patients who had survived life-threatening ventricular arrhythmias to ICD versus antiarrhythmic drugs, 97 % of whom received amiodarone while the rest received EP-guided sotalol therapy [40]. The trial was terminated prematurely because of a 39 % reduction of all-cause mortality in the ICD group.

Similarly, results from the Canadian Implantable Defibrillator Study (**CIDS**) [41] and the Cardiac Arrest Study Hamburg (**CASH**) [42] showed that non-significant reduction in all-cause and arrhythmic mortality in patients receiving ICDs versus antiarrhythmics drugs. However, subsequent meta-analysis and sub-analysis of the AVID, CIDS, and CASH results [41, 43] showed a significant risk reduction in total mortality (25–27 % decrease) and arrhythmic death (50–52 % decrease) in ICD patients ($p < 0.001$).

Primary Prevention Trials in Patients with Ischemic Cardiomyopathy – Antiarrhythmic Drugs vs. ICDs

Results from the secondary prevention trials firmly established the superiority of ICDs to antiarrhythmic drugs in reducing mortality in patients with ischemic cardiomyopathy who have had life-threatening ventricular arrhythmias. Several large multicenter primary prevention trials followed to examine the efficacy of

Table 33–2. Antiarrhythmic drugs vs. ICD trials

Trial	Number of patients	Patient characteristics	Treatment design	Follow-up duration	Major findings
Secondary prevention trials					
AVID	1,016	VF or sustained VT with syncope or with LVEF ≤40 % or with hemodynamic compromise	ICD vs. antiarrhythmic drug (97 % received amiodarone)	18 months	1. Study was stopped prematurely because overall survival was greater for the ICD group (39 % reduction in risk for death $p < 0.02$) 2. Sub-analysis showed that in patients with LVEF ≥35 % ICD therapy had no survival benefit
CIDS	659	VF, cardiac arrest, sustained VT with syncope or with symptoms and LVEF ≤35 %, or inducible VT	Amiodarone vs. ICD	36 months, 5.6 years	1. ICD group showed trend toward reduction in all-cause mortality (by 20 %) and arrhythmic death (by 32 %) but difference was not statistically significant ($p = 0.14$) 2. Follow-up study showed that survival benefit of ICD over amiodarone increases with time (27 % mortality vs. 47 % in amiodarone group, $p = 0.0213$ 3. Significant patient crossover in treatment, 27 % ICD patients received amiodarone and 21.4 % patients in the amiodarone group received an ICD. 4. Eighty-two percent of patients in amiodarone group developed side-effects 50 % of whom required discontinuation or dose reduction
CASH	288	Cardiac arrest or symptomatic VT	ICD vs. amiodarone, metoprolol or propafenone	57 months	1. Propafenone arm discontinued due to excess mortality 2. ICD group had a non-significant reduction in all-cause mortality (by 23 %) compared with amiodarone/metoprolol ($p = 0.08$) 3. ICD group had a significant reduction in risk of sudden death compared with the antiarrhythmic group ($p = 0.005$)
Primary prevention trials					
MADIT	196	h/o MI, NYHA I-III LVEF <35 %, NSVT with inducible non-suppressible VT	ICD vs. conventional medical therapy (80 % on amiodarone)	27 months	1. ICD group had significant reduction in cardiac mortality (12 % vs. 27 %) and in all-cause mortality (15 % vs. 39 % in conventional therapy group, $p = 0.009$) 2. Low level of β-blocker used (27 % in ICD group vs. 8 % in medical therapy group. 3. Forty-four percent of ICD patients took antiarrhythmics, 23 % in medical therapy group did not take antiarrhythmics

(continued)

Table 33–2. (*continued*)

Trial	Number of patients	Patient characteristics	Treatment design	Follow-up duration	Major findings
MUSTT	704	CAD with LVEF ≤40 %, NSVT Inducible VT	EP-guided antiarrhythmic or ICD therapy vs. no therapy	39 months	1. EP-guided therapy group had significant reduction in cardiac death (27 % decrease) and total mortality (20 % decrease) 2. All benefits in the EP-guided therapy group were due to ICD therapy. Sudden death was significantly reduced in ICD patients (9 % vs. 37 %) as was total mortality (24 % vs. 55 %) 3. Mortality was higher in antiarrhythmic group compared with the no therapy group
AMIOVERT	103	Nonischemic dilated cardiomyopathy LVEF ≤35 % Asymptomatic NSVT	Amiodarone vs. ICD	2 years	1. Study was stopped early because results were unlikely to show a difference between the two groups 2. Study had unusually low mortality rates
SCD-HeFT	2,521	NYHA II-III CHF, LVEF ≤35 %	Amiodarone vs. ICD vs. placebo	45 months	1. ICD group had significant reduction in total mortality vs. control or amiodarone groups ($p = 0.007$) 2. Most of the ICD benefits were due to reduction in arrhythmia death 3. Most of the ICD benefits occurred in those with Class II CHF and not in those with Class III symptoms

ICD versus antiarrhythmic drugs in patients with ischemic cardiomyopathy without prior significant ventricular arrhythmia events. The results of these trials further confirmed the dominance of ICD in the prevention of sudden cardiac death in patients with ischemic cardiomyopathy (Table 33.2).

The Multicenter Automatic Defibrillator Implantation Trial (**MADIT**) examined whether prophylactic ICD therapy, as compared with conventional medical therapy, would improve survival in patients with previous MI, LV dysfunction, and non-sustained VT [44]. The study was terminated after a mean follow-up of 27 months because the ICD group showed significant reduction in cardiac mortality (12 % vs. 27 %) and all-cause mortality (15 % vs. 39 %, $p = 0.009$) compared to patients on conventional medical therapy (80 % on amiodarone). However, MADIT was criticized for the relatively low level of β-blockers used overall, with a higher level of use in patients with ICD (27 % vs. 8 %).

The Multicenter Unsustained Tachycardia Trial (**MUSTT**) examined the usefulness of electrophysiological testing for risk stratification in patients with coronary artery disease, LVEF ≤40 %, and unsustained VT [24]. The study randomized 2,202 patients to therapy or no therapy. Patients assigned to therapy first received antiarrhythmic drugs but if inducible VT was not suppressed, an ICD would be implanted. Five-year Kaplan-Meier analysis showed the EP-guided therapy group had a 27 % reduction in cardiac death and 20 % reduction in total mortality. Notably, all the survival benefits occurred in patients who received an ICD. The results of MUSTT confirmed that ICD therapy has significant beneficial survival outcomes in high-risk patients with ischemic cardiomyopathy; in contrast, antiarrhythmic drugs did not reduce the risk of sudden death in these patients.

The beneficial effects of ICDs were further substantiated by the results of the Multicenter

Automatic Defibrillator Trial II (MADIT II) [45], which randomized 1,232 patients with a history of previous infarct and reduced LVEF of ≤30 % to ICD or conventional medical therapy. During an average follow-up of 20 months, there was a 31 % reduction in total mortality in the ICD group (14.1 % vs. 19.8 %, p = 0.016). These results significantly broadened the clinical indications of ICD therapy to include all patients with ischemic cardiomyopathy with reduced systolic ventricular function. These results virtually eliminated antiarrhythmic drugs as a frontline consideration in sudden death prevention.

Antiarrhythmic Drug Trials in Patients with Non-ischemic Cardiomyopathy and Congestive Heart Failure

In patients with congestive heart failure (CHF), Class I antiarrhythmic drugs have been associated with significant proarrhythmia adverse effects. In the Stroke Prevention in Atrial Fibrillation Study, treatment with Class I antiarrhythmic drugs had a 2.5-fold increase in cardiac mortality and a 2.6-fold increase in arrhythmia death, with more pronounced adverse effects in patients with a history of CHF [46]. In contrast, amiodarone has a relatively low propensity for proarrhythmia side effects, has a favorable hemodynamic profile, and is usually well-tolerated by patients with CHF. Thus, it has been the focus of several clinical trials examining its efficacy in reducing mortality in CHF patients.

The Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiac en Argentina (**GESICA**) trial showed that in patients with severe heart failure randomized to 300 mg/day amiodarone, there was a 28 % reduction in total mortality (33.5 % vs. 41.4 %, p = 0.024) and a 31 % reduction in hospitalization due to worsening heart failure (45.8 % vs. 58.2 %, p = 0.0024) over a 2-year follow-up [47]. Wide applicability of the results of the GESICA trial is questionable because a high percentage of patients in the study had dilated cardiomyopathy and Chagas disease (61 %).

The Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (**CHF-STAT**) showed that in patients with class II-IV symptoms of CHF, amiodarone had no significant effect on overall mortality but was significantly more effective in suppressing ventricular arrhythmias and increased the LVEF by 42 % at 2 years [48].

The Amiodarone Versus Implantable Cardioverter-Defibrillator Trial (**AMIOVERT**) randomized 103 patients with nonischemic dilated cardiomyopathy, LVEF ≤35 %, and asymptomatic nonsustained VT to amiodarone or ICD and found no difference in survival between the two groups at 1 or 3 years or in quality of life [49]. The study, however, was criticized because of the relatively low mortality rate in the two groups, the small number of patients, and the short follow-up.

The Sudden Cardiac Death in Heart Failure Trial (**SCD-HeFT**) studied 2,521 patients with NYHA class II (70 %) or III (30 %) CHF and a LVEF ≤35 % who were randomized to placebo, amiodarone, or ICD and followed for a mean period of 45.5 months [50]. Overall risk of death was similar between the placebo (29 %) and amiodarone (28 %) groups, but was reduced by 23 % in the ICD group for both ischemic and non-ischemic cardiomyopathy patients (22 %, p = 0.007). The survival benefit of ICD therapy was entirely due to reduction in arrhythmia deaths. These results further substantiated the benefits of ICD therapy in CHF patients with ischemic and non-ischemic cardiomyopathies.

Use of Antiarrhythmic Drugs in the Prevention of Sudden Cardiac Death

Given the results of the recent primary and secondary prevention trials, ICD has emerged as the superior modality of treatment compared to antiarrhythmic drugs in patients at high risk for sudden death. Class I antiarrhythmic drugs should be avoided in these patients because of proarrhythmia adverse effects, while amiodarone has an overall neutral effect. ICD therapy is now considered the cornerstone treatment for patients at increased risk for sudden death. Nevertheless, there are several areas in which antiarrhythmic drugs may play a role in the prevention of sudden death.

Patients in Whom ICDs Do Not Offer Benefits

In patients with ischemic heart disease with only moderate reduction in LV function, ICD therapy does not offer survival benefits over amiodarone. Sub-analysis of the AVID results showed that in patients with LVEF ≥35 %, there was no difference in survival between antiarrhythmic-treated and ICD-treated patients [51]. Further subgroup analysis showed that patients who presented with VF, no prior arrhythmia, no cerebrovascular disease, and LVEF ≥27 % constituted a low-risk subgroup that did not benefit from ICD implantation compared with amiodarone therapy [52]. Hence, in these patients amiodarone can be used for the prevention of sudden cardiac death, especially in patients who do not have access to ICDs.

There are also other subgroups of patients with ischemic heart disease who do not benefit from ICD implantation. First, patients with coronary artery disease, LV dysfunction, and high risk for developing ventricular arrhythmia who have undergone coronary artery bypass grafting surgery do not benefit from prophylactic ICD implantation. The Coronary Artery Bypass Graft (CABG) Patch Trial randomly assigned 900 patients with coronary artery disease, LVEF <36 %, and abnormal signal-averaged ECGs to receive an ICD or not [53]. After an average follow-up of 32 months, there was no evidence of improved survival in patients with a prophylactic ICD implant. These results underscore the importance of coronary perfusion in the development of life-threatening ventricular arrhythmias and the role of surgical revascularization in the prevention of sudden cardiac death.

Second, patients who have had a recent MI do not benefit from ICD implantation. The Defibrillation in Acute Myocardial Infarction Trial (**DINAMIT**) examined the role of ICD in 674 patients who were 6–40 days after a MI with reduced LV function (LVEF ≤35 %) and impaired cardiac autonomic function [54]. There was no difference in overall mortality between the ICD group and the control group over a mean follow-up of 30 months. These findings were supported by results from the Beta-blocker Strategy plus ICD (**BEST + ICD**) trial [55] and the Immediate Risk Stratification Improves Survival (**IRIS**) trial [56]. Recent sub-analysis of MADIT II results also confirmed a time dependence of mortality risk and ICD benefit after MI. Mortality risk in patients with ischemic cardiomyopathy increased as a function of time from MI. Implantation of ICD minimized the time dependent change in mortality in these patients. Hence, the survival benefits associated with ICDs are substantial for remote MI, but nonexistent for recent (<18 months) MI.

Third, patients with coronary artery disease and ischemic cardiomyopathy who have had recent coronary revascularization do not benefit from ICD therapy. A sub-analysis of the MADIT II results (n = 951) showed that ICD reduced mortality by 36 % (p = 0.01) and the risk of sudden death by 66 % among patients who were enrolled more than 6 months after coronary revascularization, while no such benefits were observed among patients who had ICD implantation in the early post-coronary revascularization period [57].

When ICD does not offer obvious survival benefits, the use of amiodarone can be considered judiciously in some situations.

Brugada Syndrome

Brugada Syndrome is thought to be caused by an imbalance between the inward (sodium and L-type calcium currents) and outward currents (mainly the transient outward currents) at the end of phase 1 of the epicardial action potential [58]. Hence, conditions that reduce inward currents (loss-of-function mutations in SCN5A, which encodes the α subunit of the sodium channel, or Class I antiarrhythmic drugs) or enhance the transient outward currents (male gender) can unmask or exacerbate the Brugada phenotype and increase the risk of VF. Hence, pharmacotherapies that inhibit the transient outward potassium currents or enhance the L-type Ca^{2+} currents are postulated to be protective [59]. Continuous infusion of isoproterenol, which enhances the Ca^{2+} currents, has been employed to restore normal EKG and successfully treat electrical storm with frequent episodes of VF in Brugada Syndrome patients [60]. Cilostazol, an oral phosphodiesterase inhibitor that augments the L-type Ca^{2+} currents through

elevation of intracellular cAMP, was successfully used to suppress the daily episodes of VF in a patient with Brugada Syndrome [61]. The Class IA antiarrhythmic drug quinidine, which has transient outward K^+ current blocking properties, was shown to prevent induction of VF in 22 of 25 (88 %) Brugada Syndrome patients who had inducible VF in baseline EP studies. Of these 25 patients, 16 were subsequently treated with quinidine, 6 received ICD therapy, and 3 were treated with both ICD and quinidine. After 6 months to 22.2 years of follow-up, there were no deaths. Similarly, hydroquinidine prevented VT/VF inducibility in 76 % of asymptomatic Brugada Syndrome patients who underwent EP-guided therapy [62]. In patients who had frequent ICD shocks, hydroquinidine prevented recurrence of VT/VF in all patients during a mean follow-up of 14 months. These studies were non-randomized and have small numbers of patients, but the results suggest that quinidine and hydroquinidine may be effective treatments for patients with Brugada Syndrome. Currently, ICD is the only proven effective therapy for patients with Brugada Syndrome. However, quinidine and hydroquinidine should be considered in those who do not have access to ICD or to be used as an adjunctive modality to ICD, since patients with Brugada Syndrome experience frequent appropriate (8–15%) and inappropriate (20–36 %) ICD therapies after ICD implantation [63, 64].

Long QT Syndrome

Sudden death is a common presentation of congenital long QT (LQT) syndrome, which affects 1 in 2,500 people. However, this is a rather heterogeneous group with different underlying molecular defects and channelopathies [65, 66]; thus, genotype-specific pharmacological therapy is desirable [67].

β-Adrenergic blockers are known to be effective in the treatment of congenital LQT syndromes, especially LQT1 and LQT2, which are caused by loss-of-function mutations in KCNQ1 and KCNH2 encoding I_{Ks} and I_{Kr} respectively [65, 66]. The role of adrenergic blockade in the treatment of LQT syndrome is underscored by the effectiveness of left cardiac sympathetic denervation [68, 69]. A recent retrospective study in 216 genotyped LQT1 patients treated with β-blocker and followed for a median time of 10 years showed that β-blockers are extremely effective in LQT1 and routine ICD implantation is not justified in these patients [70]. These conclusions were supported by a 10-year follow-up study of 459 patients with genetically confirmed LQT syndrome, which showed that the vast majority of these patients can be treated effectively without an ICD [71], unless they have had syncope [72].

The congenital long QT 3 syndrome (LQT3) is caused by gain-of-function mutations in the cardiac voltage-gated sodium channels with non-inactivating sodium currents that lead to prolongation of the cardiac action potential, predisposing the heart to develop torsade de pointes [73]. This unique genotype-phenotype correlation provides an opportunity for tailoring genotype-specific therapy. Class I antiarrhythmic drugs are natural choices for treatment of LQT3. When mexiletine (12–16 mg/kg/day) was given to patients with LQT syndrome, QTc was significantly shortened in LQT3 patients, but not in LQT2 patients [74]. These results suggest that mexiletine may be effective in the treatment of LQT3 patients; however, larger prospective clinical studies are needed.

Flecainide has also been used to treat patients with LQT3. The D1790G mutation in SCN5A produces LQT3 not by promoting sustained inward sodium currents but by a negative shift in the steady-state channel inactivation, thus responding to flecainide but not to Class IB antiarrhythmics like lidocaine and mexiletine. Eight asymptomatic D1790G mutation carriers treated with flecainide (75–150 mg BID) showed 9.5 % shortening of QTc ($p = 0.011$), whereas control subjects showed QTc prolongation [75]. However, this treatment strategy should be applied with caution because there is overlap between Brugada Syndrome and LQT3. Flecainide administration elicits EKG patterns typical of Brugada Syndrome in some LQT3 patients, raising concern about the safety of flecainide therapy in LQT3 patients without the D1790G mutation [76]. Larger prospective studies are needed before Class I antiarrhythmic drugs should be employed as the primary therapeutic agent in

patients with LQT3. Recently, ranolazine, which has been shown to block the late sodium current, was found to shorten QTc by 26 ms in five LQT3 patients after an 8-h intravenous infusion and may potentially be helpful in the treatment of these patients [77].

Timothy syndrome (LQT8) is caused by a gain-of-function mutation in CACNA1C, resulting in sustained $I_{Ca,L}$ and Ca^{2+} overload [66]. Verapamil and diltiazem have been shown to be efficacious in the acute management of VF storm in patients with Timothy syndrome [67]. Because of the limited clinical experience with these rare disease entities, treatment is empirical and ICD is usually indicated because of the poor prognosis of these patients.

Short QT Syndrome

Short QT (SQT) syndrome is a hereditary primary electric disorder characterized by abnormally short QT intervals of <360 ms and a high incidence of sudden death and atrial fibrillation [66, 78]. Given the high propensity for sudden death, ICD implantation is needed for primary and secondary prevention. Pharmacological therapy can be helpful for young children in whom placement of an ICD would be problematic, in patients who refuse an ICD, or as an adjunct to ICD in patients with frequent appropriate shocks.

Recently, Giustetto et al. reported the largest long-term study of patients with SQT syndrome [79]. Fifty-three patients were followed for 64 ± 27 months. Twenty-four patients received an ICD and 12 patients received long-term prophylactic treatment with hydroquinidine. The arrhythmia event rate was 4.9 % per year in patients without antiarrhythmic therapy and no arrhythmia event occurred in patients receiving hydroquinidine. Compared to amiodarone, sotalol, and disopyramide, hydroquinidine was more efficacious in normalizing QTc intervals and in preventing ventricular tachyarrhythmia induction as well as arrhythmia events during follow-up. However, of the 22 patients who were initiated on hydroquinidine, the drug was discontinued in 6 because of poor therapeutic noncompliance, in 2 because of no effect on QT intervals, and in 2 because of gastrointestinal adverse effects [79].

Other antiarrhythmic drugs that have been reported to be effective in the treatment of patients with SQT syndrome include quinidine [80], disopyramide [81], amiodarone [82], and Nifekalant [81]. However, Class IC drugs and Class III antiarrhythmic drugs including sotalol and ibutilide failed to produce a significant QT prolongation in these patients [80].

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia is a rare arrhythmogenic disorder associated with sudden death in children and young adults who have structurally normal hearts. It typically presents as exercise- or emotion-induced syncope. The hallmark of this disease is the occurrence of bidirectional VT, polymorphic VT, or VF provoked without QT prolongation or Brugada Syndrome, reproducible by exercise or exposure to catecholamines [83]. The underlying genetic abnormalities produce defects in Ca^{2+} homeostasis by the sarcoplasmic reticulum (SR). Mutations of the cardiac ryanodine receptor (RYR2), the Ca^{2+} release channel in SR [84, 85], and calsequestrin, which binds Ca^{2+} and serves as the major Ca^{2+} reservoir in the SR [86], are associated with this condition.

β-Blockers are the treatment of choice and are effective in the acute termination of refractory VT/VF [13]. In a 7-year follow-up of 21 patients with catecholaminergic polymorphic VT, all β-blockers were effective, but the long-acting ones such as nadolol were preferred [83]. Later reports showed less favorable outcomes with β-blocker treatment alone [85, 87]. The importance of adrenergic blockade in the treatment of patients with catecholaminergic polymorphic VT, however, is underscored by the effectiveness and favorable outcome of left cardiac sympathetic denervation [68, 88].

A recent study showed that flecainide was effective in reducing exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic VT not controlled by conventional drug therapy [89]. Flecainide is known to directly inhibit RYR2 channels [90] and prevent the development of arrhythmogenic

Ca^{2+} waves. Thirty-three genotype-positive patients with documented exercise-induced VT or VF were treated with flecainide, with 31 also receiving β-blockers and 4 Ca^{2+} channel blockers. After a median follow-up of 20 months, 76 % had partial (28 %) or complete (48 %) suppression of exercise-induced ventricular arrhythmias [89].

β-blockers are still considered first-line therapy for catecholaminergic polymorphic VT, but are not always completely effective in preventing life-threatening arrhythmias. ICDs are also not totally protective and can be proarrhythmic as shocks can trigger catecholamine release, resulting in VT/VF storms and death [91,92]. Flecainide provides another effective treatment option with a promising mechanism-based therapy for catecholaminergic polymorphic VT.

Use of Antiarrhythmic Drugs as an Adjunct to ICD Therapy

ICD has emerged as the treatment of choice in the prevention of sudden cardiac death for high-risk patients. Meanwhile, antiarrhythmics have been relegated to an adjunctive and palliative role. Despite their lackluster record, antiarrhythmic drugs remain widely used in patients who have received ICDs. In fact, in some medical centers, about 40 % of the ICD patients also received an antiarrhythmic drug [93]. There are potential benefits associated with the use of antiarrhythmic drugs in patients with an ICD. The major indication for the use of antiarrhythmic drugs is suppression of frequent recurrent VT/VF and reduction of ICD shocks. Indeed, 50–70 % of the patients with ICD implantation for prevention of sudden death received appropriate ICD therapies within the first 2 years after ICD implantation [94]. Antiarrhythmic drugs are helpful in reducing the frequency of ICD therapies in the following situations.

Treatment of Electrical Storm

Electrical storm, defined as having three or more episodes of VT or VF within a 24 h period, occurs in 10–20 % of the patients who have received an ICD for prevention of VT/VF recurrence. Storms tend to occur 4–20 months after ICD implantation and the number of arrhythmic episodes per storm ranges from 4 to 51 [95, 96].

While some studies have found that electrical storms do not confer increased mortality [96], other studies differ [95]. Ninety of the Four hundred and fifty seven patients (20 %) enrolled in the ICD arm of AVID experienced electrical storms [95]. The occurrence of electrical storms was associated with a remarkable 5.4-fold increase in risk of mortality in the 3 months following the storm, and most of the deaths were due to cardiac non-sudden causes [95] such as heart failure [96]. Multiple ICD shocks result in elevation in cardiac troponin levels [97], with acute cellular damage, myocardial injury, and fibrosis [98]. Hence, it is possible that repetitive ICD shocks for electrical storm may directly contribute to an increase in mortality.

Treatment of electrical storm involves the optimization of β-blocker therapy, followed by initiation of antiarrhythmic drugs, particularly amiodarone, which is efficacious both for acute termination and suppression of recurrent storms [96]. Experience from a single tertiary medical center showed that only 12 % of patients treated with amiodarone had recurrence of electrical storm versus 53 % of those not treated with amiodarone ($p < 0.001$) [96]. In patients with electrical storms treated with aggressive use of IV amiodarone followed by oral administration, long-term outcomes were similar to patients without storms.

Reduction of Frequent Appropriate ICD Therapy

Of the 3,344 patients in the European Registry of ICD (EURID), 49.5 % had ICD interventions during a 1 year follow-up, including 39.8 % with appropriate therapies and 16.2 % with inappropriate therapies [99]. Similarly, in the MADIT patients who received an ICD, 60 % experienced an ICD shock within 2 years of enrollment [44]. Hence, there is a need to suppress recurrent ventricular arrhythmias even on ICD therapy. While Class I antiarrhythmic drugs are no longer used routinely in patients with ischemic heart disease, Class III anti-arrhythmic drugs do not

significantly increase mortality in patients with heart disease and are useful as adjunct therapies in ICD patients.

Sotalol

In a prospective study in which 143 patients with a history of VT/VF underwent EP-guided sotalol therapy, sotalol prevented induction of VT/VF in 53 patients who were subsequently treated with sotalol only [100]. The 93 patients in whom sotalol failed to suppress induction of VT/VF underwent ICD implantation and were randomized to also take sotalol or placebo. Over a follow-up period of more than 1 year, 53.2 % of the patients in the ICD-only group had VT/VF recurrence, versus 28.3 % in the sotalol group and 32.6 % in the ICD/sotalol group ($p = 0.0013$).

In a multicenter double blind, randomized study, 151 patients with ICDs assigned to treatment with sotalol were compared with 151 matched placebo controls over 12 months [101]. The sotalol group had a significantly lower risk of death from any cause and of the delivery of first ICD shock for any reason, as well as a significantly reduced mean number of shocks per year (1.43 vs. 3.89 in control, $p = 0.008$). However, 27 % of the patients assigned to sotalol discontinued the medication because of adverse effects (versus 12 % in the placebo group).

Amiodarone

The role of amiodarone in the reduction of ICD therapy has recently been demonstrated by the results of the Optimal Pharmacological Therapy in Implantable Cardioverter (OPTIC) Study, a landmark, multicenter, open label trial. Four hundred and tweleve patients who received ICDs for secondary prevention of spontaneous or inducible VT/VF and with an LVEF ≤40 %, were randomized to treatment for 1 year with amiodarone plus β-blocker, sotalol alone, or β-blocker alone [102]. ICD shocks occurred in 38.5 % of patients who received β-blocker alone, in 24.3 % who received sotalol, and in 10.3 % assigned to amiodarone plus β-blocker ($p < 0.001$). Patients taking amiodarone had significantly higher adverse pulmonary and thyroid effects as well as symptomatic bradycardia.

Azimilide

Azimilide is a novel investigational Class III antiarrhythmic that blocks both the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier potassium channels. In a double-blind, placebo-controlled pilot study, 172 patients with ICDs were randomized to receive placebo, 35 mg azimilide, 75 mg azimilide, or 125 mg azimilide [103]. After a mean follow-up of 247–279 days, azimilide significantly reduced the frequency of appropriate ICD therapies at all administered doses by 69 % compared with placebo ($p < 0.00001$).

The results of the pilot study were substantiated by the Shock Inhibition Evaluation with Azimilide (SHIELD) Study, a placebo-controlled, double-blind randomized clinical trial that enrolled 633 ICD recipients [104]. Over a follow-up period of 273 days, the total number of ICD shocks plus antitachycardia pacing for symptomatic VTs was significantly reduced by azimilide. Notably, five patients in the azimilide groups and one patient in the placebo group developed torsade de pointes, and one patient on azimilide developed severe but reversible neutropenia.

Dofetilide

In a multicenter, double-blind, randomized cross-over comparative study of 135 patients with ischemic heart disease and inducible sustained VT, dofetilide was as efficacious as sotalol in preventing the induction of sustained VT by EP study but had fewer adverse effects [105]. Long-term treatment with dofetilide also showed efficacy and safety profiles comparable to sotalol and was deemed a viable alternative.

Reduction of Inappropriate ICD Therapies

Despite advances in modern technology and improvement in features in today's ICDs, inappropriate ICD shocks remain a challenge, occurring in 10–20 % of ICD recipients [101, 102, 104]. In the MADIT II cohort, atrial fibrillation was

the most common trigger for inappropriate shocks (44 %), followed by SVT (36 %) and abnormal sensing (20 %). Importantly, patients with inappropriate shocks had a greater risk of all-cause mortality. Implantation of an ICD for primary prevention rather than for secondary prevention of VT/VF increases the risk of inappropriate shocks [106]. Implantation of a dual chamber device lowers the risk of inappropriate ICD detection by 47 % [107], and use of detection enhancement features reduces the risk of inappropriate ICD therapies by 53 % [108]. Remote monitoring of ICD from home is also thought to facilitate rapid monitoring of arrhythmias and reduce inappropriate ICD therapies (109).

Of the antiarrhythmics, only sotalol and amiodarone are efficacious in reducing inappropriate ICD therapies. Inappropriate ICD shocks for SVT has been shown to be reduced by 64 % with sotalol [101] and by 78 % with amiodarone [102]. In the SHIELD trial, there was no difference in inappropriate ICD therapies among patients taking placebo, 75 mg azimilide, or 125 mg azimilide daily [104].

In a sub-analysis of MADIT II data, patients who received high dose β-blockers showed significant reduction in their risk for VT/VF requiring ICD therapies compared to those who did not receive β-blockers, but β-blocker therapy did not reduce the frequency of inappropriate ICD therapies [110].

Effects of Antiarrhythmic Drugs on Defibrillation Threshold

An important consideration for the use of antiarrhythmic drugs in patients with ICDs is their effects on defibrillation threshold (DFT). Class IA antiarrhythmic drugs do not seem to have a significant effect on DFT [111–113], but the Class IB drug lidocaine has been found to consistently increase DFT. In 27 patients undergoing intraoperative testing for ICD, lidocaine increased DFT from a baseline of 14 ± 5 J to 18 ± 7 J ($p < 0.02$) [111]. However, in a prospective randomized study, the ICD DFT in patients taking 720 mg/day of mexiletine showed no significant change after a 24-month follow-up [114, 115]. The effects of Class IC antiarrhythmic drugs on DFT appear to be variable, with no significant effects or only a small increase [112, 113, 116].

In contrast, Class III antiarrhythmic drugs, with the exception of amiodarone, have been consistently shown to lower or to have no effect on the DFT [112, 113, 117]. Although Class III antiarrhythmic drugs (except amiodarone) are not routinely used with the sole purpose of lowering DFTs, they are sometimes instituted in patients with marginal DFTs when revising the ICD system is not an option [117]. Indeed, ibutilide and other Class III antiarrhythmic drugs have been used to lower the defibrillation energy requirement for converting atrial fibrillation to sinus rhythm, and they enhance the efficacy of cardioversion [118]. Amiodarone, on the other hand, is generally associated with a significant increase in DFT [113, 117].

However, the issues related to the effects of antiarrhythmic drugs on DFT may have become irrelevant in patients with newer generation devices with high output and biphasic defibrillation waveforms. In a retrospective study with 89 patients, those on chronic amiodarone therapy receiving a monophasic ICD had a significantly higher DFT (29 ± 8.8 J, n = 7) than patients without antiarrhythmic treatment (19.1 ± 5.1 J, n = 11, $p = 0.021$). However, in patients with a biphasic device, the DFT was not significantly different between patients on amiodarone (15.3 ± 7.3 J, n = 22), sotalol (14.4 ± 7.2 J, n = 20), or no antiarrhythmic drug (17 ± 6.1 J, n = 22, $p = 0.44$) [100]. A sub-study of the OPTIC trial examined the DFTs in 94 patients at baseline and again after 8–12 weeks of therapy with β-blocker, β-blocker plus amiodarone, or sotalol [119]. Patients randomized to β-blocker therapy had a significant mean DFT decrease from 8.77 ± 5.15 J at baseline to 7.13 ± 3.43 J (n = 29, $p = 0.027$), but the amiodarone (n = 35) and the sotalol (n = 30) groups did not have significant DFT changes, suggesting routine DFT reassessment after institution of amiodarone or sotalol may not be necessary. It is important to note that DFTs can be affected by various other parameters, including the sympathetic tone and levels of catecholamines, the length of procedure time, left ventricular end-diastolic dimensions, body size, LVEF, NYHA Class, and the concomitant administration of other medications.

Other Considerations

Quality of Life

ICD therapy has become standard treatment for life-threatening arrhythmias and is generally well-accepted because of its survival benefits. However, anxiety and fear of the device are common [120] and ICD firings have a significant adverse impact on device recipients [121]. Studies on the quality of life 6 months after CABG in the CABG Patch trial showed that ICD negatively affected the patients' perceived and measured quality of life [122]. The difference was mainly due to the negative impact of ICD shocks; there was no difference in quality of life indicators between controls and ICD patients who did not receive ICD shocks.

Quality of life assessment in CIDS patients showed that over 12 months, participants who received an ICD (n = 86) had statistically significant better quality of life indicators compared to those who received amiodarone (n = 92) [123]. However, the quality of life benefits of ICD were lost in patients who have received ≥5 shocks. The AVID quality of life substudy found that ICD and antiarrhythmic drug therapies were associated with similar changes in quality-of-life among patients who survived at least 1 year (n = 800) [124]. The occurrence of any shock was associated with significant reductions in mental wellbeing and physical functioning.

Cost-Effectiveness of Treatment

With the rapid expansion of indications for ICD implantation, the financial implication is enormous [125]. It was estimated that device implantation and care of the 55,000–65,000 new MADIT-II eligible patients each year would incur an additional expenditure in excess of $5 billion annually in the United States [126]. Results from primary and secondary prevention trials showed that ICD therapy is expensive with varied cost-effectiveness [127–129]. A recent report from MADIT II, however, showed an appalling cost effectiveness ratio of $ 235,000 per year-life saved during the 3.5-year period of the study [126]. Hence, the economic burden of ICD therapy is substantial and the cost-effectiveness of therapy must be taken into account in future health care delivery planning. Alternative effective treatments should be further explored.

Potential Adverse Interactions between Antiarrhythmic Drugs and ICD

Although antiarrhythmic drugs can be beneficial in the management of patients with an ICD, there are also potential adverse interactions between antiarrhythmic drugs and ICDs. First, amiodarone and certain Class I antiarrhythmic drugs can increase DFT as discussed above. This may lead to failure to defibrillate, rendering the device ineffective. Second, antiarrhythmic drugs can slow VTs to below the rate of detection. Third, antiarrhythmic drugs may produce significant sinus bradycardia, especially in patients taking β-blockers and other negative chronotropic agents concomitantly. This may result in excessive right ventricular pacing, leading to an increase in generator energy consumption and depletion, as well as inducing deterioration in ventricular function [130]. Fourth, Class I antiarrhythmic drugs are known to increase pacing threshold [93]. Although the almost universal use of steroid eluting leads has helped to improve capture thresholds, isolated reports suggest that antiarrhythmic drugs may cause failure to pace under certain circumstances. Fifth, antiarrhythmic drugs have the potential to increase the incidence of arrhythmia. Class I drugs can be proarrhythmic and Class III drugs facilitate the development of torsade de pointes [131]. These drugs can also stabilize arrhythmia circuits so that atrial and ventricular arrhythmias can become sustained and incessant; the combined effects of tachycardia slowing and facilitation of AV nodal conduction can result in 1:1 atrial flutter conduction or atrial fibrillation with rapid ventricular response [131].

Summary

The role of antiarrhythmic drugs in the prevention of sudden death has substantially changed in the last 20 years. ICD therapy is now considered

first-line treatment in patients at high risk of VT/VF development, while antiarrhythmic drugs have been relegated to an adjunctive role. Yet use of antiarrhythmic drugs is prevalent in ICD recipients to treat electrical storm and to reduce ICD shocks. In sudden death syndromes associated with specific genetic derangements, genotype-specific antiarrhythmic therapy is recommended. Judicious use of antiarrhythmic drugs may provide cost-effective treatment, improve quality of life and in some cases produce better long-term outcomes.

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34
Non-antiarrhythmic Drugs in Sudden Death Prevention

Leonard Ilkhanoff, Alan H. Kadish, and Jason T. Jacobson

Abstract

Despite a decline in mortality from cardiovascular disease in the last decade, the number of sudden cardiac deaths (SCD) has remained constant and is estimated to be at least 300,000 deaths annually. The most common mechanism of SCD is ventricular fibrillation. Antiarrhythmic drugs (AARx) that modulate cardiac ion channels have been shown to be effective in a variety of experimental models in possibly decreasing the risk of arrhythmic death and held the promise of possibly reducing the incidence of SCD. However, translation of these animal experiments to human studies has been disappointing, largely because AARx have been shown to be proarrhythmic in clinical settings in which there was great promise to reduce the incidence of SCD in susceptible populations. Unfortunately, drugs that block sodium or potassium channels overall have been ineffective in preventing SCD and in many cases have, paradoxically, increased the risk of life-threatening ventricular arrhythmias. In contrast, in a number of studies of patients after myocardial infarction and those with heart failure, other classes of drugs, such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers, that are not considered traditional antiarrhythmic drugs, have been shown to be effective in reducing overall mortality and potentially sudden death mortality in patients with underlying structural heart disease. This chapter will review those drugs and also describe potential pathophysiological mechanisms by which these agents may reduce sudden death.

Keywords

Sudden death • Prevention • Nonantiarrhythmic drugs

L. Ilkhanoff, MD, MS (✉)
Division of Cardiology, Electrophysiology Section,
Department of Medicine,
Northwestern Memorial Hospital,
Northwestern University, 251 E. Huron St.,
Feinberg Pavilion, Suite 8-503, Chicago, IL 60611, USA
e-mail: leonard.ilkhanoff@gmail.com

A.H. Kadish, MD
Office of the President, New York Medical College,
Valhalla, NY, USA

J.T. Jacobson, MD
Division of Cardiology, Columbia University,
Mount Sinai Medical Center, Miami Beach, FL, USA

Introduction

Despite a decline in mortality from cardiovascular disease in the last decade, the number of sudden cardiac deaths (SCD) has remained constant and is estimated to be at least 300,000 deaths annually [1]. The most common mechanism of SCD is ventricular fibrillation. Antiarrhythmic drugs (AARx) that modulate cardiac ion channels have been shown to be effective in a variety of experimental models in possibly decreasing the risk of arrhythmic

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death and held the promise of possibly reducing the incidence of SCD. However, translation of these animal experiments to human studies has been disappointing, largely because AARx have been shown to be proarrhythmic in clinical settings in which there was great promise to reduce the incidence of SCD in susceptible populations. Unfortunately, drugs that block sodium or potassium channels overall have been ineffective in preventing SCD and in many cases have, paradoxically, increased the risk of life-threatening ventricular arrhythmias. In contrast, in a number of studies of patients after myocardial infarction and those with heart failure, other classes of drugs, such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers, that are not considered traditional antiarrhythmic drugs, have been shown to be effective in reducing overall mortality and potentially sudden death mortality in patients with underlying structural heart disease. This chapter will review those drugs and also describe potential pathophysiological mechanisms by which these agents may reduce sudden death (Table 34.1).

Pathophysiology

Although bradycardia and electromechanical dissociation may be more common mechanisms of sudden cardiac death in patients with advanced congestive heart failure, evidence suggests that ventricular tachycardia and/or ventricular fibrillation are the major mechanisms of SCD in patients with a history of myocardial infarction. Thus, therapies that decrease the incidence of these arrhythmias (without being proarrhythmic) may help reduce the incidence of SCD. It is well established that the risk of ventricular tachycardia and ventricular fibrillation varies inversely with left ventricular function. Additionally, left ventricular dilation may contribute to arrhythmogenesis by altering cardiac electrophysiological properties through contraction–excitation feedback. Thus, pharmacological agents that alter cardiac hemodynamics exert antiarrhythmic effects by altering ventricular structure and function, without having direct effects on ion channels. Despite extensive research, a unified pathophysiological construct for SCD has not been accepted. The majority of patients who experience sudden cardiac death have coronary disease and myocardial ischemia, of whom only a minority has SCD during an acute myocardial infarction. Patients with nonischemic cardiomyopathy and other structural heart diseases also have a substantial risk for SCD. Therefore, sudden death must invoke a broad spectrum of complex, underlying pathophysiologic mechanisms than merely acute myocardial infarction.

Current antiarrhythmic drugs non-selectively target sodium or potassium channels present throughout the myocardium, and, therefore, do not act specifically on the arrhythmic substrate. In contrast, if adrenergic surges due to mental or physical stress are potential contributing factors to SCD, then drugs that block these triggers, or minimize the formation of substrate, may not engender the same risks as traditional antiarrhythmic drugs. Therefore, the greater efficacy of nontraditional drugs for the prevention of SCD may depend on these more global myocardial effects than on specific electrophysiologic targets, such as ion channels.

Beta Blockers

Adrenergic Blocking Drugs

β-Adrenergic blockers (also known as beta blockers) have emerged as important pharmacological agents for both primary and secondary prevention of sudden cardiac death. They have been shown to be effective in reducing SCD across a spectrum of disorders in patients with and without heart failure. The mechanism of this class of drugs involves competitive adrenergic receptor blockade of sympathetically mediated triggering mechanisms, slowing of the sinus rate, and possibly inhibition of excess calcium release by the ryanodine receptor [20].

Steinbeck [21] randomized 115 patients with ventricular tachycardia to one of two treatment approaches: beta blocker therapy or electrophysiology testing-guided therapy. The 1-year recurrence rate/sudden death rate in the beta

Table 34–1. Nonantiarrhythmic Drugs[a]

	Drug	Study	Control	Patients	Total N	Total mortality (RR or HR) (95 % CI)	SCD (RR or HR) (95 % CI)
ACE inhibitors	Ramipril	AIRE [2]	Placebo	Post-MI + CHF	2,006	RR 0.73 (0.60–0.89)	RR 0.70 (0.53–0.92)
	Ramipril	HOPE [3]	Placebo	CV disease of DM + CRF	9,297	RR 0.84 (0.75–0.95)	RR 0.62 (0.41–0.94)[b]
	Captopril	SAVE [4]	Placebo	Post-MI↓ + EF	2,231	RR 0.81 (0.68–0.97)	NS
	Enalapril	CONSENSUS I [5]	Placebo	AMI	6,090	RR 1.10 (0.93–1.29)	NS
	Enalapril	SOLVD-P prevention [6]	Placebo	↓EF	4,228	RR 0.92 (0.79–1.08)	RR 0.93 (0.70–1.22)
	Enalapril	V-Heft II [7]	Hydral/isosorbide	CHF	804	RR 0.72	RR 0.65
	Zofenopril	SMILE [8]	Placebo	AMI↓	1,556	RR 0.78 (0.52–1.12)	RR 0.37 (0.11–1.02)
	Trandolapril	TRACE [9]	Placebo	Post-MI + EF	1,749	RR 0.78 (0.67–0.91)	RR 0.76 (0.59–0.98)
ARB	Valsartan	Val-Heft [10]	Placebo	CHF	5,010	RR 1.02 (0.88–1.18) 98 % CI	NS
	Losartan	ELITE [11]	Captopril	CHF	722	RR 0.54 (0.31–0.95)	RR 0.36 (0.14–0.97)
	Losartan	ELITE II [12]	Captopril	CHF	3,152	HR 1.13 (0.95–1.35) 95.7 % CI	HR 1.30 (1.00–1.69)
	Losartan	LIFE [13]	Atenolol	HTN + LVH	9,193	HR 0.90 (0.78–1.03)	HR 1.91 (0.99–1.43)[c]
	Losartan	OPTIMAAL [14]	Captopril	Post-MI + CHF	5,477	RR 1.13 (0.99–1.28)	RR 1.19 (0.99–1.43)[d]
Beta Blockers	Class	1999 Meta-analysis [15]	Placebo	Post-MI	24,974	RR 0.77 (0.69–0.85)	
	Class	Medicare database [16]	Placebo	Post-MI↓	201,752	RR 0.60 (0.57–0.63)	
	Carvedilol	CAPRICORN [17]	Placebo	Post-MI + EF	1,959	HR 0.77 (0.60–0.98)	HR 0.74 (0.51–1.06)
	Metoprolol	MERIT-HF [18]	Placebo	CHF	3,991	RR 0.66 (0.53–0.81)	RR 0.59 (0.45–0.78)
	Bisoprolol	CIBIS-II [19]	Placebo	CHF	2,657	HR 0.66 (0.54–0.81)	HR 0.56 (0.39–0.80)

Abbreviations: *AMI* acute myocardial infarction, *CHF* congestive heart failure, *CI* confidence interval, *CRF* cardiac risk factor, *CV* cardiovascular, *DM* diabetes mellitus, *EF* ejection fraction, *HR* hazard ratios, *HTN* hypertension, *LVH* left ventricular hypertrophy, *MI* myocardial infarction, *NS* not significant, *RR* relative risk, *SCD* sudden cardiac death. See text for study abbreviation

[a] *ACE* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, Beta blockers

[b] Cardiac arrest

[c] Resuscitated cardiac arrest

[d] Sudden cardiac death + resuscitated cardiac arrest

blocker group exceeded 40 %, which was significantly greater than 10 % at 1 year in the group treated with an antiarrhythmic drug proven to be efficacious by electrophysiological testing. In both the European Myocardial Infarct Amiodarone Trial (EMIAT) [22] and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) [23], amiodarone therapy showed a greater reduction in mortality in those patients on beta blockers [24]. In CAMIAT, there was an 87 % reduction in relative risk ($p < 0.008$) related to amiodarone therapy (versus placebo) in patients who were receiving concomitant therapy with beta blockers. Most recent implantable cardioverter defibrillator (ICD) trials have shown that even in patients treated with beta blockers, ICD therapy can further reduce mortality (SCD-HeFT, DEFINITE) [25, 26].

Efficacy of Beta Blockers After Myocardial Infarction

Beta blockers competitively block the effects of catecholamines on cell membrane beta receptors. Beta-1 adrenergic receptors are located primarily in the myocardium; inhibition of catecholamine action at these sites reduces myocardial contractility, sinus node rate, and AV node conduction velocity. Through these actions, they blunt the heart rate and contractility responses to chest pain, exertion, and other stimuli. They also decrease systolic blood pressure. All of these effects reduce MVO_2. In contrast, beta-2 adrenergic receptors are located primarily in vascular and bronchial smooth muscle; the inhibition of catecholamine action at these sites produces vasoconstriction and bronchoconstriction. In ustable angina/non-ST elevation myocardial infarction (UA/NSTEMI), the primary benefits of beta blockers are due to inhibition of beta-1 adrenergic receptors, which results in a decrease in cardiac work and myocardial oxygen demand. Slowing of the heart rate also has a favorable effect, acting not only to reduce MVO_2 but also to increase the duration of diastole and diastolic pressure-time, a determinant of forward coronary flow and collateral flow [27].

In 1993, Teo et al. [28] published an overview of results from these randomized controlled trials that included more than 50,000 patients. There was a substantial reduction in mortality due to beta blocker treatment (relative risk, 0.81; 95 % confidence intervals, 0.75–0.87; $p < 0.00001$). The Norwegian Multicenter Study Group [29] demonstrated a survival benefit for at least 6 years after myocardial infarction. The largest report includes over 200,000 patients in the Medicare database [16]. After adjusting for baseline differences, beta blocker therapy was associated with a 40 % decrease in mortality at 2 years. The benefits of beta blocker therapy have withstood the test of time despite the advent of therapies such as thrombolytic therapy [30], ACE inhibitors [31–35] and revascularization [36]. In the CAPRICORN study, 1,959 patients who had a MI within 3–21 days and an ejection fraction ≤40 % were randomly assigned to treatment with either carvedilol ($n = 975$) or placebo ($n = 984$). Although all-cause mortality was not the primary endpoint, after a mean follow-up of 1.3 years, 12 % mortality was seen in patients treated with carvedilol and 15 % mortality in those treated with placebo (risk reduction, 23 %; 95 % confidence interval, 2–40 %) [17]. Further analysis from this study showed a lower incidence of malignant ventricular arrhythmias in the carvedilol treated group (0.9 % vs. 3.9 % in the placebo group; $p < 0.0001$) [37]. In an analysis of the VALIANT registry, Piccini and colleagues found that patients presenting with VT/VF in the setting of acute MI had higher mortality if they did not receive beta blocker therapy within 24 h (relative risk 0.28, CI 0.10–0.75, $p = 0.013$) [38].

In these trials, the doses of beta blockers were generally titrated up to doses equivalent to 200 mg of metoprolol or 160 mg of propranolol daily. However, a majority of patients who are treated with beta blockers following a myocardial infarction receive ≤50 % of the dose found to be effective in randomized clinical trials [39, 40]. In an analysis of the database from the northern California Kaiser Permanente hospitals [39], low-dose beta blocker therapy for myocardial infarction was shown to be beneficial; in addition, the mortality was actually lower in patients receiving low-dose beta blockers (25 % of the dose used in large-scale clinical trials). In those patients given up to 49 % of the dose found to be effective in clinical trials, the long-term mortality was 3.4 %, while in those given ≥50 %

of the dose found to be effective in clinical trials, the mortality was 6.9 %; in those not treated with beta blockers, the mortality was 18.8 %. Similarly, in a study of elderly people receiving low, standard, and high-dose beta blocker therapy after myocardial infarction, there was a 60 % reduction in mortality in the low-dose group with similar reductions in the standard and high-dose groups [41]. Finally, in observational trials [16, 42] in the Medicare population, it is unlikely that full-dose beta blockers were used in a majority of patients, yet a marked survival benefit was demonstrated.

Efficacy of Beta Blockers in the ST Elevation Myocardial Infarction Setting

The benefits of routine early intravenous use of beta blockers in the fibrinolytic era have been challenged by 2 randomized trials of intravenous beta blockade [43, 44] and by a post hoc analysis of the use of atenolol in the GUSTO-I trial [30]. A subsequent systematic review of early beta-blocker therapy in STEMI found no significant reduction in mortality [15]. Most recently, the utility of early intravenous followed by oral beta blockade (metoprolol) was tested in 45,852 patients with MI (93 % had STEMI, 7 % had NSTEMI) in the COMMIT study [45]. Neither the composite of death, reinfarction, or cardiac arrest nor death alone was reduced for up to 28 days in the hospital. Overall, a modest reduction in reinfarction and ventricular fibrillation (which was seen after day 1) was counterbalanced by an increase in cardiogenic shock which occurred early, and primarily in those who were hemodynamically compromised or in heart failure or who were stable but at high risk for development of shock. Thus, based on these results, early aggressive beta blockade may pose a substantial net hazard in hemodynamically unstable patients and should be avoided [46]. Risk factors for shock were older age, female sex, time delay, higher Killip class, lower blood pressure, higher heart rate, ECG abnormality, and previous hypertension. There was a moderate net benefit for those who were relatively stable and at low risk of shock. Whether to start beta blockade intravenously or orally in these more stable patients is unclear, and patterns of use vary. In an attempt to balance the evidence overall for UA/NSTEMI patients, oral beta blocker use is recommended in the guidelines, in the absence of contraindications (e.g., heart failure), within the first 24 h. Greater caution is now suggested in the early use of intravenous beta blockers, which should be targeted to specific indications and should be avoided with heart failure, hypotension, and hemodynamic instability [46]. However, beta blockers are strongly recommended before discharge in those with compensated heart failure of left ventricular systolic dysfunction.

The choice of beta blocker for an individual patient is based primarily on pharmacokinetics and side effect profiles. There are no comparative studies between members of this class in the acute setting. Beta blockers without intrinsic sympathomimetic activity are generally preferred. Agents studied in the acute setting include metoprolol, propranolol, and atenolol. Carvedilol may be considered for post-MI use. Comparative studies among different beta blockers in the chronic setting after UA/NSTEMI also are not available to establish a preference among agents. In patients with heart failure, one study suggested greater benefit with carvedilol, with mixed beta-blocking and alpha-adrenergic-blocking effects, than metoprolol, a relatively selective beta-1 blocker [47]. Initial studies of beta-blocker benefits in ACS were small and uncontrolled. Pooled results from the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation of PTCA and Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade (EPILOG), Evaluation of Platelet IIb/IIIa Inhibitor for STENTing (EPISTENT), CAPTURE, and ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomization Trial (RAPPORT) studies were used to evaluate the efficacy of beta-blocker therapy in patients with ACS who were undergoing PCI [46]. At 30 days, death occurred in 0.6 % of patients receiving beta-blocker therapy versus 2.0 % of patients not receiving such therapy ($p < 0.001$). At 6 months, death occurred in 1.7 % of patients receiving beta-blocker therapy versus 3.7 % not receiving this therapy ($p < 0.001$). Thus, patients receiving beta-blocker therapy who undergo PCI for UA or MI have a lower short-term mortality [48].

Overall, the rationale for beta-blocker use in all forms of CAD, including UA, is generally favorable, with the exception of initial heart failure. In the absence of contraindications, the new evidence appears sufficient to make beta blockers a routine part of care. A recent exception to beta-blocker benefit was COMMIT [49], a large trial of mostly STEMI patients, which showed no overall mortality benefit. In subgroup analysis, any potential modest benefits in reduction of reinfarction or ventricular arrhythmias in this setting were offset by an increased risk in those with initial HF or risk factors for cardiogenic shock. In contrast to this adverse experience with early, aggressive beta blockade, carvedilol, begun in low doses 3–10 days after MI in patients with LV dysfunction (ejection fraction of 0.40 or less) and gradually uptitrated, decreased subsequent death or nonfatal recurrent MI when given in conjunction with modern ACS therapies in the most contemporary oral beta blocker post-MI trial, CAPRICORN [50].

Efficacy of Beta Blockers in Patients with Congestive Heart Failure

Beta blockers are also emerging as important agents in the prevention of sudden cardiac death in patients with congestive heart failure. Packer et al. [51] showed that carvedilol reduced total mortality by 65 %. In the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) [19], 2,647 patients with Class III or IV congestive heart failure and an ejection fraction less than 35 % were randomized either to bisoprolol (N = 1,327) or to placebo (N = 1,320). The trial was terminated prematurely because of the significant survival benefit due to bisoprolol. The estimated annual mortality was 8.8 % in patients treated with bisoprolol and 13.2 % in those receiving placebo (risk reduction 34 %; 95 % confidence interval 19–46 %). Metoprolol has also been shown to improve survival in patients with congestive heart failure [18, 52]. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial [18] 3,991 patients with Class II to IV (96 % were Class II and III) congestive heart failure (ejection fraction less than 40 %) were randomly assigned to treatment with metoprolol ($N = 1{,}990$) or placebo ($N = 2{,}001$). Mortality was 7.2 % per patient-year of follow-up in the metoprolol group versus 11.0 % in the placebo group (relative risk reduction 34 %; 95 % confidence interval 19–47 %).

Efficacy of Beta Blockers in the Secondary Prevention of Sudden Death

There are some data supporting the efficacy of beta blockers in patients known to have ventricular tachyarrhythmias. Hallstrom et al. [53] reported an adjusted relative risk reduction of 38 % (95 % confidence interval 23–50 %) related to beta blocker therapy in survivors of cardiac arrest. In the Antiarrhythmics Versus Implantable Defibrillators (AVID) registry [54], 366 patients with hemodynamically significant ventricular tachycardia or ventricular fibrillation did not receive therapy with either amiodarone, sotalol, or an implantable defibrillator. Approximately 150 of these patients were treated with beta blockers at the discretion of the treating physician. There was an approximately 50 % reduction in adjusted relative risk of mortality due to beta blocker therapy. Sotalol, which has both beta-blocking and Class III antiarrhythmic properties [55], and, to a greater extent, metoprolol [56] have been shown to reduce the incidence of ventricular tachyarrhythmias in patients with implantable defibrillators. Limited data [57] suggest that beta blocker therapy in patients with nonischemic dilated cardiomyopathy and ICDs is associated with a marked reduction in appropriate therapy for ventricular tachyarrhythmias. In a multivariate analysis from this study [57], beta blocker therapy was associated with a 0.15 relative risk (95 % confidence intervals 0.05–0.45, $P = 0.0007$) of appropriate ICD therapy. Additionally, Hreybe et al. [58] showed that time to first appropriate shock in patients who had received an ICD for secondary prevention was longer in patients treated with beta blockers compared to those who were not.

Renin–Angiotensin–Aldosterone System

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors have been extensively studied in patients at risk for sudden cardiac death. Although studies involving

ACE inhibitors have shown substantial reductions in total mortality (with risk reductions ranging from 8 to 40 %) and/or cardiovascular mortality, very few have shown similar effects with respect to arrhythmic death. Excluding the postinfarction period, ACE inhibitors have several possible antiarrhythmic actions. A direct antiarrhythmic effect has been reported, but supporting results are inconsistent [59, 60]. In patients with or without heart failure, hypokalemia has been shown to be an important risk factor for ventricular arrhythmias. Angiotensin-converting enzyme inhibitors can raise serum potassium levels, which may lead to a possible beneficial effect on the myocardial substrate, minimizing arrhythmic risk [2]. These results have not been consistent in other studies. However, ACE inhibitors have several direct and indirect effects on the autonomic nervous system that could modify the risk of ventricular arrhythmias [61]. They enhance baroreflex sensitivity, thereby reducing sympathetic and increasing parasympathetic tone. They may improve hemodynamics, leading to a decrease in circulating catecholamines. Adverse ventricular remodeling has been shown to have adverse effects on the conduction system, including increasing risk for ventricular arrhythmias. Angiotensin converting enzyme inhibitor treatment limits adverse remodeling and, additionally, may lead to reductions in ventricular arrhythmias [62]. It is also possible that SCD risks conferred by the ACE pathways are in part genetically determined [63].

The Acute Infarction Ramipril Efficacy Study (AIRE) and the Trandolapril Cardiac Evaluation (TRACE) study were the only placebo controlled trials with ACE inhibitors to show significant reductions in sudden cardiac death [2, 9]. In the AIRE study, 2,006 patients with recent MI and clinical evidence of heart failure were randomly assigned to treatment with ramipril (5 mg daily) or placebo. At 15 months, the ramipril group had 27 % reduction in total mortality. There was also a 30 % reduction in sudden cardiac death (12.3–8.9 %). In the TRACE study, 1,749 patients with an acute MI and ejection fraction ≤35 % were randomly assigned to treatment with trandolapril or placebo. At follow-up of 24 and 50 months, there was a 25 % decrease in cardiovascular deaths and a 26 % reduction in sudden cardiac death. A meta-analysis of intermediate or long-term post-MI ACE inhibitor trials (including AIRE and RACE) involving a total of 15,104 patients showed a trend toward decreased sudden cardiac death in all of the larger trials and an overall reduction in sudden cardiac death with an odds ratio of 0.80 (95 % confidence intervals, 0.70–0.92). There were also similar significant reductions in total and cardiovascular mortality [64].

In the Heart Outcomes Prevention Evaluation (HOPE) study, more than 9,000 patients with vascular disease or diabetes mellitus and cardiac risk factors were randomly assigned to treatment with ramipril or placebo [3]. After 5 years, there was a 26 % reduction in cardiovascular mortality and a 37 % reduction in cardiac arrest. Sudden cardiac death was not specifically studied. No randomized, controlled trials of an ACE inhibitor versus placebo in patients with chronic heart failure have shown a reduction in sudden cardiac death. The three major trials that have reported results for sudden death are the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS), the Studies of Left Ventricular Dysfunction (SOLVD)-Treatment, and SOLVD-Prevention [5, 6]. In the Second Veterans Administration Vasodilator-Heart Failure Trial (V-HeFT II), 804 men with New York Heart Association (NYHA) Class I through IV heart failure were randomly assigned to treatment with enalapril (20 mg daily) or the combination of hydralazine (300 mg daily) and isosorbide dinitrate (160 mg daily) [7]. At 2 years, the enalapril group had a 28 % reduction in total mortality. This effect was due to a 38 % decrease in the incidence of sudden cardiac death. It is possible that the beneficial effect of enalapril was due to an increase in sudden death in the hydralazine–isosorbide arm.

Angiotensin Receptor Blockers

Physiologically active levels of angiotensin II persist despite long-term therapy with ACE inhibitors and may also be formed by non-ACE dependent pathways. Possible arrhythmogenic mechanisms of angiotensin II include activation of neurohormonal agents (including norepinephrine, aldosterone, and endothelin) as well

as increased conduction velocity and shorter refractory periods in cardiac myocytes [65]. Furthermore, unlike ACE inhibitors, angiotensin II receptor blockers (ARBs) do not increase bradykinin levels, which also can increase norepinephrine levels [66]. Elevated catecholamine levels theoretically could result in more ventricular arrhythmias and sudden death. Therefore, direct blockade of angiotensin II receptors might further reduce morbidity and mortality in patients requiring blockade of the renin–angiotensin–aldosterone system. The beneficial effects of ARBs on arrhythmogenic substrate following myocardial infarction has been supported by a study which showed a decrease in the rate of positive findings on signal-averaged ECG in those patients taking ARBs [67]. Patients with congestive heart failure treated with ACE inhibitors and randomly assigned to treatment with spironolactone had significant decreases in sudden death despite significant increases in plasma angiotensin II [68]. Both ARBs as well as ACE inhibitors increase serum potassium levels, which may provide a potential protective mechanism against ventricular arrhythmias.

Angiotensin II receptor blockers have mostly been compared to ACE inhibitors in several heart failure or hypertension trials. Importantly, a meta-analysis has shown that the overall mortality rates for the two classes are similar [69]. Only one study showed a reduction in sudden death with ARBs compared with ACE inhibitors, and results of larger trials have countered these findings. In the Evaluation of Losartan in the Elderly (ELITE) study, 722 patients with NYHA Class II–IV heart failure and ejection fractions ≤40 % were randomly assigned to treatment with losartan or captopril [11]. At 48 weeks, the losartan group had a 45 % reduction in total mortality. There was also a decrease in the number of deaths attributable to sudden cardiac death (5 vs. 14 patients) with a relative risk reduction of 36 %. However, in the much larger ELITE II, 3,152 patients (with heart failure and ejection fraction ≤ 40 %) were randomly assigned to treatment with losartan or captopril [12]. At 1.5 years, there were strong trends toward reductions in overall mortality and sudden death with captopril compared to losartan. In the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL), losartan and captopril were also studied in patients after MI with heart failure, and favorable results for captopril, similar to those for ELITE II, were reported [14]. Thus, it appears that both ACE inhibitors and ARBs may reduce mortality and probably sudden death.

Aldosterone Receptor Antagonists

Neurohormonal suppression of the renin angiotensin-aldosterone system by ACE inhibitors alone is incomplete. Aldosterone can continue to exert harmful effects on the cardiovascular system in patients with heart failure. Aldosterone promotes sodium retention, magnesium and potassium wasting, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and vascular damage and impairs arterial compliance. Spironolactone, an aldosterone receptor antagonist and potassium-sparing diuretic, has gained wide acceptance for the treatment of severe congestive heart failure. In the Randomized Aldactone Evaluation Study (RALES), 1,663 patients with NYHA Class III or IV heart failure and ejection fraction ≤35 % were randomly assigned to treatment with spironolactone (25 mg daily) or placebo [70]. After a mean follow-up of 24 months, cardiac death was reduced by 31 %. This was due to a 36 % decrease in death from progressive heart failure and a 29 % reduction in sudden cardiac death. A selective aldosterone blocker, Eplerenone, was evaluated in the EPHESUS study in which 6,632 patients who had an ejection fraction of less than 40 %, experienced a myocardial infarction within 30 days, and had clinical signs of heart failure, were randomly assigned to Eplerenone treatment or standard treatment groups. The Eplerenone group had a reduction of all-cause mortality by 15 % ($p < 0.008$) [71] and a significant reduction in cardiac deaths (relative risk, 0.83; 95 % confidence interval, 0.72–0.94; $p < 0.005$) [72].

There are several possible mechanisms for a direct antiarrhythmic effect of spironolactone. One possible explanation is that aldosterone seems to enhance cardiac remodeling. Fibroblasts and inflammatory cells invade the perivascular space of damaged vessels, leading to fibrosis.

These changes can have adverse effects on the mechanical function, vasodilatory reserve, and electrical system of the heart [73]. A recent substudy of the RALES trial evaluated serum markers of collagen synthesis, which have been shown to correlate with morphological evidence of cardiac fibrosis [74]. Spironolactone decreased the levels of these markers at 6 months. Several studies have shown that non-potassium-sparing diuretics are associated with a dose-dependent increase in sudden cardiac death. One case–control study showed that the risk of primary cardiac arrest was increased with thiazide diuretics and the addition of a potassium-sparing diuretic reduced that risk [75]. Modification of electrophysiologic substrate is another potential mechanism of aldosterone blockade. In a canine model of heart failure induced by rapid ventricular pacing, Eplerenone attenuated increases in refractory periods and dispersion of refractoriness, as well as ventricular tachyarrhythmia induction [76].

Modulators of Cholesterol and Inflammation

3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Inhibitors

While the benefit of statin therapy in patients with coronary artery disease has been well-established in multiple large-scale randomized clinical trials, only a few studies have focused on the effect of statins on ventricular tachyarrhythmias in patients with coronary artery disease [77–79] or in patients with nonischemic cardiomyopathy [80–84]. Statins are a group of lipid-lowering drugs that are 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. Statins reduce CAD death and MI. As a class, they may indirectly exert an antiarrhythmic benefit by reducing the overall ischemic burden by preventing plaque progression. In addition, statins modulate endothelial function, signaling pathways for inflammation, endothelial nitric oxide synthesis, plasminogen, endothelin-1, platelet activation, angiotensin II receptor regulation, oxidative stress, sympathetic nerve activity, left ventricular mass regression, and left ventricular reverse remodeling. Statins may also have a direct antiarrhythmic property by modulating sarcolemmal ion channel function. Meta-analysis of 10 RCTs involving 22,275 patients who had CAD reported that statins reduced the rate of SCD from 3.8 % in the control group to 3.0 % in patients treated with statin (hazard ratio, 0.81; 95 % CI, 0.71–0.93) after 4.4 years [85].

A number of nonrandomized clinical studies have demonstrated dramatic reductions in arrhythmic events by statins in patients who have implanted ICDs. In an observational study, De Sutter et al. [86] reported that in patients with coronary artery disease receiving ICDs for secondary prevention of ventricular arrhythmias, treatment with lipid lowering drug therapy (59 % statins, 41 % fibrates) resulted in a substantial reduction in appropriate shocks (22 % in the group treated with lipid lowering drugs and 57 % in those not treated). In another observational study in patients with coronary artery disease receiving ICDs, Chiu et al. [87] reported that 30 % of patients taking statins received ICD therapy versus 50 % among those who were not receiving statins (hazard ratio 0.60). In the AVID trial [79, 86, 87], there was a reported 0.40 reduction in relative hazard (95 % confidence interval 0.15–0.58) for recurrence of ventricular tachycardia/fibrillation.

Effects of statins on mortality reduction in patients with coronary disease could be due to a number of potential pathways, including direct lipid lowering and reduction of atherosclerosis burden or possibly via antiarrhythmic effects. Several small randomized studies [82–84] in patients with nonischemic cardiomyopathy have shown that statin therapy was associated with significant improvement in NYHA class and left ventricular ejection fraction, suggesting that statins may operate through pathways mediating ventricular remodeling. The effect of statin use on time to death or resuscitated cardiac arrest and time to arrhythmic sudden death was evaluated in 458 patients enrolled in the DEFINITE (DEFIbrillators in Non-Ischemic cardiomyopathy Treatment Evaluation) study [88]. The unadjusted hazard ratio (HR) for death among patients on, versus those not on, statin therapy was 0.22 (95 % confidence interval 0.09–0.55; $p = 0.001$). The unadjusted HR for arrhythmic

sudden death among patients on, versus those not on, statin therapy was 0.16 (95 % CI 0.022–1.21; $p = 0.08$). The HR for appropriate shocks among patients on, versus those not on, statin therapy was 0.78 (95 % CI 0.34–1.82) after adjustment for baseline differences in the two groups. Statin use in the DEFINITE study was associated with a 78 % reduction in mortality [88]. Moreover, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) investigators found in a subgroup analysis that statin use was associated with reduced mortality risk in both ischemic and nonischemic cardiomyopathy, further supporting the hypothesis that statin use may reduce overall mortality and arrhythmic risk [89]. Overall mortality risk was significantly lower in those taking a statin (HR [95 % CI], 0.70 [0.58–0.83]). Mortality risk was lower with statin use in all prespecified subgroups: ischemic cardiomyopathy, nonischemic cardiomyopathy, implantable cardioverter defibrillator (ICD), and New York Heart Association II or III. Patients in MADIT-II [90] were evaluated for the effect of statin use on the probability of ICD therapy for the combined endpoint of VT/VF or cardiac death and for the end point of VT/VF alone. The cumulative rate of ICD therapy for VT/VF or cardiac death, whichever occurred first, was significantly reduced in those with ≥ 90 % statin usage compared to those with lower statin usage (p = 0.01). Horwich et al. [81] described the outcomes of 551 patients referred to a specialized cardiomyopathy center for heart failure or transplant evaluation; 55 % of the patients had a nonischemic cardiomyopathy. Forty-five percent of the total population was treated with statins, but only 22 % of those with nonischemic cardiomyopathy. There was a significant improvement in 1-year survival, without the need for urgent heart transplantation, in patients with nonischemic cardiomyopathy treated with statins. A meta-analysis of ten randomized controlled trials of statins (22,275 patients) demonstrated a 19 % risk reduction in SCD independent of lipid lowering effects [85].

The mechanism for possible antiarrhythmic effects of statins and sudden death and survival in patients with nonischemic cardiomyopathy remains unclear. In patients with coronary artery disease, statins have been reported to improve regulation of coronary arterial tone and nitric oxide-mediated endothelial function, inhibit cell proliferation, stabilize atherosclerotic plaques, exert anti-inflammatory properties, and provide anti-oxidant effects. The mechanism by which statins reduce ventricular tachyarrhythmias may relate indirectly to one or more of these effects. For example, the antioxidant and anti–cell-proliferative effects of statins may play a role in plaque stabilization and thus contribute to an anti-arrhythmic effect by reducing ischemia-related ventricular tachyarrhythmias. An antiischemic effect also is plausible, as a substantial proportion of patients with nonischemic cardiomyopathy are found to have coronary artery disease at autopsy [91]. Moreover, statins have been reported to be effective in the prevention of atrial fibrillation suggesting a direct antiarrhythmic effect [92–94]. Finally, small studies that have found improvements in ejection fraction and exercise capacity related to statin therapy support the notion that statins may have beneficial effects on left ventricular remodeling. Thus, it is most likely that statin therapy exerts multiple beneficial effects in patients with nonischemic cardiomyopathy by its lipid-lowering, antiinflammatory, antioxidant, autonomic effects and/or other effects [95].

Polyunsaturated Fatty Acids

Important n-3 polyunsaturated fatty acids (PUFAs) include eicosapentaenoic acid, docosahexaenoic acid, and alpha-linolenic acid. The cardioprotective mechanisms of n-3 PUFAs may include suppression of ventricular arrhythmias, favorable lipid metabolism, a decrease in blood pressure, antiinflammatory actions, platelet stabilization, and anticoagulant effects. Numerous studies have shown an inverse relation between fatty fish intake and coronary heart disease. Data from several trials, however, have suggested that the predominant effect of PUFAs may be a primary reduction in sudden cardiac death. Experimental evidence in isolated myocytes, animals, and preliminary studies in humans, points to a possible direct antiarrhythmic effect of n-3 PUFAs. In myocardial infarction models of canines fed n-3 PUFAs, a significantly decreased risk of ischemia-induced ventricular

fibrillation was noted [96]. Through their actions on I_{Na} and I_{Ca} L channels, the n-3 PUFAs cause mild hyperpolarization of the resting membrane potential, resulting in a larger threshold voltage and stimulus, and prolonging the refractory period of the cardiac cycle [97]. These properties may explain an enhanced electrical stability in the setting of ischemia and toxins. Several recent studies have investigated the role of n-3 PUFA in preventing arrhythmic events [98–101]. An epidemiological study has shown that Japanese who consume a high intake of n-3 PUFAs had a threefold decrease in the risk of myocardial infarction and nonfatal coronary events. However, studies on the antiarrhythmic effect of PUFAs have been less consistent. A randomized trial performed in the United States by Leaf et al. [102] in 402 patients with ICDs showed that there was a 28 % reduction to the time of first appropriate ICD shock, which was of borderline significance. A more recent larger trial performed in Europe failed to show a substantial decrease in ICD shocks with fish oil supplementation [98]. Differences in fish oil content or the definition of appropriate ICD shocks could have accounted for these differences.

Several prospective cohort studies have shown an association with n-3 PUFAs and sudden cardiac death in patients with and without known coronary disease. An analysis of the Nurses' Health Study cohort showed that of 76,763 participants, those with the highest intake of alpha-linolenic acid experienced significantly less SCD without a decrease in other fatal and nonfatal myocardial infarction [103]. In the DART trial, men who recently survived a myocardial infarction were randomly assigned to one of eight groups of dietary intervention [104]. In the group assigned to receive an increase in fatty fish consumption, at 2 years, there was a 33 % relative decrease in deaths due to coronary heart disease, whereas there was a nonsignificant increase in the incidence of nonfatal MI. The mortality benefit was mostly seen in the first 6 months. Similar results were reported in the Lyon Diet Heart study, in which patients randomly assigned to consume a Mediterranean diet, with a high alpha-linolenic acid content, had a 73 % decrease in the combined endpoint of cardiac death and nonfatal MI [105]. The GISSI Prevenzione study, a multicenter, open label, randomized trial, tested 11,323 patients with recent myocardial infarction [106]. Patients were randomly assigned in a 2 x 2 factorial design to receive n-3 PUFAs (1 g daily), vitamin E (300 mg daily), both, or neither. All patients received standard medical care and, in general, consumed a Mediterranean diet, with high amounts of fish and olive oil. Overall, there were 265 sudden deaths: 146 were instantaneous, 103 occurred within 1 h of symptom onset, 10 were documented to be arrhythmic, and six were unwitnessed. At an average of 42 months of follow-up, sudden death occurred in 2.7 % of control subjects and 2 % of patients receiving n-3 PUFAs ($P < 0.001$), accounting for 59 % of the total mortality benefit. Bucher and co-workers [107] conducted a meta-analysis of randomized, controlled trials of n-3 PUFAs in coronary heart disease. In their analysis, total mortality, fatal MI, and sudden death were significantly decreased by n-3 PUFAs, whereas there was a trend toward reduction in nonfatal MI. Lastly, Siscovik et al. [108] and Albert et al. [109] have recently linked the consumption of fatty acids with reduction of sudden death, building on the hypothesis that these compounds may provide anti-arrhythmic properties.

Electrolytes

Administration of potassium and magnesium, either intravenously in the acute setting or orally for chronic augmentation of blood levels of these electrolytes, can favorably influence the electrophysiologic substrate involved in ventricular arrhythmias. Pharmacologic agents that counter hypokalemia and hypomagnesemia can be considered as adjunctive therapies. Several agents, such as ACE inhibitors, angiotensin II antagonists, and aldosterone blockade, not only improve the myocardial substrate through reverse remodeling and other mechanisms described, but also modulate electrolyte levels, especially in heart failure, where diuretic use is common. These pharmacologic agents may help reduce the propensity for abnormally low electrolyte levels, which can heighten risk of ventricular arrhythmias through a number of mechanisms.

Genetic Polymorphisms: Molecular Pathways for the Prevention of Sudden Cardiac Death

With the advent of genomic medicine, polymorphisms may play a greater role in understanding risk for sudden death. One promising area has been the beta-2 adrenergic receptor, which is located on cardiac as well as on a number of non-cardiac tissues including vasculature, lung parenchyma, adipocytes, and platelets; its effects on these tissues may influence SCD risk. For instance, in adipocytes, catecholamine stimulation leads to lipolysis and release of non-esterified fatty acids. Higher non-esterified fatty acid levels are associated with ventricular ectopy and SCD. Lanfear et al. [110] explored certain beta-2 adrenergic receptor polymorphisms in the acute coronary syndrome setting and found a differential survival pattern in those prescribed beta blockers. This report suggested that certain polymorphisms in this receptor may influence sudden death risk. Sotoodehnia et al. [111] also has explored polymorphisms in the beta-2 adrenergic receptor and found that individuals with Gln27 (homozygous) were at increased risk of SCD and suggested that this receptor plays an important role in SCD in humans. These studies provide a glimpse of the future of sudden cardiac death research, which will likely involve the interface of genetics, physiology, pharmacology, and epidemiology.

Conclusions

In contrast to traditional Vaughan-Williams Class I and III antiarrhythmic drugs, medications with antiadrenergic, neurohormonal, lipid-lowering, and anti-inflammatory effects have been shown to decrease both total and sudden death mortality in patients with underlying structural heart disease [4, 8, 10, 13, 15]. There are some lessons that can be learned from the results of drug trials to decrease sudden death mortality.

Life-threatening cardiac arrhythmias that are by nature highly sporadic or at least in part dependent on a complex series of extracardiac influences can be modulated by drugs that modify the adrenergic and the renin–angiotensin–aldosterone systems. In addition, nonspecific drugs whose primary mode of action is on cardiac ion channels are not effective at reducing sudden death. This observation suggests that despite advances in our knowledge of the basic mechanisms for cardiac arrhythmias, our current understanding of the mechanisms of sudden death is not adequate to target specific ion channels to prevent sudden death. Further basic research is needed to more fully understand the mechanisms of sudden death. The implantable cardioverter-defibrillator (ICD) in combination with drug therapy remains the mainstay of SCD prevention but is likely to benefit only the small population at high risk who can be identified before a SCD event. The complexity of the problem cannot be overstated and integrative strategies spanning a broad range of scales from molecular through organism and population studies will be required to make progress in this area.

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35
Non-surgical Treatment and Prevention of Atrial Fibrillation

Patricia Tung and Peter J. Zimetbaum

Abstract

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Electrical, contractile and structural remodeling of the left atrium underlies the development of AF. AF can be classified as paroxysmal if the arrhythmia terminates within 7 days, persistent if it lasts longer than 7 days, or permanent if cardioversion was not attempted or failed. AF can be further classified according to mechanism of initiation. In general, AF can be expected to recur, although the pattern and tempo of recurrence is widely variable. AF is considered recurrent after two or more episodes, regardless of whether the patient is symptomatic.

Initial diagnosis of AF should include a thorough evaluation including family history of arrhythmia, structural heart disease and thyroid disorders. Management of new-onset AF may include electrical or pharmacologic cardioversion. Chronic management emphasizes symptom control and prevention of heart failure and thromboembolic disease through either a rate or rhythm control strategy and anticoagulation. For those who remain symptomatic, catheter ablation or surgical Maze procedure may be considered. As conventional antiarrhythmic medications are limited by efficacy and side effects, efforts are underway to identify therapeutics aimed at preventing conditions associated with the development of AF including hypertension and arrhythmogenic remodeling.

Keywords

Atrial fibrillation • Epidemiology • Classification • Acute treatment • Rate control • Rhythm control • Antiarrhythmic medications • Anticoagulation

Background

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice. Historically, the population prevalence of AF was estimated to be 0.4–1 %. However, it is now believed that the prevalence is increasing, with a projected six to ten million cases of AF in 2050 [1, 2]. AF is also known to increase

P. Tung, MD • P.J. Zimetbaum, MD (✉)
Cardiology Division,
Medicine Department,
Beth Israel Deaconess Medical Center,
185 Pilgrim Road,
Baker 4, Boston,
MA 02215, USA
e-mail: pzimetba@bidmc.harvard.edu

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dramatically with age and is estimated to affect 20 % of individuals older than 85 years [3]. AF affects men to a greater degree than women, and has a greater prevalence in whites than non-whites [1, 2, 4–6].

Classification

AF is characterized by rapid, irregular electrical activation of the atria with varying ventricular heart rates. The most commonly associated clinical conditions include hypertension, structural heart disease (valvular disease, hypertrophic cardiomyopathy, myocardial infarction), aging, and congestive heart failure. Pulmonary disease is also associated with AF and atrial flutter.

Multiple classification systems exist for AF that is not associated with a reversible cause. This multitude of systems reflects the difficulty in categorizing the wide variability in symptoms and presentations of AF. The classification system proposed by the American Heart Association, American College of Cardiology and the Heart Rhythm Society is based on the first detected episode of AF, whether symptomatic or not. The episode is classified as paroxysmal if it terminates within 7 days, or persistent if it lasts longer than 7 days. A patient is considered to have recurrent AF with two or more documented episodes. AF is permanent in cases where cardioversion has failed or has not been attempted [7].

Lone AF has been used to describe generally younger patients who present with AF in the absence of structural heart disease, pulmonary disease, hypertension, or other metabolic abnormality. This terminology has been largely abandoned with the understanding that AF in the absence of associated clinical risk factors is an increasingly heterogeneous entity. In some cases AF may be an inherited condition in which KCNQ1, KCNE2 or other genetic mutations result in defective I_{ks}, shortened action potentials and refractory periods [8, 9]. The presence of increased collagen deposition, the precursor to arrhythmogenic atrial fibrosis, has also been observed in the atria of many patients without other established risk factors for AF [10].

Autonomically-Triggered AF

There are several sub-categories of AF that are based on the mechanism of initiation. Autonomically-triggered AF occurs during exercise or in association with heightened vagal tone. The latter is frequently associated with sleep, large meals, or the termination of exercise. This form of AF frequently develops during middle age and is often paroxysmal or self-terminating and highly symptomatic [11].

AF in Hyperthyroidism

AF occurs in 10–25 % of patients with hyperthyroidism, although only 1 % of newly diagnosed cases of AF are due to hyperthyroidism. It is exceedingly difficult to maintain sinus rhythm in the context of hyperthyroidism. Therefore, a rate control strategy with beta blockers as first-line therapy should be employed. There is scant evidence that thromboembolic risk is increased in the presence of hyperthyroidism, and thus some practitioners choose to anticoagulate patients in this circumstance even in the absence of other risk factors for stroke [7].

AF in the Post-operative Setting

There is an approximate 50 % risk of developing AF following cardiovascular surgery. The risk is slightly greater following valvular surgery than for coronary artery bypass surgery [11]. Both beta-blockade and treatment with amiodarone pre-operatively has been shown to decrease the incidence of post-operative AF. Although the likelihood of being in sinus rhythm 4 weeks following surgery is the same regardless of whether a rate- or rhythm-control strategy is used, the presence of post-operative AF is associated with a higher mortality rate, length of stay and cost [7].

AF frequently occurs following surgical MAZE procedure or percutaneous AF ablation. In these situations, AF should be differentiated from atrial tachycardia, which may occur as an arrhythmic complication of these procedures. These arrhythmias typically resolve over several weeks, and many practitioners choose to treat patients with an antiarrhythmic drug (AAD) for 4–12 weeks following the procedure [11].

AF in Acute Ischemia

AF can be a consequence of acute ischemia or infarction with associated mitral regurgitation or congestive heart failure. AF is rarely the sole indicator of myocardial infarction or acute ischemia in the absence of significant chest pain or ECG changes [12]. However, chronic atrial ischemia can promote AF by impairing conduction and allowing stabilization of reentry via heterogeneous electrical activation.

AF and Dietary Triggers

Alcohol intake, particularly in a binging pattern, often precipitates AF. Chronic, excessive alcohol intake also seems to predispose to AF. In clinical practice, dietary caffeine intake is an inconsistent trigger for AF [11].

AF in Association with Congestive Heart Failure

AF and congestive heart failure share common risk factors such as hypertension and diastolic dysfunction. In addition, mechanisms such as atrial fibrosis and contractile remodeling are common to both and these entities are frequently encountered together. AF in patients with left ventricular dysfunction and congestive heart failure is known to increase mortality [13]. Pharmacologic therapies such as betablockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, and digoxin can be used in the treatment of both. In addition, antiarrhythmics can be beneficial in restoring of sinus rhythm. Amiodarone and dofetilide have been shown to reduce mortality and hospitalizations for heart failure in this population [14, 15].

Natural History

Paroxysmal AF may last minutes to hours and often terminates spontaneously. This pattern may persist for many years, or may progress to chronic AF. AF rarely occurs in isolation, and can be expected to recur, although in an often unpredictable pattern. The exception to this rule is AF associated with a reversible cause such as hyperthyroidism or cardiac surgery. The presence of AF carries an increased risk of stroke, congestive heart failure and overall mortality. The mortality rate for AF patients is approximately double that for those in sinus rhythm [5, 16, 17].

The majority of patients with new-onset AF experience symptoms of dyspnea, palpitations and fatigue. Patients with diastolic dysfunction, in particular hypertrophic cardiomyopathy or aortic stenosis, develop symptoms due to the loss of atrial contribution to ventricular filling. However, the majority of symptoms result from rapid ventricular rates. Most report diminishment of symptoms with time and therapy, but for many AF remains a significant source of morbidity.

Mechanisms of Atrial Fibrillation

There are multiple theories regarding whether the primary mechanism underlying AF is that of multicircuit reentry versus a focal ectopic source leading to fibrillatory conduction. However, it is increasingly recognized that AF requires abnormal or remodeled atrial tissue as a substrate. Remodeling describes any change in atrial structure or function. Electrical, contractile, and structural remodeling are well-described processes that occur in the atria of AF patients. Many theories exist regarding which process is the primary determinant of AF. In all likelihood, a combination of these mechanisms precipitates the development of AF.

Electrical Remodeling

It is generally accepted that rhythm disturbances can lead to persistent electrophysiologic changes. This electrical remodeling is often referred to as atrial tachycardia remodeling (ATR), and can result from autonomically-triggered tachyarrhythmias, or any source of sustained, rapid heart rate. Rapid heart rates alter the electrical properties of atrial myocytes, principally by shortening the atrial effective refractory period (AERP). Wijfells demonstrated that perpetuation of tachyarrhythmias increases the propensity of the atrial myocytes to develop electrophysiologic characteristics that allow for

stabilization of AF; thus leading to the concept that "AF begets AF" [18].

ATR is believed to shorten the action potential duration (APD), and consequently the AERP, via reduced inward L-type Ca2+ currents as well as enhanced outward K+ channels. This occurs when rapid atrial rates cause an abrupt increase in calcium loading. In response, atrial myocytes respond by decreasing I_{cal} in an attempt to protect from calcium overload. This leads to shortened action potential duration. The I_{to} potassium channel has also been shown to be decreased in ATR [19]. The combination of these electrophysiologic changes is thought to lead to a reduced APD and AERP. Changes in connexin function leading to heterogeneous conduction and AF susceptibility have also been described as a result of ATR [20].

Contractile Remodeling

Contractile remodeling is believed to occur primarily following conversion to sinus rhythm following a period of AF, and results in reduced atrial contractility. This reduction in contractility enhances atrial dilation, which may allow for the perpetuation of AF through longer and more numerous electrical circuits. Furthermore, the reduced contractility is believed to increase the risk of stroke and thromboembolism in the period following cardioversion to sinus rhythm [21].

Structural Remodeling

Fibrosis is a hallmark of atrial structural remodeling and a common final pathway for multiple clinical conditions. Fibrosis is closely associated with the development of AF and two types of fibrosis have been described by Burstein and Nattel. In reparative fibrosis, collagen deposits replace degenerating myocytes within the normal geometry of myocardial tissue. In contrast, reactive fibrosis involves the deposition of fibrillar collagen between myocytes, causing expansion of the interstitium [22]. The two processes often occur concurrently. See Fig. 35.1 for an illustration of atrial fibrosis mechanisms.

Several factors including angiotensin II (ATII), transforming growth factor beta-1 (TGF-B1), platelet-derived growth factor (PDGF) and connective tissue growth factor (CTGF) have been implicated in atrial structural remodeling. AT II is known to mediate fibrosis in a variety of clinical conditions including CHF, hypertensive heart disease, and myocardial ischemia. TGF-B1 is secreted by cardiac myocytes and fibroblasts and acts as a mediator of ATII in a positive feedback loop. PDGF also stimulates fibroblast growth. Finally, CTGF is regulated by both ATII and TGF-b1 and directly activates fibroblasts.

Structural remodeling and ATR in concert are believed to promote AF by providing a vulnerable substrate and trigger. Fibrosis affects conduction by disrupting electrical coupling. In animal models, atrial fibrosis has been shown to cause localized regions of conduction slowing, which provides a vulnerable substrate for AF. ATR alters the electrical properties of atrial myocytes, and in doing so, may provide a trigger for arrhythmia.

ATR is also thought to precipitate AF via ectopic activity that arises from increased atrial expression of ion channel subunits leading to a steeper phase 4 slope [23]. Additionally, abnormalities in calcium metabolism can cause delayed afterdepolarizations, which may also lead to increased ectopy. Figure 35.2 illustrates the process by which remodeling promotes AF.

Evaluation of New-Onset Atrial Fibrillation

Initial evaluation of all patients with AF should include a thorough history for assessment of external precipitants such as alcohol use, thyroid disease or the presence of an additional supraventricular arrhythmia. The history should include a thorough evaluation of family history for the presence of arrhythmia and structural heart disease.

With regard to diagnostic testing, a thyroid stimulating hormone level should be assessed. Transthoracic echocardiogram is also indicated to evaluate for valvular disease, cardiomyopathy and congenital heart disease, as well as to define atrial dimensions and ventricular function. Ambulatory ECG monitoring is helpful in correlating symptom and arrhythmia presence and frequency.

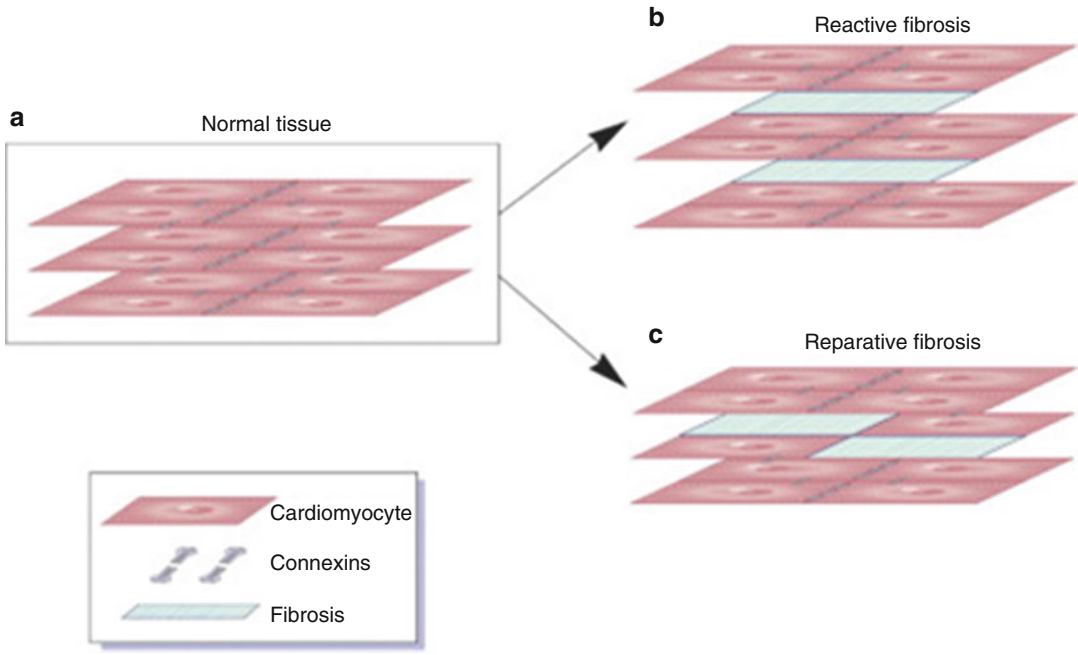

Figure 35–1. Mechanisms of atrial fibrosis. Schematic illustrating how fibrosis disrupts myocyte coupling cardiomyocytes in normal myocardial tissue (**a**) are electrically coupled primarily in an end-to-end fashion by intercellular gap-junctional complexes. Reactive fibrosis results in extracellular matrix expansion between bundles of myocytes (**b**), while reparative fibrosis replaces degenerating myocytes (**c**). Both patterns of collagen distribution become exaggerated during structural remodeling. Figure illustration by Rob Flewell (From Ref. [22]. Reprinted with permission from Elsevier Limited)

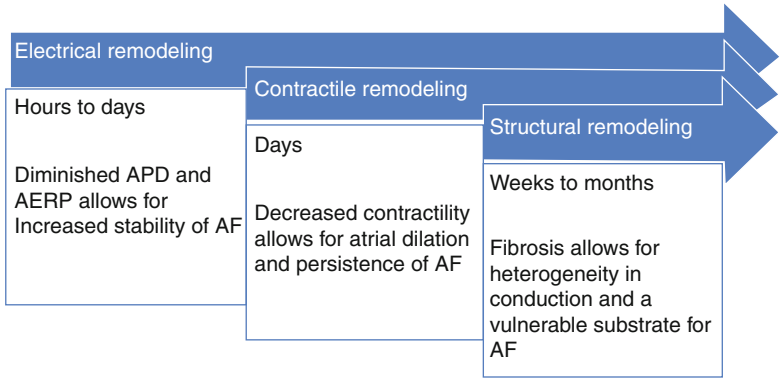

Figure 35–2. Remodeling promotes AF

For patients who present with reduced ventricular function at first diagnosis, and who are felt to have a tachycardia-induced cardiomyopathy, restoration of sinus rhythm can be attempted. Once sinus rhythm is restored or rate control implemented, an evaluation of ventricular function is repeated in 3 months for assessment of improvement.

Cardioversion

Cardioversion to sinus rhythm can occur spontaneously, via pharmacologic means or as a result of direct current electricity. Fifty-percent of patients with paroxysmal AF will spontaneously convert to sinus rhythm within the first 48–72 h. For those who do not convert, oral or intravenous

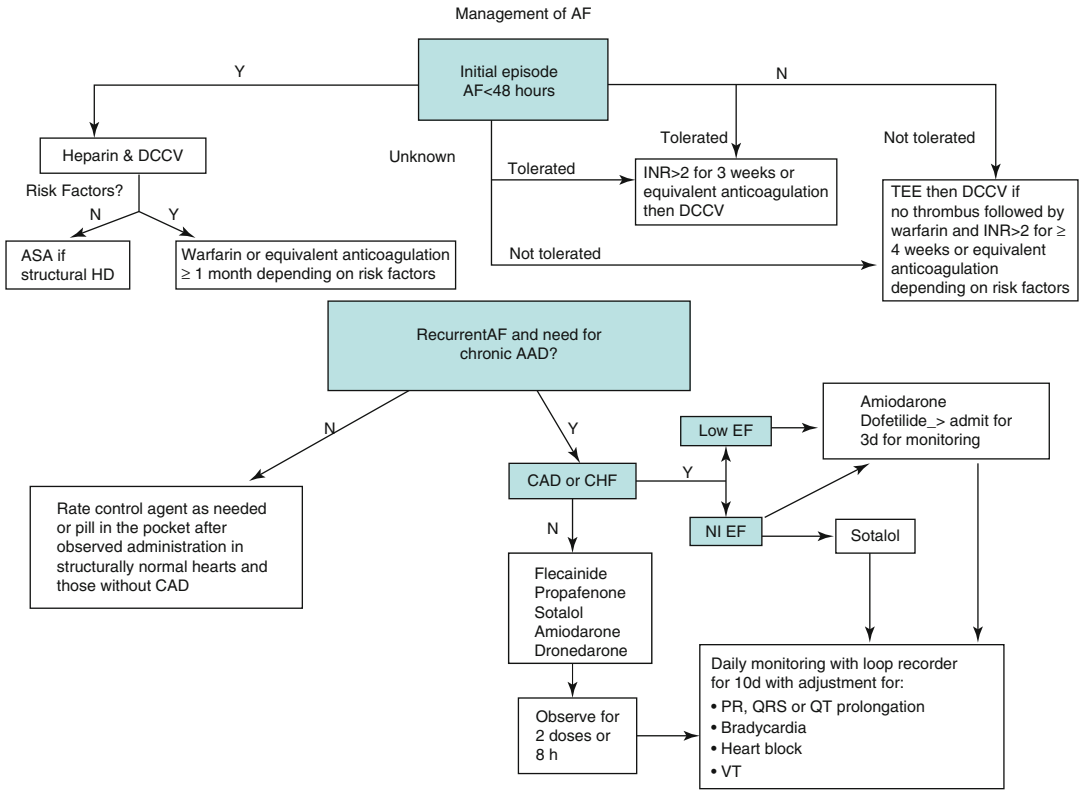

Figure 35–3. Acute and chronic management of AF

therapy can restore sinus rhythm in approximately 30–50 % of patients [11]. In patients in whom the episode of AF is felt to be of longer than 48 hours duration, anticoagulation should be initiated, and a transthoracic echocardiogram performed to evaluate for thrombus. Figure 35.3 illustrates a suggested approach to the acute and chronic management of AF.

There are multiple therapeutic options for pharmacologic cardioversion including the intravenous antiarrhythmic drugs (AADs) procainamide, ibutilide, amiodarone and vernakalant. Intravenous procainamide is effective at restoring sinus rhythm, but requires monitoring for hypotension and QT prolongation and is rarely used. Ibutilide is more effective for the conversion of atrial flutter than AF. It is also associated with QT prolongation and torsade de pointes and patients must be monitored for four hours following infusion. Intravenous amiodarone is modestly effective at restoring sinus rhythm, and its use may also be complicated by hypotension.

Vernakalant hydrochloride is the most recently developed agent for the conversion of AF. It acts primarily by blocking the I_{Kur}, I_{to}, I_{Kr}, and I_{KACh} channels in an atrial-selective fashion. In animal and early human studies, vernakalant prolonged the atrial refractory period without prolonging the ventricular refractory period [24, 25]. In three randomized, placebo-controlled trials, intravenous vernakalant was superior to placebo in rapidly converting short duration AF to sinus rhythm [26–28]. It was not effective in converting atrial flutter to sinus rhythm.

A randomized clinical trial comparing vernakalant to amiodarone found that vernakalant was superior for rapid conversion of short-duration AF to sinus rhythm [29]. A safety and efficacy study of an oral formulation of vernakalant found similar rates of conversion of short-duration AF to sinus rhythm with similar side effects [30]. The principal side effects are transient prolongation of the QT interval and hypotension. Vernakalant is currently approved for use in Europe.

The Class 1C agents flecainide and propafenone have been administered as single high dose therapy for cardioversion. This "pill in the pocket" approach should be restricted to patients with structurally normal hearts and those without active coronary artery disease, and should be performed in a monitored setting prior to being implemented as an outpatient strategy [31]. Sotalol and dofetilide can also convert AF to sinus rhythm but should be used in a monitored setting for this purpose [32]. Finally amiodarone is reasonably safe to administer during atrial fibrillation in the outpatient setting. The rate of conversion to sinus rhythm is modest (30 %) and conversion often does not occur until a few weeks of therapy has been administered [33].

Electrical cardioversion is highly effective and restores sinus rhythm in at least 85 % of cases [34]. However, up to 40 % of cardioversions are complicated by an unstable return to sinus rhythm or early recurrence of AF (ERAF) [35,36]. ERAF has been defined variably as the return of AF from within 1 min to 1 day following cardioversion to sinus rhythm [36]. When this occurs, there is limited value to repeated attempts at electrical cardioversion in the absence of additional treatment such as an AAD [37]. Typically, treatment with an AAD is initiated and repeat cardioversion is attempted after several weeks [37].

Restoration of sinus rhythm is associated with a gradual recovery in atrial mechanical function over the first 2–3 weeks following cardioversion. However, during that interval, the risk for thromboembolism persists. To reduce this risk, therapeutic anticoagulation beginning at or before the time of cardioversion and continuing for 4 weeks is recommended [37]. Subsequently, continuation of anticoagulation depends on the presence of clinical risk factors for stroke and recurrence of AF.

Complications of Cardioversion

Cardioversion is considered a safe procedure. However, it can be complicated by bradycardia in the setting of intrinsic or drug-induced sinus node dysfunction. Atropine can be employed peri-procedurally in the case of marked bradycardia. QT prolongation and torsade de pointes can also occur in the setting of previous treatment with potassium blocking drugs. Post-cardioversion pulmonary edema is a poorly characterized and rare clinical entity that is thought to affect 1–3 % of cases [38,39]. It is not consistently associated with left ventricular dysfunction, generally develops within 24–48 h following cardioversion and is managed with diuretics [11]. Finally, the most serious complication of cardioversion is stroke or systemic embolism from a previously undetected thrombus. This is minimized through the appropriate use of therapeutic anticoagulation and transesophageal echocardiography prior to cardioversion.

Management

Management of AF patients is based on symptom control as well as prevention of heart failure and thromboembolic disease. Prevention of the former relies on rate or rhythm control, while prevention of the latter relies on antithrombotic therapy.

Rhythm versus Rate Control

Multiple studies in patients with and without congestive heart failure have evaluated the health outcomes associated with a strategy of rate control compared with rhythm control in patients with AF [40–47]. These studies, which included predominantly patients over age 60 with at least one risk factor for stroke, failed to demonstrate a mortality benefit associated with a rhythm control strategy. This lack of benefit was in part related to toxicities associated with antiarrhythmic drug therapy as well as excess stroke risk in patients in whom anticoagulation was discontinued [48]. Although important groups of patients, including younger individuals without thromboembolic risk factors and the elderly (>80 years) were excluded from these trials, the results were applicable to a large percentage of patients with AF.

The difficulty for clinicians remains the lack of data on rhythm control for large groups of patients with AF who were not represented in the clinical trials such as lone AF and the elderly. Lone AF represents 15–20 % of the AF population,

and those over the age 80 years represent 35 % [1]. Thus, more than 50 % of all patients with AF are not represented in the primary clinical trials. In these and other patients, considerations such as symptoms, exercise capacity and the prevention of adverse remodeling may support a decision to pursue a strategy of rhythm control. For example, the ability to prevent the progression from paroxysmal to chronic AF via rhythm control – which will likely lessen the effect of potentially curative therapies – warrants consideration. In addition, given the increase in AF-related stroke risk that occurs with aging, a rhythm control strategy in the elderly may ultimately reduce the overall risk of stroke. Current practice guidelines recommend antiarrhythmic therapy for patients with significant symptoms despite adequate rate control [49]. However, rate control as a primary management strategy will likely be challenged with advances in ablative and pharmacologic therapies for AF.

Long-Term Rhythm Control

Antiarrhythmic drugs are twice as effective as rate-control agents at maintaining sinus rhythm [50]. In a recent meta-analysis of AADs, disopyramide, quinidine, flecainide, propafenone, dofetilide, sotalol, and amiodarone all significantly reduced the rate of recurrent AF compared to placebo or no treatment. Disopyramide and quinidine were associated with an increased risk of mortality, and all antiarrhythmics except amiodarone and propafenone had an increased likelihood of proarrhythmia [51]. In further studies, amiodarone has been found to be superior to other AADs for the maintenance of sinus rhythm. It is approximately 60–70 % successful for suppressing symptomatic AF at 1 year, compared to 40–50 % for all other antiarrhythmics [11].

Newer Antiarrhythmic Drugs

Dronedarone is a non-iodinated benzofuran derivative that resembles amiodarone in its inhibition of the I_{Kr}, I_{Ks}, I_{Kur}, I_{K1}, and I_{To} potassium channels and of sodium and L-type calcium channels. However, the iodine moieties of amiodarone have been eliminated in order to reduce potential thyroid and pulmonary toxicities. It also contains a methylsulfonamide group that results in a shorter half-life and reduced accumulation in tissue [52–55]. Dronedarone was shown in two large randomized, controlled trials to be superior to placebo in maintaining sinus rhythm [56]. The median time to first episode of AF was approximately double that of placebo, and dronedarone significantly reduced the ventricular rate during the first recurrence.

In comparison to amiodarone, dronedarone is less effective at maintaining sinus rhythm but has been found to have decreased rates of thyroid, neurologic, skin and ocular toxicities than amiodarone [57]. In patients with depressed ejection fraction and decompensated heart failure, dronedarone was associated with increased mortality, and is therefore approved for suppression of AF in patients with ejection fractions greater than 35 % and without decompensated heart failure [58]. Dronedarone was also found to increase creatinine, though without affecting renal function. A large safety study of dronedarone in patients with atrial fibrillation and without decompensated heart failure found the antiarrhythmic drug to be associated with a reduction in cardiovascular mortality, hospitalizations and stroke [59]. Recently the PALLAS study, which compared dronedarone with placebo in patients with permanent atrial fibrillation, was stopped early due to excess mortality and stroke risk in patients taking dronedarone [60].

Ranolazine is a new drug approved for the management of chronic angina. It blocks multiple currents including peak and late I_{Na}, I_{CaL} and I_{kr}. Preliminary clinical data using ranolazine in a non-AF population demonstrated a reduction in supraventricular arrhythmias including atrial fibrillation [61]. Experimental data has demonstrated the synergistic potential for the combination of ranolazine with amiodarone or dronedarone to reduce the development and facilitate the termination of atrial fibrillation [62, 63]. In addition it is postulated that the late sodium current contributes to the prolongation of the action potential duration associated with reduced I_{kr} at slow heart rates. Inhibition of I_{Na} with ranolazine or vernakalant may reduce the risk of TdP associated with I_{kr} inhibition. It remains to be determined if combination therapy

with ranolazine or vernakalant and I_{kr} blockers such as sotalol, quinidine or dofetilide will reduce the risk of TdP [64–66].

Catheter Ablation

Catheter ablation is typically reserved for patients who fail antiarrhythmic medications and who remain extremely symptomatic. Early catheter ablation techniques simulated the surgical MAZE procedures, and were found to have a modest success rate and a considerable rate of serious complications. After Haissaguerre et al. demonstrated the significance of electrical triggers emanating from the pulmonary veins, catheter ablation techniques were refined, leading to improved success and decreased rates of complications [67].

Several analyses have found catheter ablation to be superior to AADs in terms of efficacy [68–70]. However, data on the long-term success is variable. One of the largest studies of outcomes following catheter ablation found cure rates of 77.6 % among those with paroxysmal AF as compared to 67 % for non-paroxymsal AF at approximately 5 years. Following repeat ablation, the cure rates at almost 5 years following ablation for paroxysmal AF and non-paroxysmal AF increased to 92.4 and 84 %, respectively [71]. Evaluation of patients with paroxysmal AF randomized to ablation versus AADs also found multiple quality of life indices to be superior among those who underwent ablation compared to those on antiarrhythmic therapy at up to 9 months following ablation [72].

However, even among patients with paroxysmal AF, the rate of recurrence remains relatively high. Many practitioners have continued the use of AADs in an effort to reduce the rate of recurrence. However, Leong-Sit et al. found that administration of AAD for 6 weeks following ablation helped to decrease the rate of early recurrence, but did not affect recurrence at 6 months [73]. One study examined the role of inflammation and found lower rates of immediate and mid-term recurrence of AF in patients who received corticosteroids in the days following ablation [74]. The mechanism for recurrence of AF following ablation remains unknown at this time.

Principles of Rate Control

For patients in whom rhythm control is not pursued, control of the ventricular rate is critical to mitigating symptoms associated with AF and for preventing tachycardia-induced cardiomyopathy. First line therapy for heart rate control in AF is beta-blockade. Calcium channel blockers are used for patients who have contraindications to beta-blocker therapy such as asthma, depression, significant fatigue or exacerbation of vascular disease. Digoxin is relatively ineffective as a single rate control agent but can be useful as an adjunctive agent in patients with cardiomyopathy [37, 49].

A recent study comparing lenient (<110 bpm at rest) versus strict (<80 bpm at rest and <110 with moderate exertion) heart rate control in permanent AF patients found no increased risk of death, hospitalization for heart failure, stroke, systemic embolism, major bleeding or arrhythmic events in lenient rate control compared to strict rate control subjects. In addition, the rate of symptoms was similar among the two groups, but there were fewer clinical encounters and a greater proportion of subjects reaching target heart rates among the lenient rate control group [75].

A particularly challenging population in which to achieve rate control is the conditioned athlete with resting bradycardia and exercise-induced tachycardia. For these patients, an increased dose of beta-blocker or calcium channel blocker prior to exercise may control the heart rate during activity. Finally, for those in whom heart rate control is not easily achieved, ablation of the atrioventricular junction may be an option. Although a junctional escape may remain following the procedure, this should not be considered reliable, and a permanent pacemaker should be inserted at the time of ablation.

Prevention of Thromboembolism

The risk of thromboembolism and stroke in AF is based on the presence of clinical risk factors. Multiple schema have been proposed to classify a patient's risk for stroke based on particular comorbidities and in some cases, on

echocardiographic parameters. The $CHADS_2$ score is the simplest stroke risk stratification system and assigns a single point for the presence of congestive heart failure, hypertension, age, and diabetes, and two points for the presence of prior TIA or stroke. Chronic oral anticoagulation is recommended for AF patients with a $CHADS_2$ score ≥2 [7].

One challenge of the $CHADS_2$ and other risk stratification systems is that the included risk factors are derived from the non-treatment arms of clinical trial cohorts and a single observational cohort, the Framingham Heart Study. Therefore, these scoring systems likely exclude important risk factors for stroke. A review of the currently measured risk factors concluded that only four (stroke/TIA, diabetes, hypertension and advanced age) of the five entities behaved consistently as independent risk factors [76]. Furthermore, there is wide variability in terms of the proportion of patients categorized as low-, intermediate-, and high-risk under different schema. Finally, existing classification systems are of modest predictive value in predicting stroke and thromboembolism, with most achieving a C-statistic of 0.6 [76–78].

In an attempt to improve the predictive value for stroke and thromboembolic disease, the CHA_2DS_2-VASc score was developed. In addition to the $CHADS_2$ risk factors, the categories of age 64–75, presence of vascular disease, and gender were included. Under CHA_2DS_2-VASc, anticoagulation is recommended for patients with 1 high risk clinical factor, defined as age ≥75 or history of prior stroke/TIA, or two or more combination risk factors. Analysis of the CHA_2DS_2-VASc score found an improved predictive value for stroke and thromboembolism compared to $CHADS_2$. Furthermore, there were low event rates in patients deemed low-risk, and the proportion of patients classified as intermediate-risk was substantially lower (15.1 % versus 61.9 %) under CHA_2DS_2-VASc [78].

Recent studies have established a correlation between burden of arrhythmia and stroke risk [79–81]. In one study, the addition of AF burden to the $CHADS_2$ and CHA_2DS_2-VASc scores improved the ability to correctly risk-stratify AF patients and risk for stroke [82]. The ASSERT study identified the presence of greater than 6 min/day of pacemaker detected AF to be a risk factor for stroke [83]. In this study stroke risk was mostly associated with an AF burden in excess of 15 h per day. It is possible that AF burden will be used in establishing stroke risk in AF patients in the future. However, at present AF burden is not routinely used in clinical practice to risk stratify patients.

Vitamin K Antagonists

Oral vitamin K antagonists have been the single option for chronic anticoagulation for the past five decades. Their efficacy in reducing the risk of stroke or thromboembolism in patients with non-valvular AF is well-established. A meta-analysis of randomized trials found a 64 % reduction in the risk of stroke or thromboembolism, and a 26 % reduction in overall mortality with vitamin K antagonists [84].

Despite its position as the gold-standard of anticoagulation, treatment with Vitamin K antagonists remains problematic for a considerable number of patients, either due to inability to regulate therapeutic levels, interaction with concurrent medications or difficulty with adherence to the medication regimen. Further complicating stroke prevention is the variability in clinical patterns of anticoagulation in AF. One study found that on average, 40 % of patients with AF receive warfarin regardless of CHADS score [85]. Furthermore, multiple studies have demonstrated that the average amount of time a patient taking warfarin is in the therapeutic range (TTR) is roughly 55–65 %, with 65 % representing the minimum TTR needed to achieve the expected benefit of warfarin [86–88]. Given these difficulties with warfarin, alternative antithrombotic regimens have been explored for the prevention of stroke in patients with AF.

Platelet Inhibition

Multiple studies have examined the effect of platelet inhibition, most commonly aspirin, on the risk of stroke. In a meta-analysis of all anti-platelet trials, the risk for stroke or thromboembolism was reduced by 22 %, with the most significant reduction in ischemic stroke [84, 89]. However, direct comparison of vitamin K antagonists to aspirin

has shown superiority of the former, with a reduction in risk of 39 % [84, 89].

Alternative Antithrombotic Regimens

Although vitamin K antagonists are superior to aspirin, alternative antithrombotic regimens have been tested for patients unable to take warfarin. The combination of aspirin plus clopidogrel was inferior to warfarin with regard to stroke reduction, with no significant difference in bleeding rates [87]. In a related study, aspirin alone was compared to aspirin plus clopidogrel. Combination anti-platelet therapy was superior to aspirin alone in stroke prevention but a significant increase in major bleeding was seen with combination therapy, with rates approaching that seen with warfarin therapy [90]. Thus, dual antiplatelet therapy offers no advantage over anticoagulation with warfarin, but single or dual antiplatelet therapy does provide some protection against stroke for patients unable to take vitamin K antagonists.

The oral Factor Xa inhibitors represent an emerging class of anticoagulants, and several have been evaluated in clinical trials. Rivaroxaban, a once daily compound, was found to be non-inferior to warfarin for the prevention of stroke in patients with AF in a large, double blind, randomized trial. The risk of major bleeding was not increased and intracranial bleeding was actually decreased [91, 92]. In subsequent analyses, rivaroxaban was not found to be superior to warfarin [92]. Rivaroxaban was recently approved for the prevention of stroke and thromboembolism in patients with AF in the United States.

Apixaban, another oral Factor Xa inhibitor, was compared in a large, randomized trial to varying doses of aspirin for the prevention of stroke and thromboembolism in AF patients deemed unsuitable for vitamin K antagonist therapy. Apixaban was superior to aspirin and the trial was terminated prematurely due to a clear clinical benefit from apixaban [93, 94]. In a large, randomized controlled trial, apixaban was superior to warfarin in reducing stroke and systemic embolism, and was found to have decreased rates of bleeding and mortality [95]. Apixaban was recently approved for the prevention of stroke and thromboembolism in patients with AC in the United States.

Direct thrombin inhibitors represent another emerging class of oral anticoagulants. Dabigatran etexilate, the first new antithrombotic therapy to become available for use in the last 50 years, was approved for prevention of stroke and systemic embolism in AF in 2010. Two doses of dabigatran were tested against warfarin with the higher dose superior in preventing stroke but with increased rates of gastrointestinal bleeding; the lower dose was non-inferior to warfarin. Both dosages were associated with significantly lower rates of intracranial hemorrhage than warfarin. Dabigatran is approved for the prevention of stroke and systemic embolism in AF in Europe and the United States [86]. For patients taking warfarin without difficulty, the new antithrombotic therapies may not offer a significant advantage. However, individual patient characteristics may prompt consideration of all therapeutic options for those with AF who merit chronic anticoagulation. Specific differentiating characteristics of these agents include side effect profiles and degree of renal clearance. See Table 35.1 for a comparison of novel anticoagulants.

Prevention

Treatment of atrial fibrillation with conventional antiarrhythmic therapies is limited by efficacy and the potential for serious side effects. Consequently, development of new therapeutics for AF has focused on both treatment of conditions known to promote AF, such as hypertension, as well as prevention of arrhythmogenic remodeling.

Risk Factor Targets

Hypertension is the most common risk factor for the development of AF. Multiple studies have examined the effect of blood pressure control on AF, as well as on stroke and heart failure. The largest of these studies, the ACTIVE-I trial found that patients receiving irbesartan were no less likely to have AF recurrences or hospitalizations [99]. However, the majority of subjects in this trial had well-controlled blood pressure, which may have obscured any benefit of irbesartan on reducing AF recurrence.

Congestive heart failure is also a significant risk factor for the development of AF, likely through

Table 35–1. Comparison of newer anticoagulants

	Dabigatran 110 mg[a] vs warfarin	Dabigatran 150 mg vs warfarin	Rivaroxaban vs warfarin	Apixaban vs warfarin
Half-life	12–17 h [96]	12–17 h [96]	5–12 h [97]	12 h [98]
Daily dosing	75 mg[a] twice daily (CrCl 15–30 mL/min)	150 mg twice daily (CrCl > 50 mL/min)	20 mg daily 15 mg daily (CrCl 30–49 mL/min)	5 mg twice daily
Clearance	Renal	Renal	Renal	25 % Renal
Bleeding risk				
Major non-CNS	RR 0.80 (0.69–0.93) p = 0.003	RR 0.93 (0.81–1.07) P = 0.31	RR 1.03 (0.96–1.11) P = 0.44	RR 0.79 (0.68–0.93) P = 0.004
CNS	RR 0.31 (0.20–0.47) P < 0.001	RR 0.40 (0.27–0.60) p < 0.001	RR 0.67 (0.47–0.93) P = 0.02	RR 0.42 (0.30–0.58) P < 0.001
Efficacy	RR 0.91 (0.74–1.11) p < 0.001 for non-inferiority p = 0.34 for superiority [86]	RR 0.66 (0.53–0.82) p < 0.001 for non-inferiority P < 0.001 for superiority [86]	RR 0.88 (0.75–1.03) p < 0.001 for non-inferiority (ITT analysis) P = 0.12 for superiority [92]	RR 0.79 (0.66–0.95) p < 0.001 for inferiority p = 0.01 for superiority [95]

[a]Dabigatran was tested at 110 mg twice daily and 150 mg twice daily in clinical trials. However, only the 75 mg twice daily and 150 mg twice daily doses were approved in the United States

the mechanism of structural remodeling of the atria. No specific therapies targeting heart failure have been studied with regard to prevention of AF. However, strategies aimed at primary and secondary prevention of ischemic heart disease that ultimately may reduce CHF have indirect benefits for the prevention of structural remodeling and AF.

Upstream Therapy

As more is understood about the mechanisms of AF, widespread efforts targeted at preventing arrhythmogenic remodeling are underway. One such target has been the renin-angiotensin-aldosterone system, which has been implicated in the development of atrial structural remodeling and fibrosis. Several initial clinical studies suggested that angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) had a beneficial effect in the primary and secondary prevention of AF [100, 101]. A recent randomized controlled trial found a lower rate of first recurrence of AF among patients taking valsartan and amiodarone compared to amiodarone alone, but the difference was not statistically significant [102].

Components of the inflammatory cytokine pathway, which are thought to contribute to atrial structural remodeling, have also been examined as targets for AF prevention. Several studies of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have shown benefit [103, 104]. The exact mechanism by which statins decrease the occurrence of AF is unknown, but is thought to be via pleiotropic and anti-inflammatory effects. Initial meta-analyses found a nearly 35 % reduction in the risk of the development or recurrence of AF in patients taking statins [105–108]. However, a more recent meta-analysis that included both published and unpublished studies found no evidence that statins prevent the occurrence or recurrence of AF [109]. Animal and small clinical studies have found an antiarrhythmic effect of omega-3 polyunsaturated fatty acids, perhaps by downregulation of connexins or stabilization of cardiac membranes [110].

Another potential target for future therapeutics is prevention of ATR or electrical remodeling. The changes in ion channels resulting from ATR have been shown to predict a decreased response to antiarrhythmic drugs. Drugs such as mibefradil and amiodarone may prevent ATR by preventing the reduction in refractory period that acts as a substrate for the development of AF [111, 112].

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36
Surgical Treatment of Atrial Fibrillation

John M. Stulak and Hartzell V. Schaff

Abstract

While most patients with atrial fibrillation (AF) are treated with medical therapy or catheter ablation, there are many instances in which surgical treatment is indicated. Surgical techniques have evolved during the past 20 years, and currently, most are performed with radiofrequency or cryoablation as an additive part to cardiac surgery for other pathology. Ablation of AF is most commonly performed during mitral valve surgery, but there are several other instances in which it offers potential benefit, including during repair of congenital heart disease, for tachycardia-induced cardiomyopathy, and during septal myectomy for obstructive hypertrophic cardiomyopathy.

New instruments have been developed to facilitate and simplify AF ablation, however, equivalency to the classic cut and sew Maze procedure has not been demonstrated. In addition, new lesion sets have been proposed, but, future comparative studies are necessary to elucidate the optimal approach when ablation of AF is considered.

Keywords

Atrial fibrillation • Maze procedure • Ablation • Radiofrequency • Cryoablation

Introduction

In current practice, most patients with supraventricular and ventricular arrhythmias are managed medically, with catheter ablation, and with implantable defibrillators. Atrial fibrillation (AF), however, is often encountered in patients having cardiac operations, and there has been considerable progress during the last decade in the direct surgical treatment of this arrhythmia. The earliest approach to eliminate medically refractory atrial fibrillation/flutter (AF) was atrioventricular (AV) nodal ablation with permanent pacemaker (PPM) implantation. Catheter-based techniques have simplified this approach. Although AV node ablation corrects the ventricular rate during AF, the patient is device dependent and at continued risk for embolic complications from left atrial thrombi. Other early surgical approaches, such as the left atrial isolation and corridor procedure did not restore atrioventricular synchrony. Subsequently, Cox and colleagues developed the maze procedure which addressed all the adverse consequences of AF including rhythm, hemodynamics, and thromboembolic risk [1, 2]. The Cox-maze procedure quickly proved to be the most effective means of eliminating AF and its morbid complications [3–5].

J.M. Stulak, MD • H. V. Schaff, MD (✉)
Cardiovascular Surgery Division,
Surgery Department, Mayo Clinic,
200 First Street SW, Rochester, MN 55905, USA
e-mail: schaff@mayo.edu

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Indications

Medical treatment is first-line therapy for most patients with AF, but surgical management should be considered for several patient groups. Operation to ablate AF is useful for younger patients with limiting symptoms, particularly those who have failed medical treatment or who are intolerant of medications and have failed catheter ablation. A significant number of young patients prefer a curative procedure rather than lifetime treatment with drugs that have bothersome side effects. In addition, there are patients who have medical contraindications to systemic anticoagulation, or a strong personal preference to avoid chronic anticoagulation.

In addition, there is a small subset of patients who have suffered a thromboembolic stroke while on anticoagulation, and these patients should be considered for a Cox-maze procedure because the operation includes removal of the left atrial appendage, and, thus, greatly reduces the risk of left atrial thrombus formation [4]. As will be discussed later, there are select patients with left ventricular (LV) dysfunction who may benefit from surgical treatment of AF in the setting of tachycardia-induced cardiomyopathy [6]. Another group of patients who may benefit from surgical ablation of AF includes patients with congenital heart disease that results in atrial dilatation. In these patients, we selectively include a right sided maze procedure at the time of intracardiac repair with incisions limited to the right atrium and interatrial septum [7].

A large group of patients who may benefit from surgical treatment includes those with valvular heart disease and associated AF who require valve repair or replacement. In these patients, elimination of the arrhythmia allows discontinuation of chronic anticoagulation.

Techniques

Cox-Maze Procedure

Modifications of Cox's original operation were made to minimize chronotropic insufficiency and mechanical dysfunction of the left atrium. Most importantly, these included simplifying the original maze I lesion set by eliminating incisions near the SA node and moving the left atrial dome incision so that it was located posterior to the SVC [8, 9]. Numerous other modifications of the classic "cut and sew" Cox-maze operation have been proposed, and most of these involve the use of alternate energy sources and creation of alternate atrial lesion sets. These new approaches are aimed at simplifying the operation and shortening the time necessary to create atrial ablation lines [10].

In our experience, the standard "cut and sew" maze operation is the most reliable and effective method to ensure transmural atrial lesions and, thus, maximize the potential to ablate AF. Two technical modifications have proved helpful (Fig. 36.1) [11]. On the medial aspect of the right atrium, we avoid incision and apply a linear cryolesion from the cut edge of the appendage to the tricuspid valve (Fig. 36.2a). This avoids division of the frequently seen branch of the right coronary artery that supplies the SA node. We have found that using a cryolesion instead of an incision in this location can reduce the risk of postoperative sinus node dysfunction. In the left atrium, we prefer to extend the incision that encircles the pulmonary veins to the orifice of the left atrial appendage, and then close the orifice transversely as part of the encircling incision. Alternatively, cryolesions can be utilized as part of the lesion encircling the pulmonary veins in order to avoid the conjunction of the encircling suture line and left atrial appendage suture line (Fig. 36.2b.) The principle advantage of the "cut and sew" technique over other methods is that full thickness lesions are assured, especially around the pulmonary veins where AF originates in many patients [12].

Alternate Energy Sources and Lesion Sets

While the classic "cut and sew" Cox-maze procedure is widely established as the gold standard for the surgical treatment of AF, its widespread adoption has been limited because of technical complexity. Alternate energy sources and alternate lesions sets have been proposed and used clinically in the interest of simplifying the procedure [13–16]. Both on-pump and off-pump maze-like procedures have been described with

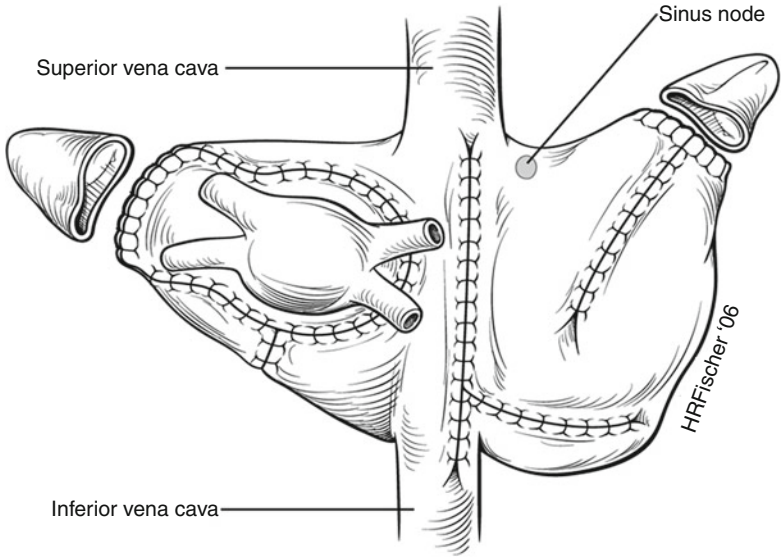

Figure 36–1. Posterior view of atrial suture lines in the modified Cox-maze procedure

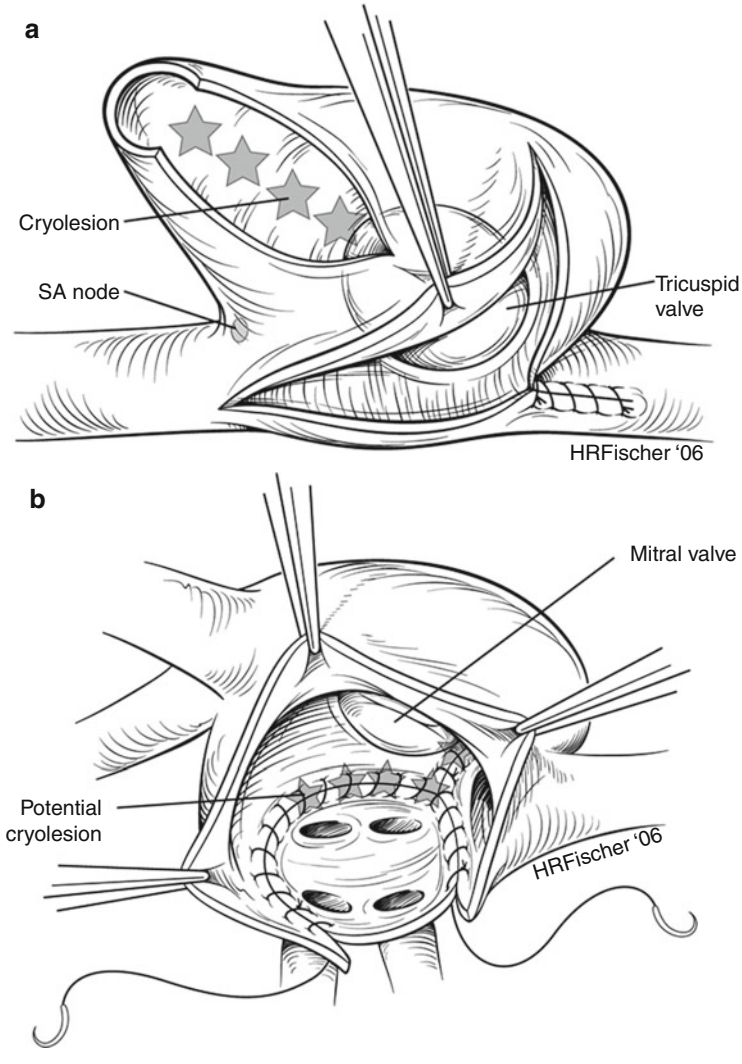

Figure 36–2. (**a**) On the medial aspect of the right atrium, instead of making an incision from the cut edge of the atrial appendage to the tricuspid valve annulus, we prefer linear cryolesions to avoid injury to the arterial blood supply to the sinoatrial node. (**b**) We routinely include the orifice of the left atrial appendage in closure of the left atrial appendage in closure of the left atrial encircling incision

epicardial, as well as endocardial application of energy [17, 18].

The largest clinical experience using alternate energy sources is with radiofrequency (RF) ablation, which employs alternating current to transfer energy and ablate atrial tissue. Success of this technology in the catheterization laboratory has led surgeons to apply RF directly to the heart during cardiac surgery [19–21]. Several different instruments have been developed to create atrial lesions including rigid unipolar probes with cooled tips [22, 23], flexible unipolar probes [24], and bipolar clamps with [25] and without irrigation [26]. Radiofrequency probes can be applied to the endocardial or epicardial surfaces of the atrium in a unipolar configuration. Potential disadvantages of this method are inconsistent depth of injury leading to nontransmural lesions, and injury to surrounding mediastinal structures.

Bipolar RF probes configured as clamps minimize potential for injury to surrounding structures and produce transmural lesions more consistently than unipolar probes. Animal studies suggest a higher rate success rate in producing transmural lesions with irrigated delivery of RF when compared to performing ablation without irrigation [25]. This may be due to prevention of char accumulation on the tissue surface due to the cooling effect of the irrigant. The energy is driven deeper into the tissues under these conditions. Both non-irrigated and irrigated RF devices have sensing systems that indicate when transmurality is achieved.

Availability of the new technologies has led to numerous alternate lesion sets aimed at elimination of re-entrant atrial fibrillation and flutter [27, 28]. These lesion sets include bilateral isolation of the pulmonary veins, with either exclusion or excision of the left atrial appendage, and some variation of a connecting incision between the pulmonary vein lesion sets and the mitral valve annulus. Some authors believe that omission of the connecting incision between the pulmonary vein isolation lesion and the mitral valve annulus leads to increased atrial arrhythmias in the early postoperative period.

Another modification has been termed the mini-maze procedure, and essential elements include a pulmonary vein encircling incision, an atrial isthmus lesion to the orifice of the left atrial appendage, and the lateral left atrial incisions without cryolesions [29]. This method is advocated as a simpler approach which does not seem to compromise effectiveness in controlling AF.

Postoperative Management

Protocols for the postoperative management of patients who have undergone a Cox-Maze operation vary. For arrhythmia control, some centers utilize antiarrhythmic drugs, such as amiodarone, prophylactically in all patients and maintain the drug for 3 months. We prefer to use these medications selectively in patients who experience atrial or ventricular arrhythmias during hospitalization. We monitor potassium and magnesium levels and keep them in the high normal range. Postoperative atrial fibrillation is treated promptly with amiodarone, and electrical cardioversion is used as needed. If atrial fibrillation occurs early after operation and is treated with amiodarone, we continue the drug for 3 months.

It is important to use diuretics liberally early after operation. Removal of the atrial appendages during the Cox-maze procedure eliminates an important source of atrial natriuretic peptide, and this, along with elevations of aldosterone and antidiuretic hormone early postoperatively predisposes the patient to fluid retention [30, 31].

We recommend systemic anticoagulation with Coumadin for 3 months postoperatively, but there is no consensus on the need for anticoagulation beyond this interval. Some clinicians prefer to continue Coumadin believing that risk of thromboembolism is not reduced sufficiently to avoid systemic anticoagulation. Others argue that if AF is eliminated and ventricular function is normal, the risk of an intracardiac source of thromboemboli from a postoperative patient without a left atrial appendage is very low. Thus, the additional risk and inconvenience of using Coumadin is not justified.

Although a number of patients in our series had evidence of a junctional rhythm postoperatively, with some subsequently dismissed in this rhythm, we do not routinely utilize antiarrhythmic medications or stimulants, such

as theophylline, as have been suggested. A significant number of such patients will regain a stable sinus rhythm, and it has been reported that up to 50 weeks are required until this occurs. Persistent junctional rhythm may reflect sinus node dysfunction, and this will predispose the patient to recurrent arrhythmias and stroke. In these patients, a permanent pacemaker should be considered.

Outcomes

Outcome of procedures for ablation of AF are influenced by thoroughness of follow-up as well as the method of assessment of cardiac rhythm. The electrocardiogram is a "snap-shot" in time and has limited ability to detect those patients who may have transient atrial arrhythmias in the follow-up period. A better method is the Holter monitor, but widespread use for routine follow-up is not feasible. After clinical evaluation and follow-up of rhythm status are obtained, the second difficulty is in how the results of the analysis are reported. "Rhythm at last follow-up" may underestimate the recurrence rate of atrial arrhythmias in the follow-up period and, thus, overestimate success of the procedure. Conversely, actuarial methods used to delineate time-related events, such as "freedom from AF", define *any* recurrent arrhythmia as a failure of the procedure, and, thus, may underestimate the actual clinical success. Other factors that contribute to confusion in assessing the results of surgical treatment of AF are viable terminology (intermittent versus paroxysmal, etc.) and differing patient populations (lone paroxysmal AF, permanent AF, AF with mitral valve disease, etc.). Fortunately, 2 publications address the need for the standardization of the AF literature. The Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation proposed standard preoperative definitions and indications for treatment of AF [32], and the Society of Thoracic Surgeons Workforce on Evidence-based Surgery has recently published "Guidelines for reporting data and outcomes for the surgical treatment of atrial fibrillation" [33]. This latter group proposes standard descriptions of preoperative AF, of the surgical procedure, and of the lesion set performed. Furthermore, the guidelines propose uniform reporting of postoperative protocols, follow-up methodologies, and outcome rhythm.

Mayo Clinic Experience

Success with the standard Cox-maze procedure has varied in published reports [5, 11, 34–38]. In general, approximately 90 % of patients who undergo the Cox-maze operation are free from AF at last follow-up, with new pacemakers required in 10–15 % of patients. Our experience is similar to others in that operative risk is low, 1.5 % overall, which includes patients having concomitant intracardiac repair; risk of operation for isolated AF is less than 1 %, which is comparable to the risk of closure of an atrial septal defect (ASD). New permanent pacemakers were required in less than 10 % of patients, and the indication in almost all was sick sinus syndrome. This incidence of pacing postoperatively is lower than expected based on the original reports of the Cox-maze operation. In the earlier experience, clinicians were hesitant to allow patients to remain in junctional rhythm early postoperatively, but in many such patients, a stable sinus mechanism will return. Thus, some patients may have had pacemakers implanted prematurely. Additionally, technical modifications to the original Cox-maze operation may reduce injury to the SA node.

Preoperatively, patients are counseled that this operation reliably eliminates AF in most individuals, but does not necessarily restore sinus rhythm. In older patients especially, there is an underlying incidence of sick sinus syndrome, and when AF is eliminated, permanent pacemakers may be necessary to manage sinus node dysfunction. Important also is the fact that conduction disturbances may also develop in those patients who require concomitant intracardiac procedures at the time of surgery for AF. Eighty percent of patients undergoing the standard biatrial maze procedure at Mayo Clinic have combined procedures.

In our experience, approximately 90 % of patients are free from AF upon dismissal from

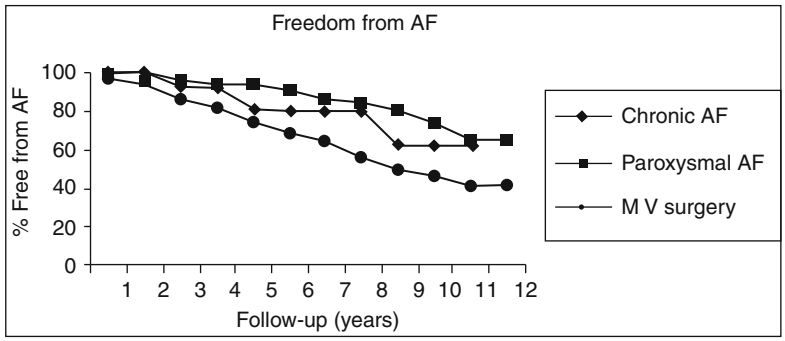

Figure 36–3. Freedom from atrial fibrillation (*AF*). Kaplan-Meier curve demonstrating freedom from AF in patients who have undergone a Cox-maze procedure separated according to lone preoperative paroxysmal AF (squares), lone preoperative chronic AF (*diamonds*), and combined maze-mitral valve surgery (*circles*) (From Ref. [11] reprinted with permission from Elsevier Limited)

the hospital. This includes patients with sinus rhythm, paced rhythm, or junctional rhythm with an adequate rate. It is important to recognize that the Cox-maze procedure, like other cardiac operations, predisposes patients to transient atrial fibrillation in the early postoperative period.

Surgical cure of AF appears to be durable, and at last follow-up (median, 34 months), overall freedom from AF is approximately 85 %. When outcome is analyzed in a product limit estimate (Kaplan-Meier), freedom from AF was 76 % at 5 years and 51 % at 10 years. In our series, late outcome and cure of AF depends on preoperative characteristics. At last follow-up (median, 41 months), 93 % of patients with preoperative lone paroxysmal AF were free from their arrhythmia with an actuarial freedom from AF of 90 % at 5 years and 64 % at 10 years. Patients with preoperative lone chronic AF had 83 % freedom from AF at a last follow-up (median, 28 months) with an actuarial freedom from AF of 80 % at 5 years and 62 % at 10 years. The Cox-maze operation is less durable for patients undergoing combined Cox-maze and mitral valve surgery with 70 % of patients free from AF at last follow-up (median, 33 months) and an actuarial freedom from AF of 68 % at 5 years and 41 % at 10 years (Fig. 36.3).

Surgical AF Ablation and Mitral Valve Surgery

A large group of patients to be considered for Cox-maze operation are those with valvular disease and associated AF in whom repair or replacement of the valve with a bioprosthesis could result in avoidance of both antiarrhythmic medication and chronic anticoagulation with warfarin. Up to 40 % of patients who undergo mitral valve repair or replacement have associated chronic AF, and addressing the mitral valve disease alone fails to restore sinus rhythm in the majority of patients. Chronic enlargement of the left atrium in these patients creates a substrate for the development of AF, and consequently, these patients have high rates of failure when AF is treated with drugs or catheter-based ablative techniques. The routine addition of the Cox-maze procedure to mitral valve surgery was not embraced initially because of concern regarding the potential increased morbidity and mortality added to a procedure that already resulted in a low risk of postoperative thromboembolism. However, if sinus rhythm did not return after successful mitral valve surgery, patients continued to require anti-arrhythmic medications and chronic anticoagulation with warfarin. Although warfarin therapy decreases risk of stroke in AF, its chronic use carries a risk of bleeding as high as 3 % per year. Additionally, careful clinical follow-up and dose adjustment is necessary for optimal therapeutic efficacy.

Because the pulmonary veins provide a trigger for AF in approximately 90 % of patients with paroxysmal arrhythmia, pulmonary vein isolation alone would be expected to cure a majority of patients with this type of AF. However, pulmonary vein isolation will fail as an ablative procedure in those 10 % of patients in whom the pulmonary veins do not contribute the substrate for AF. More chronic AF leads to atrial remodeling and the development of macroreentrant pathways that sustain electrical re-entry. In patients with chronic AF, the goal of treatment shifts from isolating the

trigger of the arrhythmia (pulmonary veins in paroxysmal AF) to ablating the macroreentrant pathways responsible for its maintenance. In this setting, the arrhythmia is not dependent on stimuli from the pulmonary veins, and as such, pulmonary vein isolation may be inadequate treatment. This remodeling is present in a significant portion of patients with mitral valve regurgitation, and especially those that have evidence of left atrial enlargement. Again, in such patients with mitral valve regurgitation and chronic AF, pulmonary vein isolation would not be expected to be as effective as a standard Cox-maze procedure.

Handa et al. reported that the Cox-maze operation is a safe adjunct to mitral valve repair for patients with preoperative AF [39]. In this study from our Clinic, the addition of the Cox-maze procedure was particularly useful in patients with continuous AF of more than 3 months duration preoperatively. Freedom from AF was 82 % in patients who underwent combined maze and mitral valve repair compared to 53 % in patients who underwent mitral valve repair alone. Morbidity and mortality were not increased by the addition of the maze procedure, and 75 % of patients regained sinus rhythm by last follow-up. In this series, only the omission of the maze procedure and the presence of chronic AF were predictors of arrhythmia recurrence.

Some groups advocate only left-sided maze lesions to ablate AF in patients having mitral valve surgery in an attempt to keep morbidity and mortality at a minimum. Handa et al. found no significant difference in perioperative morbidity and mortality in patients that underwent mitral valve surgery alone and those who had an additional maze procedure [39]. It is very unlikely that the omission of the right-sided atrial lesions would have lessened the already low complication and death rate that was observed when the biatrial procedure was performed.

While we continue to prefer a concomitant cut-and-sew maze procedure during mitral valve surgery for patients who are significantly symptomatic from their AF, we do employ radiofrequency ablation or cryothermy for left atrial ablation frequently. While the pulmonary veins may less likely serve as the initiating factor for AF in patients with mitral valve disease, isolating the pulmonary veins still remains a crucial maneuver in any attempt to ablate AF. After the heart has been arrested and a standard left atriotomy is performed, we are able to perform complete encircling of the pulmonary veins with two "half-oval" lesions created with a flexible cryoprobe. The superior limb of this oval is created from the superior end of the left atriotomy and is carried around the two superior pulmonary veins. Similarly, the inferior limb is then created from the inferior cut edge of the left atriotomy and is carried around the two inferior pulmonary veins and meets the superior lesion. These two lesions are usually joined on the left side of the left-sided pulmonary veins. A connecting lesion is then carried down from this pulmonary vein encircling lesion to the mitral valve annulus and the base of the left atrial appendage. The left atrial appendage is usually sewn closed from within the left atrium with a running Prolene. Alternatively, upon entering the left atrium, the left atrial appendage can be immediately inverted and amputated. The open left atrial appendage stump can then serve as the area of joining the cryo lesions from above and below the pulmonary veins. Bipolar RF clamps can similarly be used to create each limb of the pulmonary vein encircling lesion. In this instance, for the superior limb of the encircling lesion, one jaw of the clamp is passed epicardially through the transverse sinus and the other through the left atriotomy and placed endocardially into the stump of the left atrial appendage. The inferior limb of the encircling lesion is created in a similar fashion with one jaw placed epicardially and one endocardially with the tip meeting through the stump of the amputated left atrial appendage [40].

Tachycardia-Induced Cardiomyopathy

Atrial fibrillation impairs hemodynamic function by several mechanisms and can be a cause of cardiomyopathy in patients with the arrhythmia [41–43]. First, the arrhythmia results in loss of atrioventricular synchrony and atrial contraction. This may reduce ventricular filling and thereby reduce cardiac output. The consequence of loss of atrial contraction may be especially

pronounced in patients with impaired diastolic filling as is seen in the presence of hypertrophied ventricles, restrictive cardiomyopathy, and mitral valve stenosis. Fluctuation in the RR interval changes diastolic filling interval producing a variable stroke volume. In animals, cardiac output is reduced 15 % when ventricular rhythm is irregular compared to a regular rhythm at the same rate [44].

Second, in addition to these mechanical consequences, AF can lead to tachycardia-induced cardiomyopathy [45–48]. Cardiomyopathy caused by tachycardia is commonly thought to be associated with chronic arrhythmias having rates >120 beats per min. Our experience suggests that ventricular dysfunction may be associated with resting heart rates considerably lower than this, and further, paroxysmal AF can lead to ventricular dysfunction.

It is important to identify patients with tachycardia-induced cardiomyopathy because ventricular dysfunction can be reversed by control of the arrhythmia. Improvement in LV function has been documented in patients having cardioversion (medical or electrical) to sinus rhythm and in patients having rate control with ablation of the atrioventricular node coupled with implantation of a transvenous pacemaker [49, 50].

Surgical treatment of AF should also be considered in patients with tachycardia-induced cardiomyopathy. In our series of 99 patients undergoing maze procedure for isolated AF, 37 (37 %) had decreased LV function [ejection fraction (EF) <35 % in 11 (severe), 36–45 % in 8 (moderate), and 46–55 % in 18 (mild)]. Preoperatively, the median EF was 45 % and ranged from 25 to 55 %. The majority of these patients had poor control of heart rate preoperatively despite aggressive medical management, and importantly, two-thirds had symptoms of heart failure. At dismissal, all but three patients were free from AF, while 4 patients required a new permanent pacemaker.

Late after operation, all but 1 patient was free of AF, and 73 % of patients were free of antiarrhythmic medications. As shown in Fig. 36.4a, for all patients, the mean EF improved significantly from 44 ± 2 % to 54 ± 3 % early postoperatively ($p < 0.01$) and this increase was sustained during late follow-up at 54 ± 3 % ($p < 0.01$). The most significant improvement in EF was evident in patients with the most severe LV impairment preoperatively (EF <35 %, Fig. 36.4b) and those patients who had chronic AF preoperatively (Fig. 36.4c). Elimination of AF with the Cox-maze procedure also significantly benefitted patients with only moderate preoperative impairment of LV function in the immediate period. Importantly, improvement in LV function correlated with improvement of functional status. Thus, in contrast to earlier admonition that LV dysfunction was a contraindication to the Cox-maze procedure, our experience suggests that surgical treatment of AF should be considered in select patients with cardiomyopathy, particularly those in whom onset of tachycardia precedes or is known to coincide with development of LV dysfunction. Also, our results demonstrate that even patients with moderate LV impairment benefit in terms of ventricular function after the procedure.

Atrial Arrhythmias in Congenital Heart Disease

Congenital heart disease (CHD) resulting in right atrial dilatation is commonly associated with atrial tacharrhythmias, particularly AF, and we have used a right-sided modification of the Cox-maze procedure at the time of intracardiac repair to reduce subsequent atrial arrhythmias (Fig. 36.5). Because many repairs for patients for CHD in patients with AF are reoperations, the right-sided maze procedure has the advantage of minimizing dissection of adhesions, thus resulting in shorter cardiopulmonary bypass time when compared to the standard biatrial maze procedure. In addition, avoiding suture lines in the left atrium minimizes risk of bleeding where hemostasis can be difficult.

In our experience, 80 % of patients undergoing right-sided maze at the time of CHD repair had paroxysmal AF and the most common diagnoses were Ebstein anomaly, isolated atrial septal defect and tetralogy of Fallot. Approximately 90 % of patients were free of AF at the time of hospital dismissal and approximately 70 % manifested sinus rhythm. Permanent pacemakers

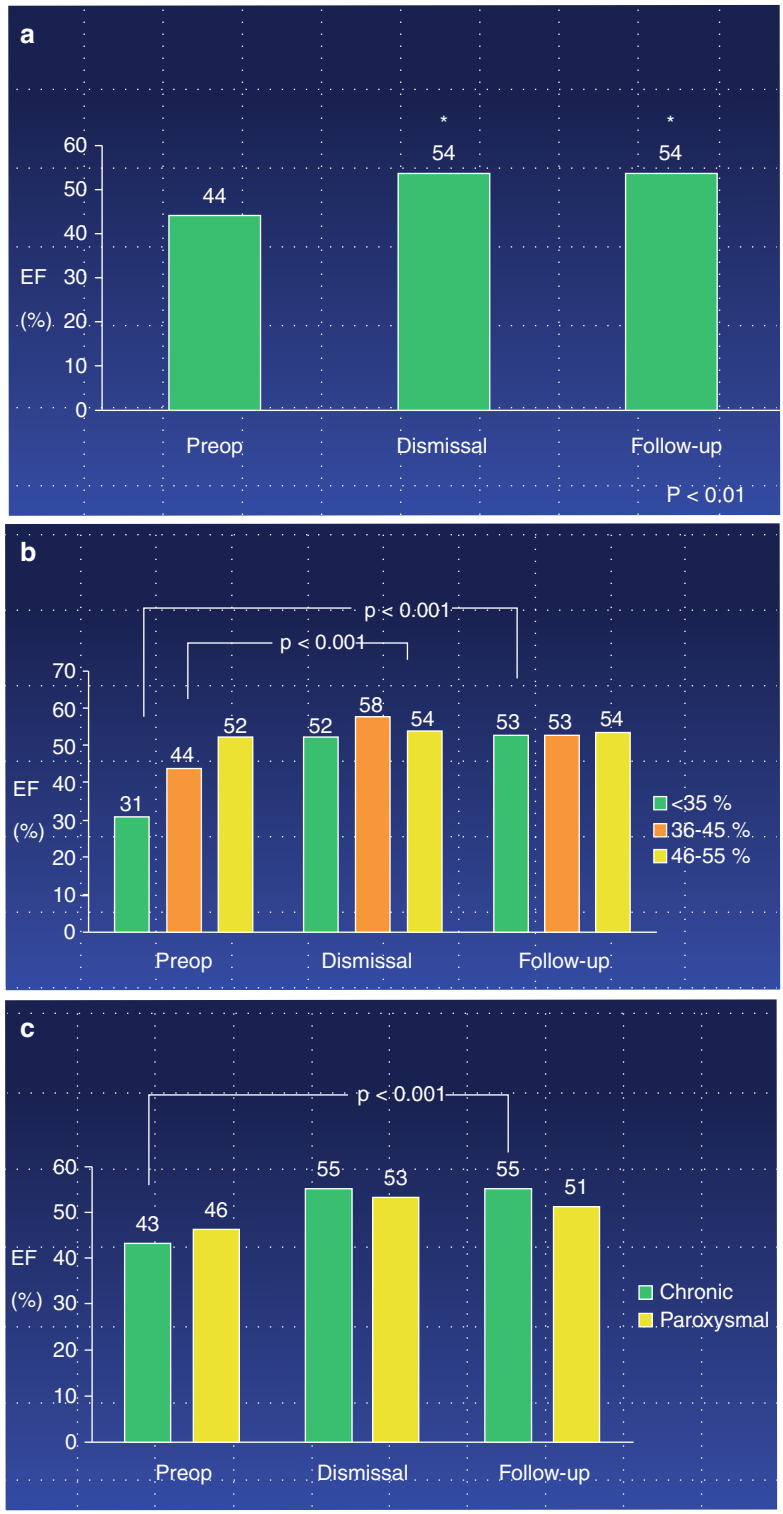

Figure 36–4. (**a**) Left ventricular ejection fraction (*EF*) at preoperative, hospital dismissal, and follow-up time periods for patients who had left ventricular dysfunction and underwent Cox-maze procedure. *$p < 0.05$ when compared with preoperative time period. (**b**) Left ventricular ejection fraction (*EF*) at preoperative, hospital dismissal, and follow-up time periods for patients separated by degree of preoperative left ventricular dysfunction. *$p < 0.05$ when compared with preoperative time period. (**c**) Left ventricular ejection fraction (*EF*) at preoperative, hospital dismissal, and follow-up time periods for patients separated by type of preoperative arrhythmia. *$p < 0.05$ when compared with preoperative time period (From Ref. [6]. reprinted with permission from Elsevier Limited)

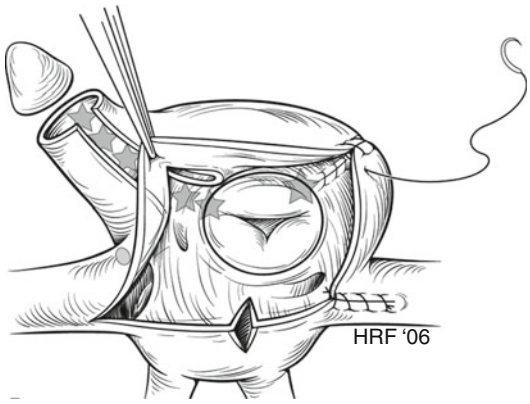

Figure 36–5. The right-sided maze procedure includes an incision in the atrial septum and cryolesions placed at the tricuspid valve annulus both anteriorly and inferiorly. (From Ref. [6] reprinted with permission from Elsevier Limited)

were required in 15 % of these patients; the overwhelming majority of these were for sick sinus syndrome postoperatively. At last follow-up, approximately 75 % of patients with preoperative chronic AF and 95 % of patients with preoperative paroxysmal AF were free from subsequent atrial arrhythmias. The addition of a right-sided maze at the time of repair for congenital heart anomalies causing right atrial enlargement appears to reduce the recurrence of late arrhythmia without increasing morbidity or mortality.

A potential disadvantage of a right-sided maze is that in some patients, the left atrium may contribute to the substrate for AF. Our patients are selected on the basis of right atrial enlargement and normal left atrial size.

Atrial Fibrillation and Hypertrophic Cardiomyopathy

While reports clearly demonstrate that patients with obstructive hypertrophic cardiomyopathy (HCM) are at increased risk for developing atrial fibrillation (AF) when compared to the general population [51, 52], conflict exists regarding whether AF portends a poor prognosis [53, 54] or follows a benign course [55, 56]. Certainly, AF can result in profound clinical deterioration due to the loss of the atrial component of left ventricular filling. Patients who undergo septal myectomy usually enjoy dramatic relief of symptoms and improved exercise capacity; however, a number of patients will be left with underlying diastolic dysfunction with resultant increased left atrial pressure and dilatation.

The question of whether addition of concomitant surgical ablation of AF at the time of septal myectomy confers benefit remains a clinical dilemma. It is unclear if surgical intervention for AF would indeed yield superior freedom from AF and improve outcomes to an appreciable extent, mostly because of the underlying substrate (extent of myocardial fibrosis) and preexisting cardiomyopathic process. In our experience, approximately two-thirds of patients who have AF preoperatively are free from AF after septal myectomy (without surgical AF ablation). Adequate myectomy relieves LVOT obstruction and allows some LV mass regression that may then decrease risk of recurrent AF.

However, concomitant maze procedure at the time of septal myectomy may be useful for patients with obstructive HCM who are extremely symptomatic from their arrhythmia preoperatively, are intolerant to antiarrhythmic medications, or have undergone prior catheter ablations that were unsuccessful. Few published reports demonstrate concomitant AF ablation at the time of septal myectomy is safe, effective and did not appear to increase operative mortality or postoperative morbidity [57–59]. Furthermore, we specifically compared outcome of our patients undergoing concomitant maze and septal myectomy and patients with AF undergoing septal myectomy alone [59]. Although there was no difference in late freedom from AF in patients with intermittent AF between groups, for patients with preoperative persistent AF, there was a greater than 2-fold freedom from AF in patients that underwent concomitant maze procedure, and a significant reduction in need for warfarin anticoagulation (maze: 0 % vs. no maze: 37 %, $p = 0.004$). Further, the addition of the Cox-maze procedure in these patients undergoing septal myectomy for obstructive HCM does not appear to increase operative morbidity beyond what is expected after an isolated maze procedure.

Atrial Fibrillation and TR Progression After Mitral Valve Surgery

Tricuspid valve regurgitation (TR) may be present in 10–50 % of patients with significant mitral valve regurgitation or stenosis, or both, as well as other left-sided valve lesions [60–62]. In most patients, concomitant TR is a functional rather than an organic phenomenon, and is commonly associated with elevated pulmonary arterial pressure and right ventricular dilatation [63]. Although TR may decrease after correction of left-sided cardiac pathology [64], in some patients, TR persists or worsens [65]. The course of TR after mitral valve surgery is difficult to predict. It is known, however, that the persistence or late occurrence of TR after correction of mitral valve surgery contributes to significant morbidity and mortality [66, 67] and reoperation to correct TR in this setting carries a high operative mortality and poor functional results [66, 68]. Atrial fibrillation is common in patients with left-sided valvular disease, and the arrhythmia often persists despite successful correction of mitral or aortic pathology, leading to poor outcome [69, 70]. In addition, AF has been identified as a significant predictor for the late development of TR after mitral valve surgery [65].

There are several possible mechanisms by which persistent AF leads to progression of TR. In our patients, persistent AF was associated with higher pulmonary artery pressure late after operation in comparison to patients who underwent the maze procedure and regained sinus rhythm. Kim and associates [71] first showed the positive effect of the maze procedure in preventing progression of late TR after left-sided valve surgery, and these authors speculated that because left atrial dilatation is frequently associated with a left atrial pressure elevation, associated pulmonary arteriolar constriction may lead to increased right ventricular afterload, right-sided enlargement, and resultant TR.

In our experience, patients who underwent the maze procedure and remained in sinus rhythm had a decrease in left atrial size and a significant decrease in systolic pulmonary artery pressures at late follow-up. In contrast, patients with persistent AF often demonstrated worsening right ventricular dilatation and right ventricular dysfunction in follow-up compared with patients in sinus rhythm. Atrial fibrillation is known to cause remodeling (enlargement) of the left atrium independent of left atrial pressure, and it is likely that the right atrium is affected in a similar fashion. Yamasaki and colleagues [72] reported that severe functional TR occurs with long-standing atrial fibrillation and causes right-heart failure. The authors speculated that TR is caused by loss of tricuspid valve systolic coaptation due to tricuspid annular dilatation that, in turn, was caused by right atrial dilatation.

As seen in Fig. 36.6a, restoration of sinus rhythm after addition of the maze procedure during mitral valve surgery leads to a reduction in left atrial size (Fig. 36.6a) and minimal progression of late TR in comparison with patients who continued to have AF postoperatively (Fig. 36.6b). Further, in a multivariable model, the performance of a maze procedure was identified as the only significant predictive factor in halting the progression of TR, thus implicating AF as the most significant factor contributing to the progression of TR in these patients.

Future Perspectives

New instruments developed to facilitate surgical ablation of AF and new lesion sets may achieve rates of AF control similar to the traditional "cut and sew" methods. However, equivalency has not yet been demonstrated, and future comparative studies are necessary. Also, there are many unanswered questions regarding the clinical application of the maze operation in conjunction with other cardiac procedures. Is the pulmonary vein isolation equally effective as a full Cox-maze procedure for patients with paroxysmal AF and mitral valve disease? Gillinov and colleagues reported that the choice of ablation procedure (full Cox-maze versus pulmonary vein isolation) did not affect the late recurrence of AF or the rate of ablation failure [28]. Perhaps the pathogenesis of AF in patients with mitral valve disease and paroxysmal arrhythmia is different from that of patients with chronic AF in the setting of mitral valve

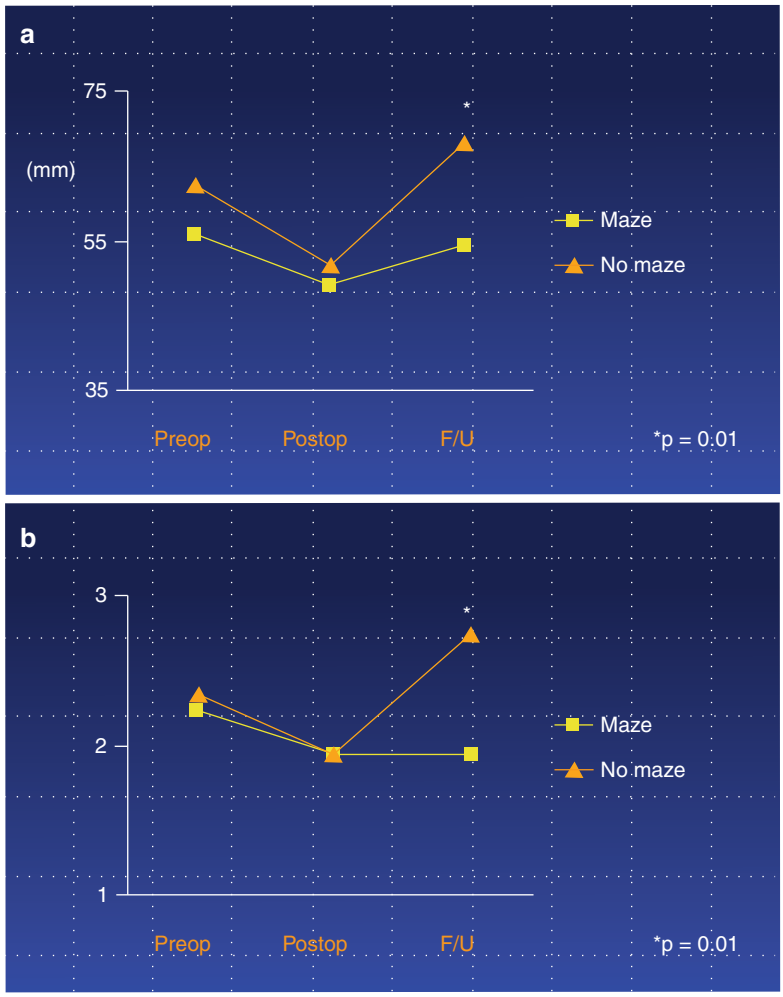

Figure 36–6. (**a**) Left atrial size. Change in left atrial dimension for both Maze (*solid circles*) and no-Maze (*solid boxes*) groups during the preoperative (*Preop*), postoperative (*Postop*), and follow-up (*FU*) time periods. (**b**) Tricuspid regurgitation (*TR grade*). Change in grade of tricuspid regurgitation for both the Maze (*solid circles*) and no-Maze (*solid boxes*) groups during the preoperative (*Preop*), postoperative (*Postop*), and follow-up (*FU*) periods

disease and a dilated left atrium [39]. Another unresolved issue is whether concomitant left reduction atrioplasty should be performed at the time of valve repair and maze procedure for patients AF and a dilated left atrium from mitral valve disease. Romano and colleagues [73] have reported an 89 % rate of return of sinus rhythm in patients who underwent left atrial reduction combined with a Cox-maze operation. Finally, should a "prophylactic" maze procedure be performed in a patient with preoperative sinus rhythm and a dilated left atrium undergoing surgery for mitral valve disease? The altered atrial tissue in these patients represents an arrhythmogenic substrate, which renders them at high risk (approximately 40 %) for the development of postoperative AF even after mitral valve disease is repaired [74]. Clearly, the risks and benefits should be weighed before an additional procedure is performed, which carries with it the added risk of permanent transvenous pacemaker implantation.

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37
Catheter Ablation for Triggered Ventricular Fibrillation and Polymorphic Ventricular Tachycardia

Frédéric Sacher, Mélèze Hocini, Sébastien Knecht, Nicolas Derval, Pierre Jaïs, and Michel Haïssaguerre

Abstract

Implantable Cardioverter Defibrillator (ICD) remains the first line therapy for patients with primary VF or polymorphic VT. However, catheter ablation of Ventricular Fibrillation (VF) is an important therapeutic option in patients with recurrent VF. These procedures mainly focus on targeting triggers. The role of Ventricular Premature Beat (VPB) initiating VF is crucial and their elimination shown to be effective to prevent recurrence in 82 % after 5 years in idiopathic VF. These VPBs, mainly (87 %) originate from the Purkinje network (right and/or left) and have some specific features. In addition, several experimental studies demonstrated that Purkinje fibers act as initiator and perpetuator of VF. Hence, by ablating an area where the triggering VPB are found to originate, catheter ablation may modify the local substrate too.

Keywords

Ventricular fibrillation • Catheter ablation • Sudden cardiac death

Introduction

While both triggers and substrate may theoretically be the target of catheter ablation strategies as in Atrial Fibrillation (AF), published literature on catheter ablation of Ventricular Fibrillation (VF) have focused on targeting triggers (1–11) except for one recent publication (12). The large mass of ventricular myocardium, the importance of maintaining normal mechanical ventricular function, and the risk of creating other forms of malignant arrhythmias render substrate modification complicated in patients with normal heart. However, previous works in AF have shown that both triggers and substrate may share a close structural relationship. The pulmonary veins play an important role in the initiation and maintenance of AF (13), recent studies have shed light on their role in the maintenance of AF in some patients. Similarly, several experimental studies demonstrated that Purkinje fibers act as initiator and perpetuator of VF (14–17). Hence, by ablating an area where the triggering ectopics are found to originate, an additional effect might be substrate modification if the area is implicated in the maintenance of VF.

F. Sacher, MD (✉) • M. Hocini, MD • S. Knecht, MD
N. Derval, MD • P. Jaïs, MD • M. Haïssaguerre, MD
Department of Electrophysiology, CHU de Bordeaux,
Hopital Cardiologique du Haut Leveque,
Avenue de Magellan, 33604 Pessac CEDEX, France

IHU LIRYC, INSERM 1045, Bordeaux University,
Bordeaux, France
e-mail: frederic.sacher@chu-bordeaux.fr

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This review focuses on mapping and ablation of VF in a variety of clinical substrates.

Mapping and Ablation Procedure

Indication and Timing of Procedure

To start we have to emphasize that Implantable Cardioverter Defibrillator (ICD) remains the first line therapy for patients with primary VF or polymorphic VT. Ablation should be considered in patients implanted with an ICD in case of multiple episodes of primary VF or polymorphic VT (eg: not VT degenerating into VF) with no curable underlying condition refractory to pharmacological therapy and with documented ventricular ectopics at the time of the procedure. In some patients, the triggering ventricular ectopics are persistent even after a long absence of VF episodes, and can be mapped easily. However, in most cases of idiopathic VF (4, 5, 18), it is likely that the ectopics are episodic, mainly appearing prior to and a few days after the onset of VF or polymorphic VT which results in a narrow time window whereby mapping and ablation can be performed under optimal conditions, hence the procedure has to be performed within a few days of the VF episodes.

It is of utmost importance that Ventricular Premature Beats (VPBs) are recorded on 12 lead ECG before the procedure. We therefore routinely record continuous 12 lead ECG immediately after the VF episode, where the electrode position on the skin is marked in order to get reproducible recordings and precise localization of the VPBs. The latter is of particular value in case of absence of VPBs during the procedure, when ablation using (Purkinje) pace-mapping technique may be the only remaining alternative.

Electrophysiology Study and Endocardial Mapping

As previously described (5), the electrophysiology study is performed with 2–4 multielectrode catheters. Surface ECG recordings and bipolar intracardiac electrograms are filtered at 30–500 Hz and recorded simultaneously (LabSystem, Bard Electrophysiology, sampling rate 1–4 kHz in our center). High gain amplification (1 mm = 0.1 mV) is used during mapping in order to clearly identify the Purkinje potential. The VPBs are localized by mapping the earliest electrogram relative to the onset of the ectopic QRS complex. Purkinje origin is defined by the presence of an initial sharp potential (<10 ms in duration) preceding the larger and slower local ventricular electrogram by <15 ms in sinus rhythm and preceding ventricular activation during ectopy (Fig. 37.1) (19). Its absence defines muscular origin.

Radiofrequency Ablation

Ablation is performed with conventional 4 mm-tip catheters with a thermocouple, using radiofrequency (RF) energy with a target temperature of 55–60 °C and a maximum power of 40–50 W. In case of low power output, irrigated-tip catheter is used with a maximal temperature of 48 °C and a power of 30–40 W. The ectopic focus is targeted first, and after abolition of the ectopics, the lesion is extended to cover a larger area around the focus to minimize recurrence. Ablation at effective site often results in temporary exacerbation of VPBs that, in some cases, are associated with runs of polymorphic VT/VF. At this site, electrograms recorded after ablation demonstrates abolition of local Purkinje potential and a slight delay in local ventricular electrogram (Fig. 37.2).

In case of polymorphic VPBs, the most frequent one is targeted and eliminated, and then, the second most frequent etc.… In the absence of ectopy during the procedure, provocative maneuvers (pacing and/or pharmacological) are used prior to pace map the Purkinje system.

Various Substrates Associated with VF

Idiopathic Ventricular Fibrillation

Clinical Presentation

Male and female are equally affected. From 2000 to 2008, 38 patients (21 men; 42 ± 13 years old) underwent VF ablation because of episodes of idiopathic VF (20) [46 patients (23 men, 39 ± 13 year old) until June 2011].

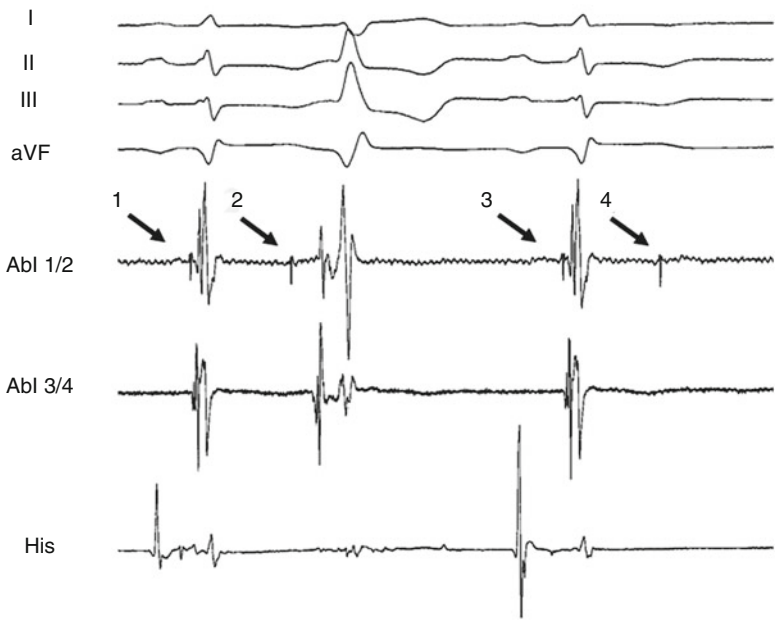

Figure 37–1. A distal Purkinje potential (*2*) precedes local activation during ectopy as well as during sinus rhythm (*1*, *3*). The second Purkinje discharge (*4*) is not conducted to the ventricle (conduction block), *arrows* indicate the Purkinje Potential (*Abl 1-2* distal ablation catheter, *Abl 3-4* proximal ablation catheter)

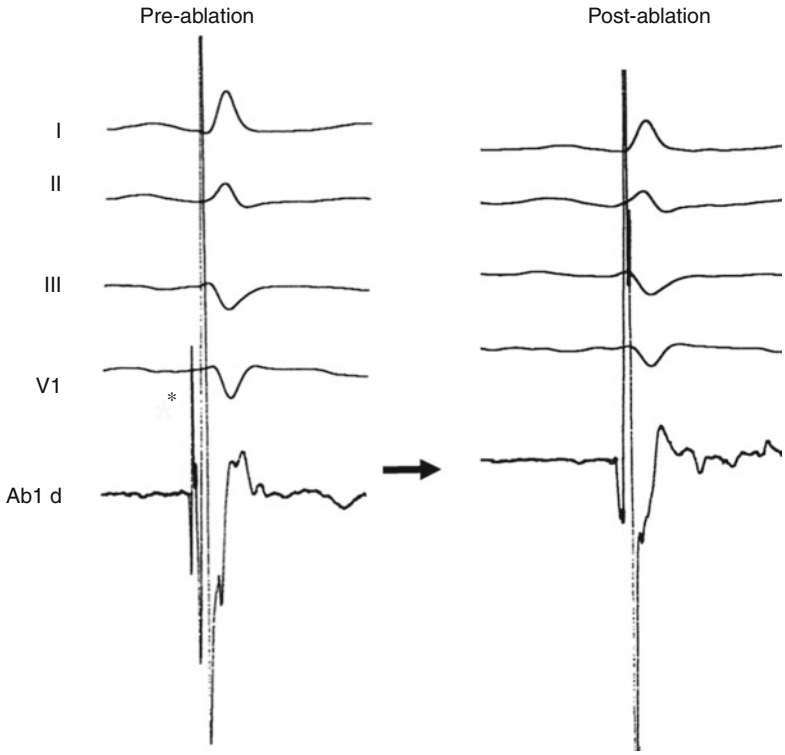

Figure 37–2. RF applications resulting in abolition of local Purkinje Potentials in sinus rhythm (*Abl d*: distal ablation catheter, * Purkinje Potential)

The median number of significant events before ablation was four [interquartile range (IQR) 3–9]. Despite the use of a median of 2 antiarrhythmic drugs, 12 patients (32 %) experienced arrhythmic storm. The median time from the first polymorphic VT/VF episode to ablation was 4 months (IQR 1–36 months). The vast majority of VF episodes occurred during

activities of daily living and it rarely appeared during sleep. Importantly, none of these patients had arrhythmia during exertion. All patients had frequent VPBs immediately after the VF storm, with 2 ± 1 (range 1–5) different morphologies. Importantly, the VPBs triggering VF were also observed to occur independently of VF episodes (Fig. 37.3).

Location of Ectopy

The VPBs that were observed to trigger VF had specific morphological features. Most patients demonstrated a positive morphology in V1, suggesting a left ventricular origin. However, in two-thirds of the group, significant morphological variations occurred especially regarding the limb leads (Fig. 37.4).

Thirty patients (81 %) had clinical VPB at the time of the procedure, whereas eight patients (19 %) did not. Clinical VPBs triggering VF arose from the right Purkinje system in 16 patients, the left Purkinje in 14 patients, in both the left and right Purkinje system in three patients, and in the myocardium in five patients (including the right ventricular outflow tract (RVOT) in four patients). They were polymorphic in 80 % suggesting different exits or sources, while those originating from the RVOT were mainly monomorphic. The Purkinje sources were localized to the anterior right ventricle or in a wider region of the lower half of the septum in the left ventricle. In the latter case VPBs from the ramifications of the anterior and posterior fascicles resulted in an inferior and superior QRS axis respectively, whereas origin from the intervening region demonstrated an intermediate axis. In addition, VPBs from the left Purkinje network demonstrated narrow QRS intervals (130 ± 24 ms). Several interesting electrophysiological phenomena were observed during intracardiac mapping: different Purkinje to local ventricular myocardial conduction times associated with altering VPBs morphologies; rapid repetitive beats demonstrating Purkinje activation suggesting that this system may drive the onset of VF; and Purkinje to local ventricular myocardial conduction block (see Fig. 37.1).

A mean of 1.7 ± 2.0 VPB morphologies were targeted per patient. The median duration of RF, fluoroscopy and procedural durations were 14 min (IQR 9–24 min), 28 min (IQR 18–52 min) and 135 min (IQR 100–215 min), respectively.

Outcome After Ablation

During a median follow-up of 63 months (IQR 40–80 months), seven (18 %) of 38 patients experienced a recurrence of VF. This occurred after a median of 24 months (IQR 1–60 months). VF recurrence was detected by the ICD and did not lead to syncope or clinical sudden cardiac arrest in any of the patients. Ablation was repeated in five of these seven patients (one patient had two repeat procedures). Four of these five patients had other VPB morphologies as compared with the initial procedure, whereas one patient had the same clinical VPB recurrence triggering VF. These five patients had no subsequent recurrence of VF or documented VPBs for 28 months (IQR 24–72 months). After a mean follow-up of 52 ± 28 months after the last procedure, 36 of 38 patients are free from VF after a mean of 1.28 ± 0.6 procedures. Predictors of VF recurrence were the total absence of documented VPBs on 12 leads ECG and bundle branch block in the targeted ventricle before ablation.

Specificity of the Substrate

In addition to ICD, catheter ablation is an option in case of recurrent VF. It's important to perform it as soon as possible from the arrhythmic episodes when VPBs are still present.

Brugada Syndrome

VF Pathophysiology

Various hypotheses have been brought forward with regard to the mechanisms of VF in Brugada syndrome. Repolarization heterogeneity with an epi/endo gradient has long been the principal pathophysiological hypothesis with phase 2 reentry as mechanism for VF initiation (21) [cf Chap. 29]. More recently, depolarization abnormalities have been reported (22–24).

However in clinical practice, it is likely that the actual triggers for VF or polymorphic VT in most cases of the Brugada syndrome are ventricular ectopic beats, most of them monomorphic (25).

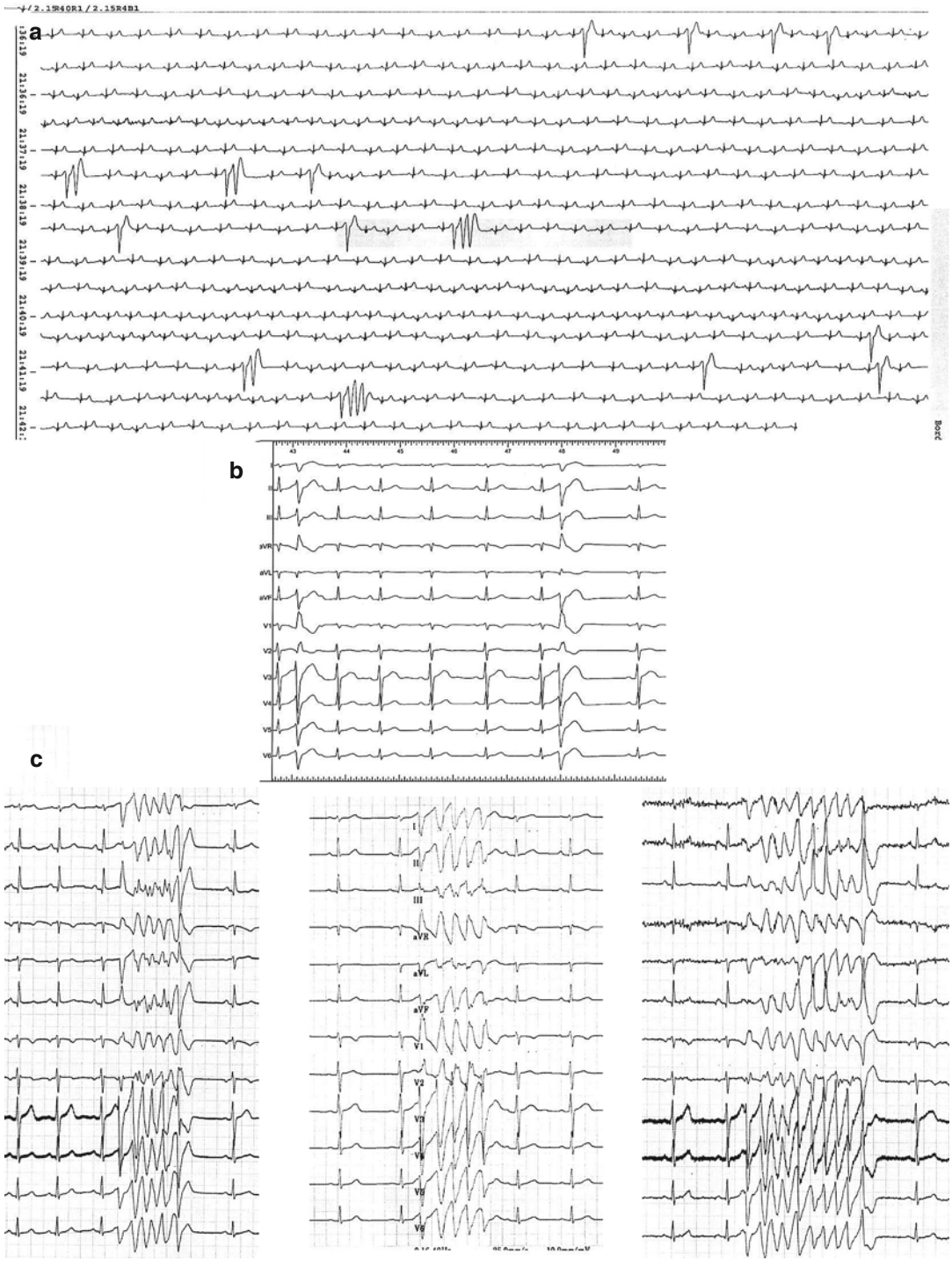

Figure 37–3. ECG examples from a 23 year female with idiopathic VF. Panel (**a**) shows isolated and short runs of VBPs. Panel (**b**) demonstrates the 12 lead ECG morphology of the dominant VBP. Panel (**c**) demonstrates short runs of non sustained polymorphic VT initiated by three slightly different VPBs, all originating from the Purkinje network

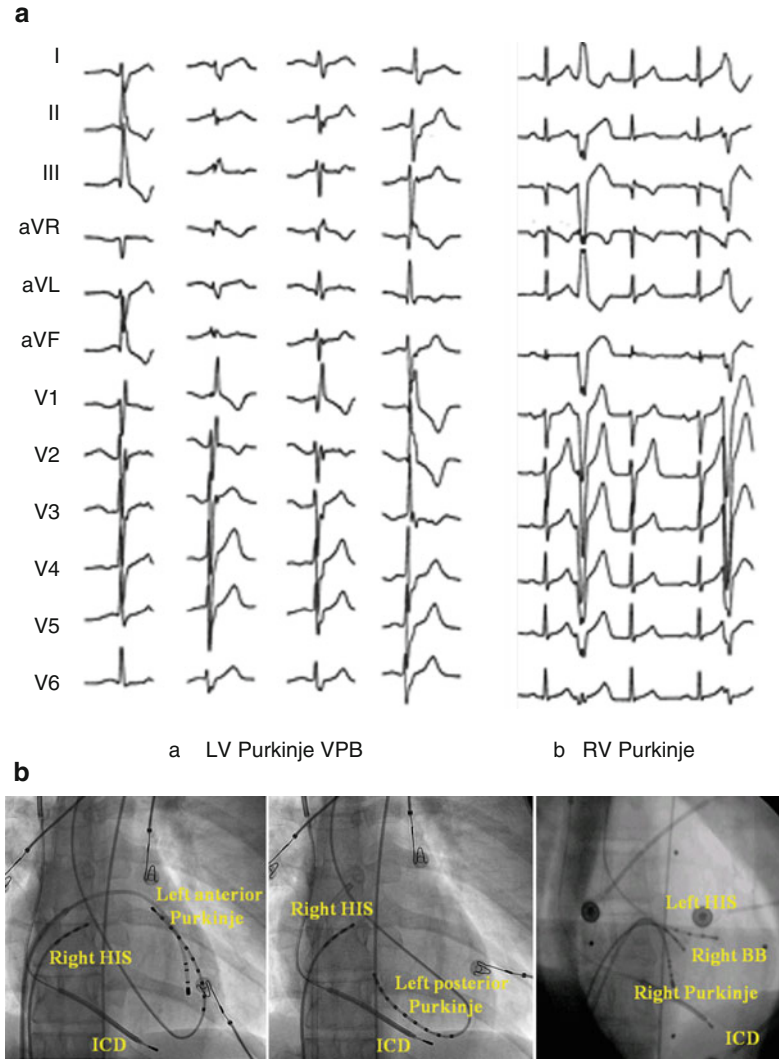

Figure 37–4. (**a**) Typical 12 lead ECG pattern of ectopics beats originating from the *left* (*Panel A*) and *right* (*Panel B*) Purkinje network. Left Ventricular (*LV*) Purkinje beats are narrow (116 ± 14 ms), and have a left, right or intermediate QRS axis. Shown in this example are four different LV Purkinje beats from one patient. Right ventricular (*RV*) Purkinje beats have a left bundle branch block pattern in V1 and are usually wider (142 ± 9 ms). (**b**) Fluoroscopy images with antero-posterior visualization of catheter positions recording Purkinje Potential (*ICD* implantable cardioverter-defibrillator, *Right BB* right bundle branch)

Nineteen patients with Brugada syndrome and ICD implanted were followed over a mean duration of 14 months, during which spontaneous VF occurred in 7 (37 %), with three having multiple episodes. Analysis of 33 episodes of VF revealed that 22 episodes (67 %) were preceded by isolated ventricular ectopics, which were identical in morphology to the ectopics triggering VF. Furthermore, in the three patients with multiple episodes, VF was always triggered by the same type of VPBs (25). Current observations suggest that ectopy arising in Brugada syndrome are predominantly of right ventricular origin. Chinushi et al. described recurrent episodes of VF in a patient with Brugada syndrome initiated by monomorphic ectopics with left bundle-branch block morphology (26). This was corroborated by Morita et al. (27), who observed ventricular ectopics in nine out of 45 patients studied. Eleven ectopic morphologies were observed in these nine patients, of which ten were of right ventricular origin (seven RVOT, two septal and one from the apex).

VF Ablation

Based on these reports and on our previous experience with idiopathic VF (4, 5), we performed ablation in patients with Brugada syndrome and arrhythmic storm targeting the VPBs initiating VF (7).

To date, we have performed mapping and catheter ablation of VF in seven patients with Brugada syndrome (five males; 36 ± 6 year old). All of them had presented with an electrical storm with multiple appropriate ICD shocks (12 ± 9). In our experience, VPBs were monomorphic in five patients. VPBs originated from the RVOT in five, from right septum in three and from right ventricular Purkinje network in two. Interestingly, fragmented potentials in RVOT were demonstrated in two patients. The monomorphic RVOT premature beats were first observed at the time of VF in three cases. However in two patients, they were documented 14 and 11 years before they triggered VF, at a time when notably, no sign of the Brugada phenotype in the 12 lead ECG was seen. Interestingly on top of VPB elimination, we noticed disappearance of type 1 Brugada pattern after a large RVOT ablation in one patient (28).

More recently, Nademanee et al. reported that the underlying electrophysiological mechanism was delayed depolarization over the anterior aspect of the RVOT epicardium (Fig. 37.5) (12). Epicardial ablation of all local abnormal ventricular activities (LAVA) rendered VF non inducible in 7/9 patients with normalization of Brugada pattern in eight/nine patients.

This approach is of particular interest in the absence of ventricular ectopy, however if VPBs can be recorded the endocardial RV approach seems less risky (29).

Outcome After Ablation

During a mean follow-up period of 62 ± 17 months, one VF recurrence as assessed by the ICD recordings was noted targeting the VPB in a patient without VPB during ablation procedure. None have any anti-arrhythmic drugs. Nademanee et al. did not have any recurrence during a follow-up of 20 ± 6 months (one was under amiodarone).

Specificity of the Substrate

In case of recurrent VF in Brugada syndrome, VF ablation targeting VPBs has to be considered. In the absence of documented VPB, epicardial mapping and ablation may be useful. However this represents a small number of patients because arrhythmic storm is quite rare in Brugada patients and quinidine is often effective in this population even if right ventricular ectopic ablation may have fewer side effects than quinidine.

Early Repolarization Syndrome

Clinical characteristics are reported in Chap. 30. In patients with ventricular arrhythmia 14 patients (four males, 38 ± 15 year old) had early repolarization (ER) with at least one VF initiation recorded on a 12 leads ECG (1.9 ± 2.3 ECG per pts). All those patients presented with arrhythmic storm (≥3episodes in 24 h).

At baseline ER was present in inferior (n = 7) or inferior and lateral leads (n = 7). Mean J wave elevation was 2.5 ± 0.9 mm at baseline increasing to 4.1 ± 2 mm ($p < 0.001$) before VF. In three patients with >50 ICD shocks, J wave amplitude at baseline was ≥4 mm and present both in inferior and lateral leads. Initiating VPBs originated from multifocal areas from both left and right ventricles (confirmed by endocardial mapping in 2). In the four other patients with J wave elevation in inferior and lateral leads, VPBs were coming from different ventricular areas (right Purkinje in 1, left Purkinje in 1 and myocardium in 2)

In the seven patients with ER only present in the inferior lead, VPB morphologies were consistent with an origin in the inferior left ventricular wall.

Outcome After Ablation

After a mean follow-up of 45 ± 17 months, the seven patients with VPB limited to the left inferior ventricular wall are free of any recurrence whereas the seven other patients with multifocal origin of their VPBs initiating VF had recurrence and were given anti-arrhythmic drugs. Unfortunately two patients deceased because of arrhythmic storm and the five other are well controlled under quinidine therapy for four and without any drugs for one.

Specificity of the Substrate

Beats triggering VF originate from the region of electrocardiographic ER thus supporting

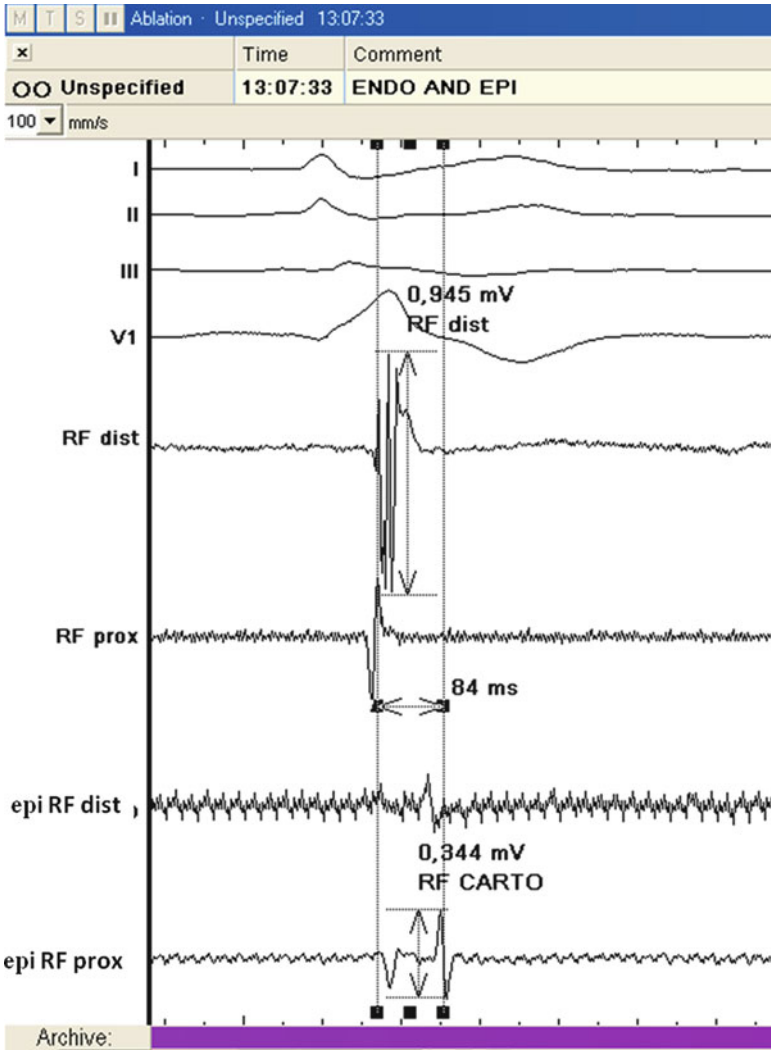

Figure 37–5. Electrograms of a 52 yo Brugada syndrome male referred for catheter ablation because of arrhythmic storm. RF catheter is positioned on the anterior endocardial wall of the Right Ventricular Outflow Tract (*RF dist* distal bipole of the endocardial ablation catheter, *RF prox* proximal bipole of the endocardial ablation catheter) and the other one on the epicardial side in regard of the previous one (*epi RF dist* distal bipole of the catheter placed in the epicardium, *epi RF prox* proximal bipole of the catheter placed in the epicardium). Potentials with low voltage, particularly on the epicardium (<0.5 mV) were found in this area with a 84 ms delay between endo and epi activation time at this side

a direct link between ER and VF. When the pattern is localized to the inferior lead, VPBs triggering VF are mainly coming from this area and catheter ablation is a reasonable option in case of recurrent VF. When the ER pattern is major and widespread, VPBs initiating VF are multifocal and ablation often fails. Quinidine may be effective in this condition (30).

Congenital Long QT Syndrome

Clinical Presentation

We have studied four patients with LQTS (two males; age 37 ± 8 years), three with a history of SCD (7). All patients presented with documented episodes of polymorphic ventricular tachycardia or VF (6 ± 4 episodes of VF or syncope prior to mapping). Medical treatment included β-blockers alone or combined with class IC drugs (3), verapamil (2) and amiodarone (1). The diagnosis of LQTS was based on established criteria and was made after the onset of ventricular arrhythmias. No mutation on KVLQT1, HERG, KCNE2, KCNJ2 or SCN5A were found.

All patients were studied within 2 weeks of their arrhythmic storm and had been documented to have frequent VPBs. The triggering role of VPBs in the initiation of VF was observed by ambulatory monitoring or stored electrograms of the defibrillator. Premature beats in the

LQTS had a coupling interval of 503 ± 29 ms; they were monomorphic in two patients (one with LBBB-inferior axis typical of RVOT and one with RBBB-superior axis), and polymorphic and repetitive with a positive morphology in lead V1 in two patients; the latter having varying cycle lengths of 280–420 ms with repetitive beats lasting 3–45 beats.

Location of Ectopy

One patient had VPBs originating from the RVOT. Two patients had polymorphic VPBs that originated from the peripheral Purkinje arborization in the left ventricle, including the ramifications of anterior or posterior fascicles, and from the intervening regions. In one patient the premature beats originated from the posterior fascicle. The earliest Purkinje potential preceded the local endocardial muscle activation by a conduction interval of 34 ± 17 ms during the VPBs. Repetitive beats were also preceded by Purkinje activity with a variable delay ranging from 20 to 110 ms (52 ± 24).

Outcome After Ablation

During a mean follow-up period of 45 ± 20 months, there has been no recurrence of VF, syncope or sudden cardiac death in any patient. One patient died of a non cardiac cause. One patient was maintained on β-blocker, another had a late recurrence of VPBs but declined further procedures.

Outcome After Ablation

Beta blockers remain the treatment of patients with long QT syndrome but catheter ablation may be considered in case of arrhythmic storm despite beta-blocker therapy.

Andersen-Tawil Syndrome

Clinical Presentation

Andersen-Tawil syndrome (ATS), also called LQT 7, describes a rare condition consisting of ventricular arrhythmias, potassium-sensitive periodic paralysis, and developmental abnormalities. In addition to isolated VPBs, VT involving a beat-to-beat variability in axis (polymorphic ventricular tachycardia), such as bidirectional ventricular tachycardia and torsades de pointes, have been described (31–33).

From initial reports, therapies such as oral potassium supplementation, sodium restriction, spironolactone, and acetazolamide have anecdotally been shown to ameliorate symptoms of weakness (34), but no therapeutic standards exist to date even if beta-blockers and flecainide have been proposed.

So far, we have performed electrophysiological study in four ATS patients (19 ± 9 years, one male), all had a history of syncope. Bidirectional ventricular tachycardia (n = 2) and frequent polymorphic VPBs (n = 2) were documented prior to the procedure.

Location of Ectopy

Interestingly rapid atrial pacing as well as isoproterenol and verapamil infusion totally suppressed ventricular arrhythmias; moreover VT could not be induced by standard programmed stimulation in the right ventricle. We managed to eliminate the most frequent VPBs morphologies (4 with preceding left Purkinje Potential, 3 without), however infrequent VPBs were still present at the end of the procedure, as well as bidirectional VT.

Outcome After Ablation

Despite persisting ventricular arrhythmias, all patients remained asymptomatic under beta-blocker therapy 43 ± 13 months after ablation.

Specificity of the Substrate

Catheter ablation does not seem effective to eliminate ventricular arrhythmias because of their high polymorphism. Interestingly, on 18 patients with ATS followed-up, none of the patients on beta-blocker therapy experienced syncope or sudden cardiac death despite the persistence of VPBs and/or bidirectional VT. Concerning patients with syncope, emotional stress was the main trigger and a torsade de pointes not related to bidirectional VT was recorded on holter-ECG in 1.

Ventricular Fibrillation Storm following Myocardial Infarction

Clinical Presentation

While VF associated with myocardial infarction is frequently short lived and managed with the use of β-blockers, lidocaine and/or amiodarone, patients occasionally present with arrhythmogenic storms that cannot be managed medically (0.0014 % of patients (8)). With experimental recognition of the subendocardial Purkinje network surviving during transmural myocardial infarction (35), some clinical studies have recently evaluated the role of such trigger elimination in the management of VF storms after myocardial infarction (MI) (8–10). Thirteen patients (13 males, 63 ± 5 year old) who experienced extensive MI underwent catheter ablation for VF. All patients experienced arrhythmic storm 9 ± 4 days after an extensive MI (with different localizations) despite the absence of coronary artery reocclusion. Although complete revascularization was initially performed, they all had significant left ventricular dysfunction but were considered on optimal pharmacological therapy. They presented in the first 2 weeks after myocardial infarction with frequent VPBs triggering VF (50 ± 54 episodes, range: 15–130).

Location of Ectopy

VPBs triggering VF were multifocal. Mapping and ablation progressively targeted the most frequent VPB morphology. In all, the origin was located to the Purkinje network bordering the infarct zone, with a coupling interval to the preceding sinus beat of 379 ± 56 ms. In three patients VPBs originated from Purkinje system AND myocardium. These findings are consistent with published data, confirming the origin of VPB from the Purkinje arborization at the myocardial scar border zone, with a number of different VPB morphologies varying from 1 to 4 (Table 37.1) (max ten in our experience).

Outcome After Ablation

At 38 ± 28 months of VF ablation, 11/13 patients were free of recurrence. Two other presented with monomorphic VT and are under amiodarone. Five died of refractory heart failure at 1 week (n = 2), 3 weeks (n = 1) and > 1 year after ablation (n = 2) without VF recurrence.

Specificity of the Substrate

This is a challenging procedure because patients are often hemodynamically unstable, and in need of hemodynamic support. VPBs are polymorphic but come from the same area (scar border) and ablation may be a life-saving procedure even if the problem of heart failure will remain afterwards.

Other Substrates

Mapping and ablation of ventricular fibrillation has been reported after aortic valve replacement (11), (with triggering VPBs originating from left Purkinje network) and with cardiac amyloidosis (36). We also performed ablation to a 32 year old male with idiopathic dilated cardiomyopathy (Ejection Fraction 45 %) with VPBs originating from the right Purkinje network and from the ventricle itself.

Conclusion

Although catheter ablation of VF is still an emerging technique, the initial experiences with idiopathic VF (4, 5), and later on in VF secondary to ischemic heart disease and repolarization disorders (7–10), provided important insights into the role of focal triggers from the Purkinje system and RVOT in different clinical substrates. In particular, it is eminently applicable to patients having frequent recurrent episodes of VF provided the triggers can be localized by mapping. Reducing the incidence of VF with localized ablation may reduce defibrillation requirement and replacement but most importantly it will improve quality of life. Furthermore in the subset of patient with VF storms, ablation may be the only remaining option for survival.

Table 37–1. Catheter ablation of VF post myocardial infarction

	Number of patients	MI site	PVT after MI	Number of VF episodes prior to ablation	Number of PVC morphology/patient	Distribution of foci	Coupling interval of initiating PVC (ms)	RF time	Success [follow-up (months)] (%)
Bänsch et al. [8]	4	2 anterior 2 inferior	1–7 days	19–60		All in the Purkinje network at the scar border zone	270–400	18 ± 10 applications	100
Marrouche et al. [9]	8	3 antero-septal 2 antero-lateral 2 postero-lateral 1 Lateral	11 ± 5 months	35–89	1	All in the Purkinje network at the scar border zone	195 ± 45		88
Szumowski et al. [10]	5	5 anterior	67 ± 85 4–170 days	Two pts with >30 external defibrillation	2.6 ± 1.1	All in the Purkinje network at the scar border zone	320–600	19 ± 9 min	100

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38
Catheter Ablation for Scar-Dependent Ventricular Tachycardia

Roy M. John and William G. Stevenson

Abstract

Ventricular tachycardia (VT) related to structural heart disease and scar is often recurrent and inadequately controlled with antiarrhythmic medication. Catheter ablation has been increasingly utilized to reduce ICD shocks and improve quality of life. With improved imaging and ablation techniques, multiple and unstable VTs can be successfully targeted with ablation resulting in significant reduction in VT recurrence. There is now substantial experience with ablation for scar VT such that it should be considered early in the course of recurrent VT. This chapter reviews the pathophysiology of scar VT, the various techniques currently utilized for mapping and ablation together with outcomes and complications relating to VT ablation.

Keywords

Ventricular tachycardia • Catheter ablation • Scar-dependant ventricular tachycardia • Epicardial ablation • Substrate based ablation for ventricular tachycardia • Mapping of ventricular tachycardia

R.M. John, MBBS, PhD (✉)
Division of Cardiology, Department of Medicine,
Brigham and Women's Hospital,
Harvard Medical School,
Boston, MA, USA

Medicine Department, Harvard University,
Boston, MA, USA

Cardiac Arrhythmia Service, SH5,
Brigham and Women's Hospital,
75 Francis Street, Boston,
MA 02115, USA
e-mail: rjohn2@partners.org

W.G. Stevenson, MD
Department of Medicine, Division of Cardiology,
Brigham and Women's Hospital,
Harvard Medical School,
Boston, MA, USA

Medicine Department, Harvard University,
Boston, MA, USA

Introduction

Ventricular arrhythmias in the context of significant structural heart disease are often associated with a high risk of sudden cardiac death. While implantable cardioverter defibrillators (ICD) remain the mainstay of therapy for these arrhythmias, the ICD has no role in the prevention of ventricular tachycardia (VT) or ventricular fibrillation (VF). Recurrent VT or VF can result in frequent shocks that are painful and reduce quality of life. In addition, there is evidence to suggest that recurrent ICD shocks are a marker for progressive heart failure and increased mortality [1]. Antiarrhythmic drugs, ablation or both are frequently necessary for control in such situations.

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Ablation strategies for VT are largely dependent on the nature of the underlying cardiac disease. In the presence of structural heart disease, re-entry involving myocardial scars form the basis for recurrent and often drug refractory VT. Myocardial infarction is the commonest cause for scarring but other diseases such as non-ischemic cardiomyopathy (NICM), sarcoidosis, Chagas disease, arrhythmogenic right ventricular cardiomyopathy (ARVC) and prior surgical interventions, such as for congenital heart disease (Tetralogy of Fallot), may be responsible.

Pathophysiology of Scar VT

Infarct scar, initially thought to be essentially fixed and complete within 6–8 weeks, is now known to be metabolically active expressing precursors of angiotensin, and transforming growth factors and with continued elaboration and degradation of collagen and the interstitial matrix [2]. Ongoing scarring and remodeling of non-infarcted tissue and infarcted myocardium occur. The substrate supporting re-entry is comprised of regions of fibrous scar interspersed with viable surviving muscle bundles. While dense scars can define anatomic borders of re-entrant circuits, regions of surviving myocardium form the substrate for slow conduction and re-entry [3]. Myocyte uncoupling, down regulation of connexin protein that govern gap junction function, and ingrowth of fibrous tissue contribute to delayed conduction in the slow conducting channels. Excitation wavefronts that normally proceed more rapidly in the longitudinal than transverse direction are channeled in a circuitous course through surviving myocardial bundles (Fig. 38.1) [3, 4].

In addition to anatomic boundaries, functional refractoriness can contribute to boundaries for re-entry. However, it is the relatively fixed anatomic nature of the substrate that promotes stable monomorphic VTs that can be recurrent over years and is often reproducibly inducible with programmed stimulation. The interaction between regions of scar, surviving muscle bundles and re-entry has been demonstrated by models of re-entry both computational and in intact heart [5–7]. Post infarct circuits can be anatomically complex. Parallel conduction barriers formed by areas of scar or a valve annulus can create multiple potential channels and loops (Fig. 38.2). In some cases a figure of 8 re-entry circuit forms. This model is composed of a critical central isthmus with slow conduction. The isthmus may have branches formed by surviving myocardium that are blind alleys without participation in a particular re-entrant arrhythmia and are termed bystander areas. Depolarization of the small mass of tissue that comprises the critical isthmus is not detectable on the surface ECG, and typically occurs during "electrical diastole" between QRS complexes. A re-entrant wavefront leaves the isthmus at the exit site of the circuit to depolarize the remaining myocardium and give rise to the QRS complex. The excitation wave front then reenters the isthmus via an inner or outer loop. An outer loop is usually a broad band of tissue in the surrounding border zone or normal myocardium. An inner loop is contained within the scar, and there can contain multiple potential conduction paths that can support reentry.

If multiple loops exist, the shortest conduction time determines the VT cycle length and is the dominant loop for that VT. Loops with longer conduction times will act as a bystander for that particular VT but can serve as the potential component of a new circuit if the initial loop is rendered refractory by a drug or blocked by ablation. Thus, a single scar can support multiple VTs. A typical post infarct scar can extend over several centimeters [8, 9]. Re-entrant circuits are 3-dimensional and involve mid and subepicardial layers particularly in scars associated with NICM and ARVC.

VT is due to a damaged Purkinje system in approximately 8 % of patients with structural heart disease and recurrent arrhythmias [10]. VT may be due to catecholamine sensitive automaticity or re-entry involving the bundle branches [11]. Bundle branch re-entry causes sustained monomorphic VT [12]. Most commonly, the circulating wavefront propagates up the left bundle and antegrade via the right bundle resulting in VT with typical LBBB pattern. This VT can be entrained from the RV apex

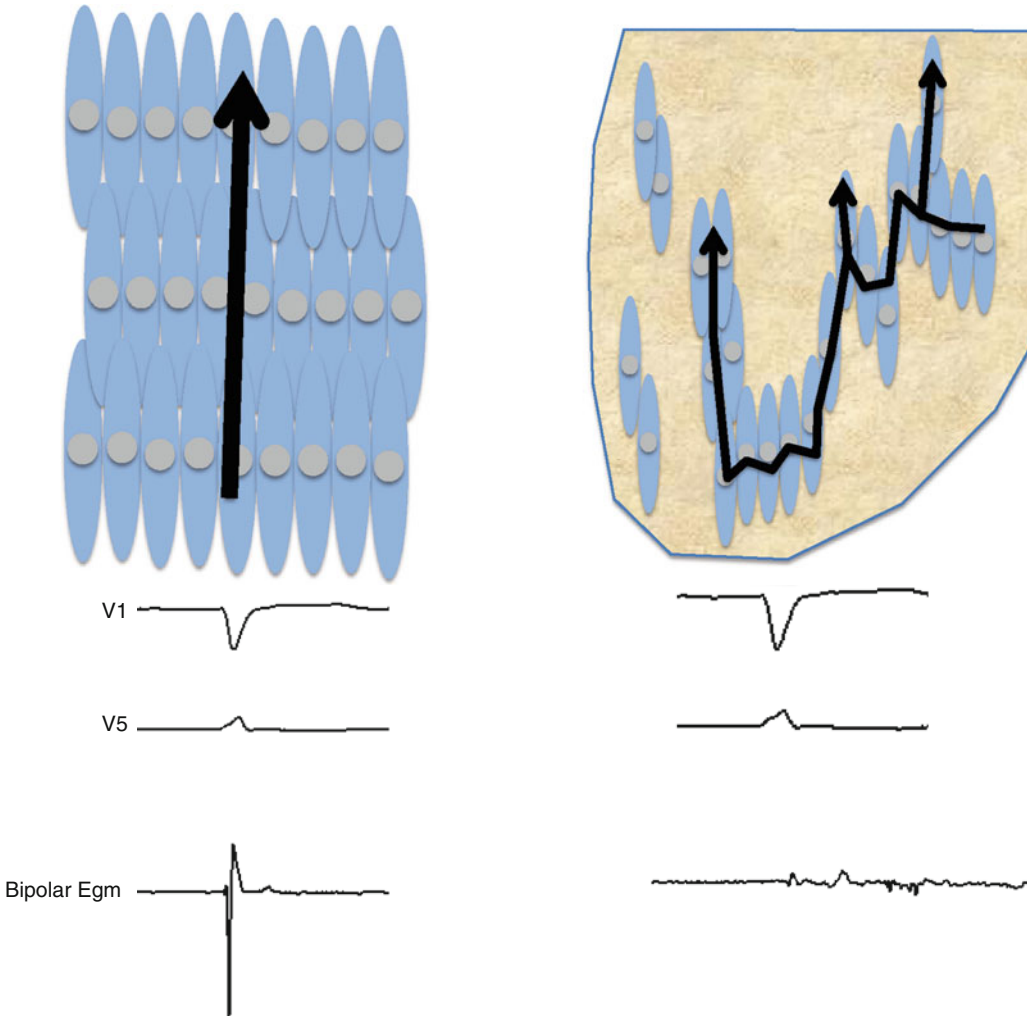


Figure 38–1. This schematic shows the mechanism of slow conduction created by circuitous conduction thorough a region of ventricular scar. Normal cardiac conduction proceeds faster longitudinal to the orientation of the myocytes (*left panel*). In scar tissue with areas of surviving myocardium, a zig-zag course of activation with delay is seen (*right panel*). Electrograms recorded from areas of scar typically show fractionation, low amplitude and late potentials. See text for discussion

with post pacing intervals approximating the tachycardia cycle length. A constant relationship of the His deflection preceding the QRS is seen, usually with any oscillation in the H-H interval preceding V-V cycle length alteration. Less frequently, the circuit revolves up the right bundle and down the left producing a typical RBBB type VT. Although both these types of VT are effectively abolished by ablation of the right or left bundle branch, many patients with bundle branch reentry also have scar-related reentrant VTs that are inducible.

Mapping and Ablation Technologies and Procedural Considerations

Current indications for VT ablation are shown in Table 38.1 [13]. Due to the relative safety and simplicity of radiofrequency (RF) current, it remains the most commonly used energy source for ablation and is delivered through electrodes mounted on steerable catheters. Lesion size is limited by coagulum formation on the electrode when temperature exceeds 70 ° C. Although 4 or

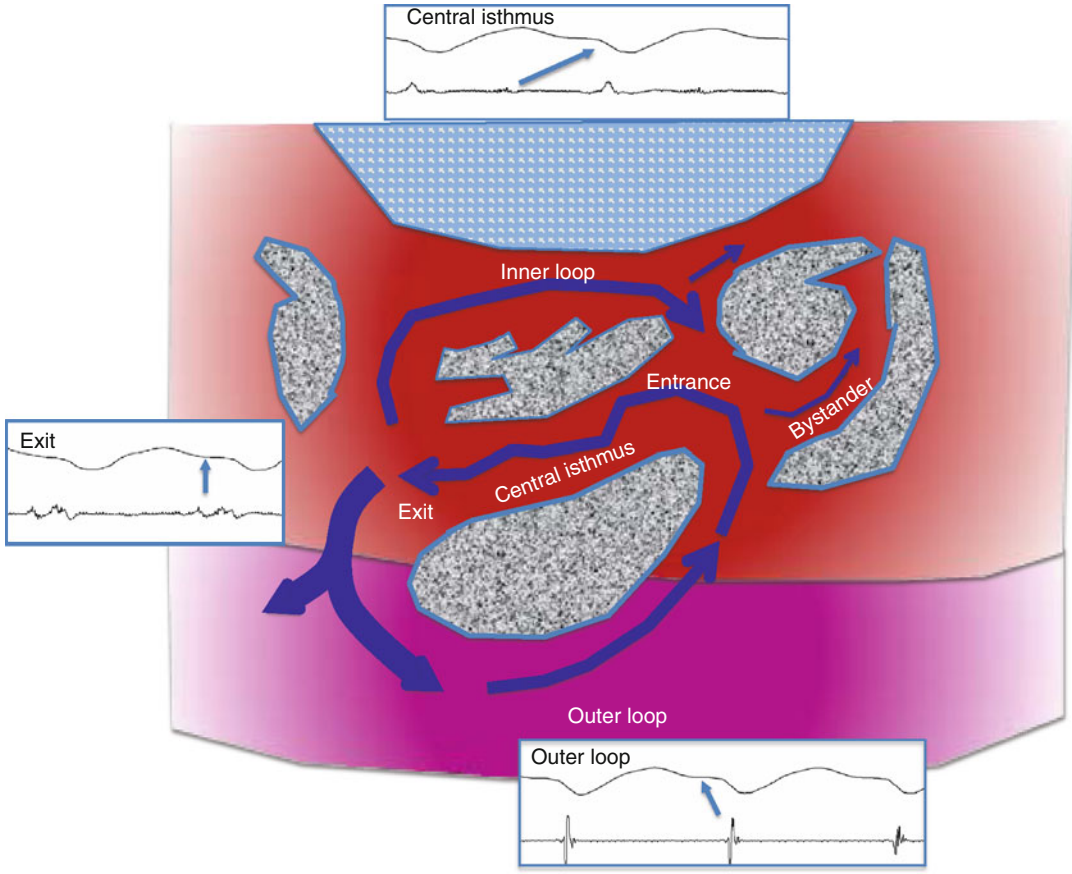


Figure 38–2. Components of a scar-related reentry circuit are shown. *Grey* regions are areas of fibrous conduction block. Propagation is indicated by *blue arrows*. A figure eight type of circuit with a channel, inner and outer loops is shown. The circulating wavefront emerges from an isthmus (also referred to as a channel) and propagates from the isthmus exit, across the ventricles to create the QRS complex. (see text for discussion). Examples of electrograms recorded from reentry circuit sites are shown. In each *panel* the *arrow* points to the QRS onset. At the exit presystolic electrograms are recorded. In the isthmus diastolic electrical activity is present, although far-field potentials from depolarization of the larger mass of myocardium may also be seen, typically inscribed during the QRS. Outer loop sites are depolarized during the QRS complex

5 mm electrodes maybe sufficient for idiopathic VT ablation, ablation of the thicker substrate of scar related VTs is facilitated with the use of irrigated electrodes to cool the catheter tip, or 8 mm tip electrodes to effect deeper and larger lesions. One problem with the 8 mm tip catheters is that signal resolution tends to be poor such that high frequency, low amplitude signals become more difficult to localize. Preliminary data using catheter based cryoablation for post infarction VT shows promise and is a consideration when ablation close to a coronary vessel is anticipated on the epicardial surface [14].

Most centers use 3-dimensional electroanatomical mapping systems to aid ablation for VT (Fig. 38.3). Mapping systems enable the creation of a three-dimensional shell of the chamber of interest, and allow for catheter manipulation with limited fluoroscopy. Point by point charting of electrograms can create visual maps of voltage (voltage map) or impulse propagation (activation map) on the shell. By altering the upper threshold of scar on a voltage map, one can visualize potential channels within a scar due to relative inequalities in voltages. Further, areas of dense scar that form borders for circuits can be

Table 38–1. Indications for catheter based ablation for ventricular tachycardia in patients with structural heart disease

1. Symptomatic sustained monomorphic VT that recurs despite antiarrhythmic drug therapy or when drugs are not tolerated or desired
2. Incessant VT or VT storm that is not due to a reversible cause
3. Frequent PVCs, non-sustained VT or VT that is presumed to cause ventricular dysfunction
4. Bundle branch rentry or interfascicular re-entrant VTs
5. Polymorphic VT or VF refractory to antiarrhythmic drugs when there is a suspected trigger that can be targeted for ablation

Catheter ablation for VT is contraindicated:

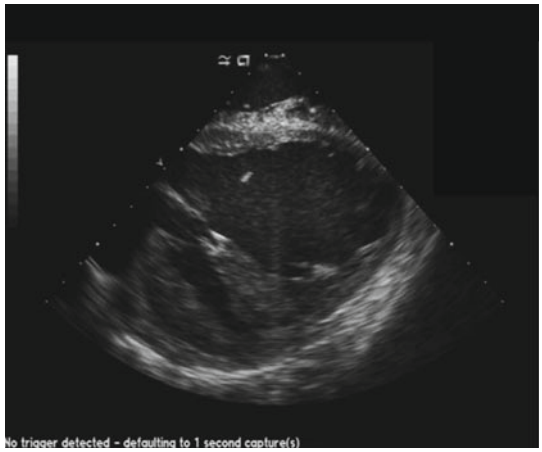
1. Mobile ventricular thrombus (epicardial ablation or transcoronary ethanol ablation can be considered)
2. For asymptomatic PVCs or non-sustained VT that is not causing or contributing to ventricular dysfunction
3. VT due to transient reversible causes or torsade de Pointes VT related to prolonged QT

Key to Abbreviations: *VT* ventricular tachycardia, *VF* ventricular fibrillation, *PVC* premature ventricular contraction (Adapted from Ref. [13]

identified by electrical in-excitability [15]. By marking them on the voltage map, one gets a visual impression of potential channels for directing ablation energy.

Concomitant use of intra-cardiac echocardiography (see Fig. 38.3) aids in the creation of the anatomic shell, and visualization of valve structures, and papillary muscles, and helps monitor for related complications, such as deteriorating ventricular function and pericardial effusion.

For endocardial ablations, access to the left ventricle is usually obtained retrogradely via the aortic valve. In the event of significant peripheral vascular disease or a mechanical aortic valve, a transeptal approach provides access to the LV by traversing the mitral valve. Deep intramural



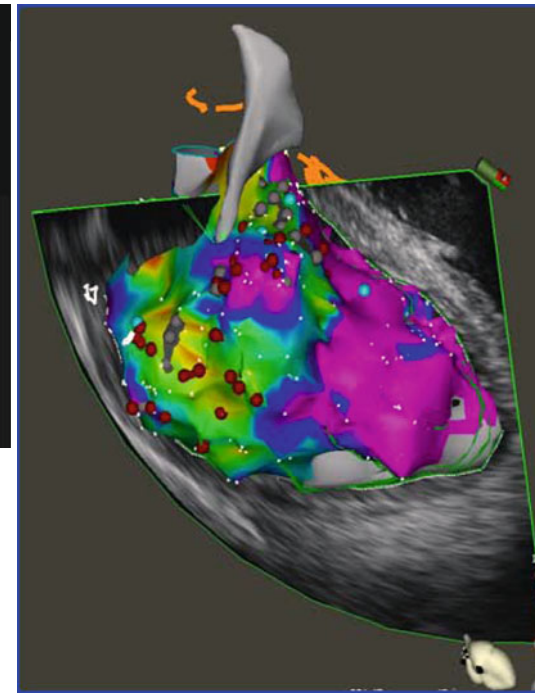


Figure 38–3. Mapping data from a patient with a prior inferior wall myocardial infarction are shown. The *left panel* shows one view from the intracardiac ultrasound. The probe was in the right ventricle, and obtained images of the LV, including the papillary muscles as shown. Serial slices were obtained to reconstruct the shell of the LV and aorta. In the *right panel*, the shell acquired by serial echo images is shown. The present ultrasound slice is also shown. The *colors* indicate mapping data (electrogram voltage) that was acquired by moving an LV catheter across the endocardium, acquiring signals at serial points and displaying each point on the LV shell. Electrogram amplitude > 1.5 mv is *purple*. Electrogram amplitude is progressively lower as *colors* proceed from *blue* to *green* to *yellow* and *red*. An inferobasal low voltage scar, consistent with prior infarction is present. Maroon circular tags are ablation sites in the infarct region

VTs or those originating from the subepicardium can be approached via the pericardial space. In the absence of prior cardiac surgery or pericarditis, the pericardial space can be accessed via the subxiphoid approach by introducing a needle under fluoroscopy and injection of small amounts of contrast to identify the pericardial space as described by Sosa et al. [16]. Once the pericardial space is entered, a guide wire is advanced followed by a sheath for the mapping and ablation catheter. In the absence of pericardial adhesions, catheters can be moved freely on the epicardial surface for mapping. Prior to any ablation, proximity to the coronary arteries is usually assessed by coronary angiography. Ablation close to a coronary artery (within 4 mm) poses a high risk of acute coronary occlusion and should be avoided [17]. Left phrenic nerve injury is another concern and high output pacing is performed prior to ablation along the anatomical course of the nerve to assess proximity of the nerve [18]. In patients with prior cardiac surgery, creation of a subxiphoid surgical window can allow access to the pericardial space in some patients. In the presence of dense adhesions, even such access maybe limited to the inferior surface of the ventricles and a full thoracotomy may be necessary [19].

In the absence of complete AV block, initial electrophysiological evaluation prior to ablation should include catheters placement to record the His bundle signal to assist with diagnosis and exclude bundle branch re-entrant VT. Once catheters are in place, it is common practice to induce the ventricular arrhythmia if the patient is not in incessant VT. In addition to confirming the diagnosis, induction helps define the number of inducible VTs and assess for hemodynamic stability. The QRS morphology of all induced VTs is documented to enable subsequent mapping techniques and to help differentiate between clinical VTs and inducible VTs of uncertain clinical relevance. Many patients have VTs that are hemodynamically unstable and will need immediate termination by burst pacing or cardioversion. Initial burst pacing from the RV apex at a cycle length 20–30 ms shorter than tachycardia cycle length to assess the post pacing intervals (PPI) at that site can be useful. A PPI – VT cycle length difference less than 30 ms suggests possible RV or septal involvement in the circuit, or bundle branch re-entry. In hemodynamically unstable patients, left ventricular hemodynamic support can be used to allow mapping during VT or facilitate hemodynamic recovery from episodes of VT [20].

Electrocardiographic Data

During monomorphic VTs, QRS morphology can direct one to the exit site where impulses emerge from a re-entrant circuit. A left bundle branch block configuration in Lead V1 (dominant S wave) suggests an exit site in the right ventricle or the inter-ventricular septum (Fig. 38.4). A dominant R wave or right bundle branch block pattern in V1 indicates a left ventricular exit site. The QRS axis defines VT origins in the coronal plane; an inferiorly directed QRS axis suggests a superior or anterior wall exit whereas a superiorly directed axis indicates an inferior wall exit. The precordial leads are more indicative of directionality in the sagittal plane. Deep S waves in the apical leads (V3 to V6) indicate earliest activation in the LV apex whereas prominent R waves in these leads point to a basal origin of activation. It should be borne in mind that areas of scar, conduction block and abnormal ventricular anatomy can render these rules misleading. Pacing from the mapping catheter during sinus rhythm (pace-mapping) in an attempt to reproduce the QRS morphology during VT is a better way of determining the anatomic exit location in any particular individual.

Subepicardial origin of VT is suggested by wider QRS complexes and delayed initial upstrokes in the precordial leads due to relatively slower impulse propagation on the epicardium compared with endocardium. Pseudo delta waves measured from the onset of the QRS to the earliest rapid deflection in any precordial lead of ≥34 ms, intrinsicoid deflection time (QRS onset to peak of R wave in V2) ≥85 ms, or a precordial RS interval >120 ms, correlated with epicardial origin in a group of patients with RBBB VT [21]. In a group of patients with non-ischemic cardiomyopathy, Valles et al. showed in a pace-mapping study that absence of a q in lead II, presence of Q waves in lead I in VT of basal

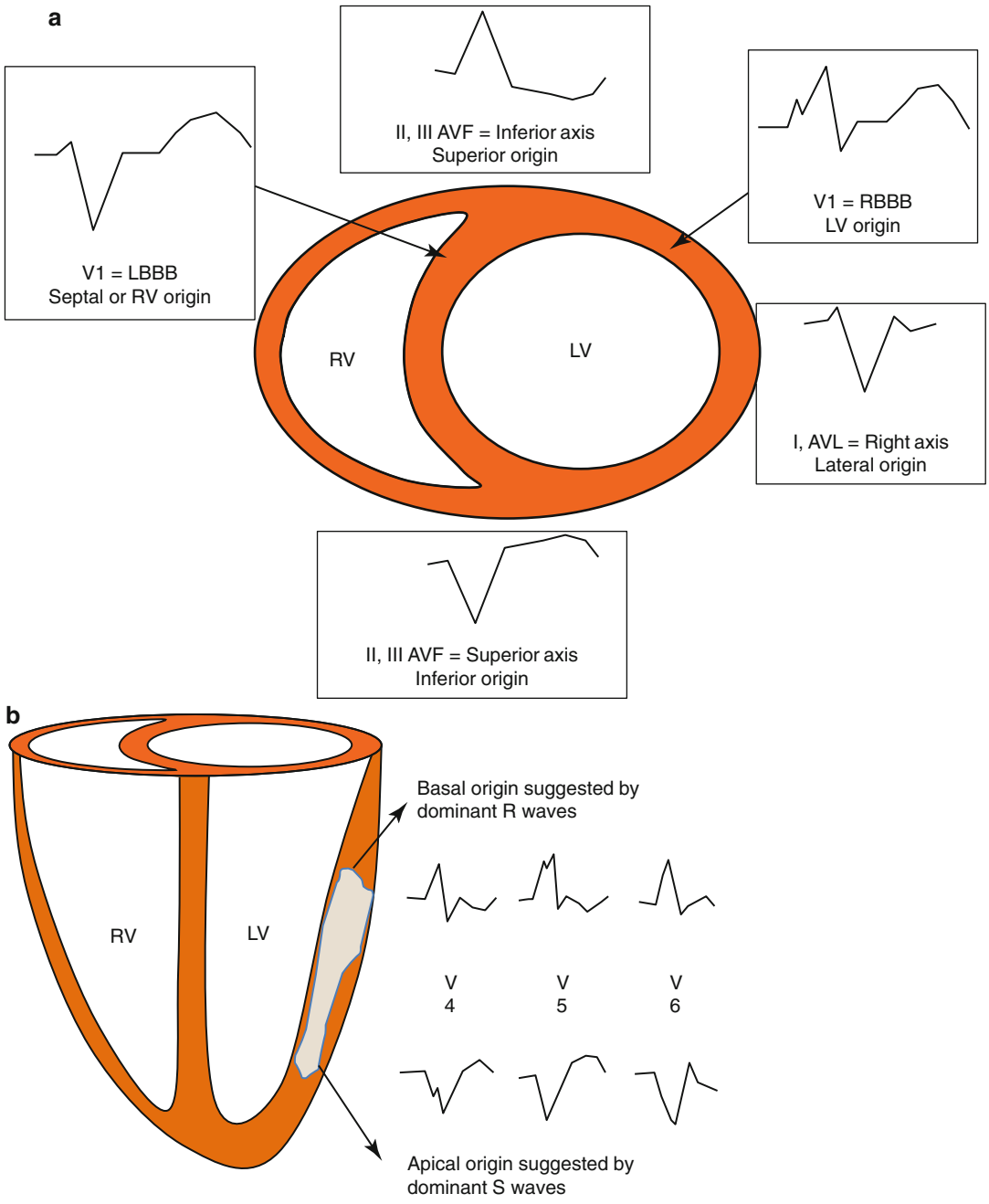


Figure 38–4. Schematics relating the likely VT exit to the QRS morphology are shown. The QRS axis determined by leads II, III and AVF indicate a superior versus inferior exit (figure 38-4a). The polarity of the lateral chest leads V4 to V6 point to a basal versus apical exit (figure 38-4b). See text for details

anterior or lateral LV origin was suggestive of an epicardial site of VT [22]. In ischemic cardiomyopathy, the ECG is not a reliable marker of endocardial versus epicardial reentry circuit location [23].

Substrate Mapping

Mapping is directed at locating and defining the extent of scar areas and using electrogram characteristics and pacing maneuvers to identify

channels that are integral to the re-entrant circuits. If the arrhythmia is tolerated hemodynamically, detailed activation and entrainment mapping can be performed to identify areas critical to the circuit before application of ablation to the site. The majority of patients (70–80 %) with scar VT, however, will have hemodynamically instability precluding mapping during prolonged periods of sustained arrhythmia [24]. Additionally, VTs of multiple morphologies maybe present or change from one to another spontaneously or during pacing maneuvers such that mapping during of any one stable VT becomes difficult. Finally, a clinical VT may not be inducible at the time of the EP study. Hence, one has to rely on techniques to target the substrate for VT during sinus rhythm, a process referred to as substrate mapping. Even when a stable VT is present, it is often useful to define the extent of the scar region by mapping during stable sinus or paced rhythm prior to ablation. Point by point interrogation of the myocardial surface with the ablation catheter is performed to define areas of low voltage and assess for viability by ability to evoke a paced response from the tissue. Local bipolar and unipolar electrograms can be used to create a voltage map on a 3-dimensional mapping system (see Fig. 38.3). Close correlations have been demonstrated between infarct scars and low electrogram voltage on endocardial and epicardial maps [9, 25]. Greater than 95 % of sites in the normal ventricular myocardium have a peak to peak bipolar electrogram voltage >1.5 mV. On the epicardial surface, average voltage tends to be slightly lower due to presence of epicardial fat and the coronary vessels. On epicardial sites 1 cm removed from large epicardial coronary arteries, 95 % of all bipolar voltages are greater than 0.94 mV [26]. More recently, endocardial unipolar voltage maps have been utilized to detect epicardial scars. Unipolar recordings with minimal filtering (high pass 0.5 Hz or less) contain substantial far-field signal. In patients with ARVC, Polin et al. found that unipolar voltage less that 5.5 mV correlated with the presence of epicardial scars overlying regions of normal (>1.5 mV) endocardial voltage [27].

Voltage maps can be created during sinus rhythm, during ventricular tachycardia or pacing. Although activation changes due to change in rhythm can potentially influence local electrogram amplitude, the area defined by voltages less than 1.5 mV seldom shifts appreciably [28]. Low voltage areas thus defined, usually harbor the re-entrant circuits but the areas are often too large for adequate ablation of the entire region with available technology. Hence, additional clues are sought to narrow the areas of interest.

Electrograms During Sinus Rhythm

Electrograms recorded from scar, in addition to being of reduced amplitude, usually demonstrates fractionation (Fig. 38.5). Such fractionation alone is however, non-specific and cannot differentiate a potential circuit from surrounding areas of fragmented conduction. Isolated and late potentials are low amplitude electograms inscribed after the completion of the QRS complex and indicate channels of slow conduction within the scar (Fig. 38.5). Ablation based on late potentials has been shown to prevent VT recurrence [29–32]. However, even late potentials do not always signify catheter location within a particular VT circuit; a bystander area can generate late potentials limiting its specificity if the goal is to target a particular VT. They are suitable targets for ablation when induced VT is unstable but multiple sites containing these electrograms will generally need to be targeted for successful abolition of VT.

Pacing During Sinus Rhythm

Pacing mapping from the scar area can provide three pieces of information: electrical excitability or capture, the morphology of the paced QRS and the presence of delayed conduction measured by the stimulus to QRS duration (S-QRS) (see Fig. 38.5). The ability to capture the myocardium indicates adequate contact of the catheter with viable tissue within the scar. Unipolar pacing between the tip electrode of the catheter and an indifferent electrode remote from the ventricle such as in the inferior vena cava, permits capture specifically from the cathodal tip electrode and may prevent potential interference with anodal capture as can occur with bipolar pacing. We typically use a current of 10 mA at a pulse width of 2.0 ms to test for

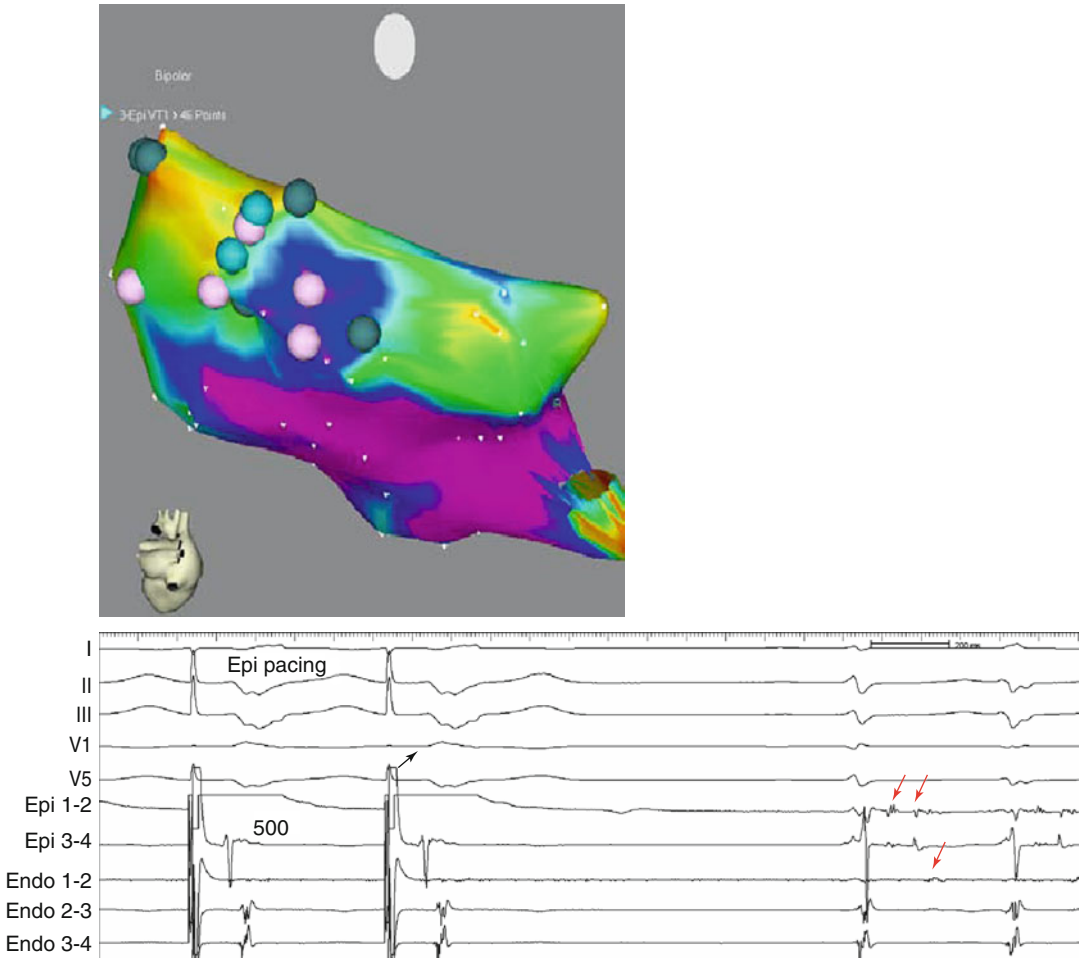


Figure 38–5. Data from substrate mapping during sinus rhythm in a patient with an inferior wall scar are shown. At the top is an epicardial voltage map of the LV as viewed from the posterior aspect. Mapping was limited by pericardial adhesions. A low voltage region (*yellow*, *green*, *blue*) is present at the basal LV. *Blue* and *pink* tags indicate regions with fractionated potentials and long conduction delays during pacing. The *bottom panel* shows data recorded from a site in the scar. From the *top* are surface ECG leads I, II, III, V1 and V5, followed by bipolar recordings from a catheter in the epicardial space (*Epi 1–2* and *Epi 3–4*) and adjacent endocardial sites (endo 1–2, 2–3, and 3–4). During sinus rhythm (last two complexes) fractionated late potentials (*red arrows*) are present in the epicardium, and a small very late potential is also seen on endo 1–2. During pacing at this site (first two beats) a delay (*arrow*) is evident between the stimulus and QRS onset, indicating slow conduction away from the pacing site

capture [15]. Surprisingly, areas recording very low amplitudes may occasionally capture with pacing. Inability to capture indicates either a dense scar or poor catheter contact with myocardial tissue. When adequate contact is confirmed, inability to capture is often due to dense scar and marked on the voltage map as such to give a visual impression of the borders of re-entrant circuits. On the epicardium, fatty tissue can insulate the myocardium to prevent adequate capture. Associated electrograms often show low frequency signals indicating a far field recording from myocardium insulated by fat, and these regions can not be reliably distinguished from low voltage due to scar. Fractionated potentials, however, are not likely to be due to fat, and are probably a reliable marker of scar.

When adequate capture is obtained, paced QRS morphology provides a clue to the proximity of the catheter to re-entrant corridor for the VT; pacing from within the channel will replicate the QRS morphology of the VT if the paced wave

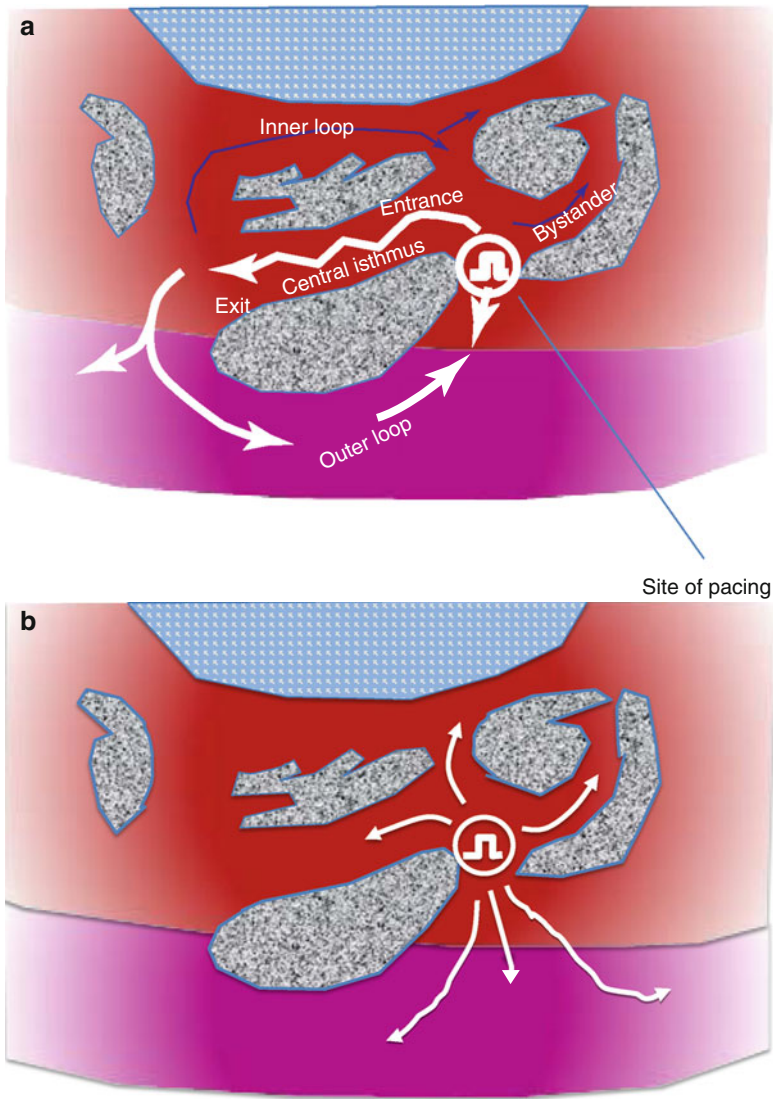


Figure 38–6. Schematics illustrating the mechanism by which pace-apping can be a misleading indicator of proximity to the reentry circuit. In panel (**a**), entrainment during VT is shown from within a proximal site in the circuit near the entrance to the isthmus. The site is in the circuit. The stimulated wavefronts emerge from the VT exit after a long S-QRS interval. Panel (**b**) illustrates pace-mapping at this site. In the absence of VT, the paced wavefronts reach the surrounding myocardium more directly, from a different region, and the QRS morphology may not resemble that of VT

front emerges from the same exit as the VT wave front. One caveat should be borne in mind however. QRS morphology different from VT during sinus rhythm maybe encountered even if pacing is performed from the expected site VT site due to alterations in exit points during VT and in sinus rhythm. Propagation in diseased myocardium not being homogenous, small differences in pacing positions can generate widely disparate propagation wavefronts and resulting QRS morphologies [33]. At some sites in the reentry circuit, the QRS morphology during pace-mapping can be substantially different from the VT QRS (Fig. 38.6). At proximal sites in the reentry circuit, pacing can entrain VT with concealed fusion due to anti-dromic wavefronts being confined close to the circuit by collision with returning orthodromic wavefronts (Fig. 38.6) (see below); yet, the pace-map during sinus rhythm can generate a different QRS because paced wavefronts can emerge from potential exits that are no longer blocked either by returning wavefronts or by functional refractoriness.

During pace-mapping the S-QRS duration is an indication of the position of the catheter relative to the entrance and exit sites of a slowly conducting channel. A short S-QRS suggests a position closer to the exit while a long S-QRS

indicates the entrance point or slowly conducting portion of a protected isthmus. An S-QRS interval exceeding 40 ms has been shown to be associated with slow conduction channels [34, 35]. A stimulated wave front that emerges from the exit with a long S-QRS and with complexes that are similar to the morphology of the VT is strongly suggestive of an isthmus involved in the re-entrant VT [36].

Mapping During VT

A stable clinical VT offers the advantage of mapping during the arrhythmia to identify an isthmus where ablation can terminate VT and render it non-inducible.

Electrograms During VT

Exit sites of a VT circuit can be identified by electrograms that precede surface QRS complexes (see Fig. 38.2). Such pre-systolic activity can be documented on endocardial sites with multipolar catheters in >85 % of cases [37]. Diastolic electrograms during VT can indicate sites of impulse propagation in regions of slow conduction activated between QRS complexes (see Fig. 38.2). Electrogram timing alone is not entirely reliable as a guide to successful ablation sites due to multiple conduction channels, some of which are bystanders and not active in VT generation [38, 39]. Dissociation of the potential from the VT is good evidence that the site is not critical to the VT but entrainment and assessment of post pacing intervals maybe necessary to differentiate bystander sites from the critical isthmus. The absence of diastolic potentials does not preclude successful ablation at a site because proximal parts of a circuit can be depolarized so early that the related electrograms may fall within or shortly after the QRS complexes [40].

Pacing During VT for Entrainment Mapping

The ability to entrain the tachycardia using criteria set out by Waldo et al. confirms re-entry as a mechanism [41]. During VT, pacing at a rate slightly faster than the VT rate will result in continuous resetting (entrainment) of the VT (Fig. 38.7). If the pacing site is within the loop of a circuit, the interval from the last paced complex to the first return cycle i.e. the post pacing interval (PPI) will approximate the tachycardia cycle length (TCL) (Figs. 38.8 and 38.9). Ablation is more likely to terminate tachycardia if the PPI is within 30 ms of TCL [5, 35, 39, 42]. In addition, the degree of fusion between paced and VT complexes is helpful in locating an isthmus. QRS fusion occurs if the stimulated wave-front alters activation over a large area to change the ECG (Figs. 38.7 and 38.8). If pacing is performed from the isthmus, the stimulated wavefront emerges from the circuit replicating ventricular activation during VT, a process termed entrainment with concealed fusion because the fusion between antidromic and orthodromic wavefronts in the circuit is concealed (Fig. 38.9). During entrainment with concealed fusion, the S-QRS interval indicates the conduction time between the pacing site and the re-entry circuit exit and matches the local electrogram to QRS during VT.

As shown in Fig. 38.2, the circulating wavefront in a VT circuit reenters the proximal portion of the isthmus by one of multiple loops. Entrainment characteristics can help locate regions within an outer loop, inner loop, central isthmus and a bystander (Figs. 38.7, 38.8, and 38.9). Outer loops border areas between the scar and normal myocardium. Activation in the outer loop coincides with QRS complexes (Fig. 38.2), and PPI during entrainment approximates tachycardia cycle length but there is manifest fusion (Fig. 38.8). S-QRS is typically less than 40 ms. Inner loops are generally confined within the scar zone and activation of the loop once again, tends to coincide with QRS inscription. During entrainment, there is concealed fusion and PPI is within 30 ms of TCL. However, S-QRS is long >70 % of TCL. Ablation at this site has a low probability of terminating VT because of the broad nature of the loop or due to the wavefront engaging a different loop. Targeting the central isthmuses offer the best chance of VT termination with focal ablation. Pacing in the central isthmus produces entrainment with concealed fusion (Fig. 38.9), PPI that approximates TCL, an S-QRS that is between 30 and 50 % of TCL and equals the electrogram to QRS interval.

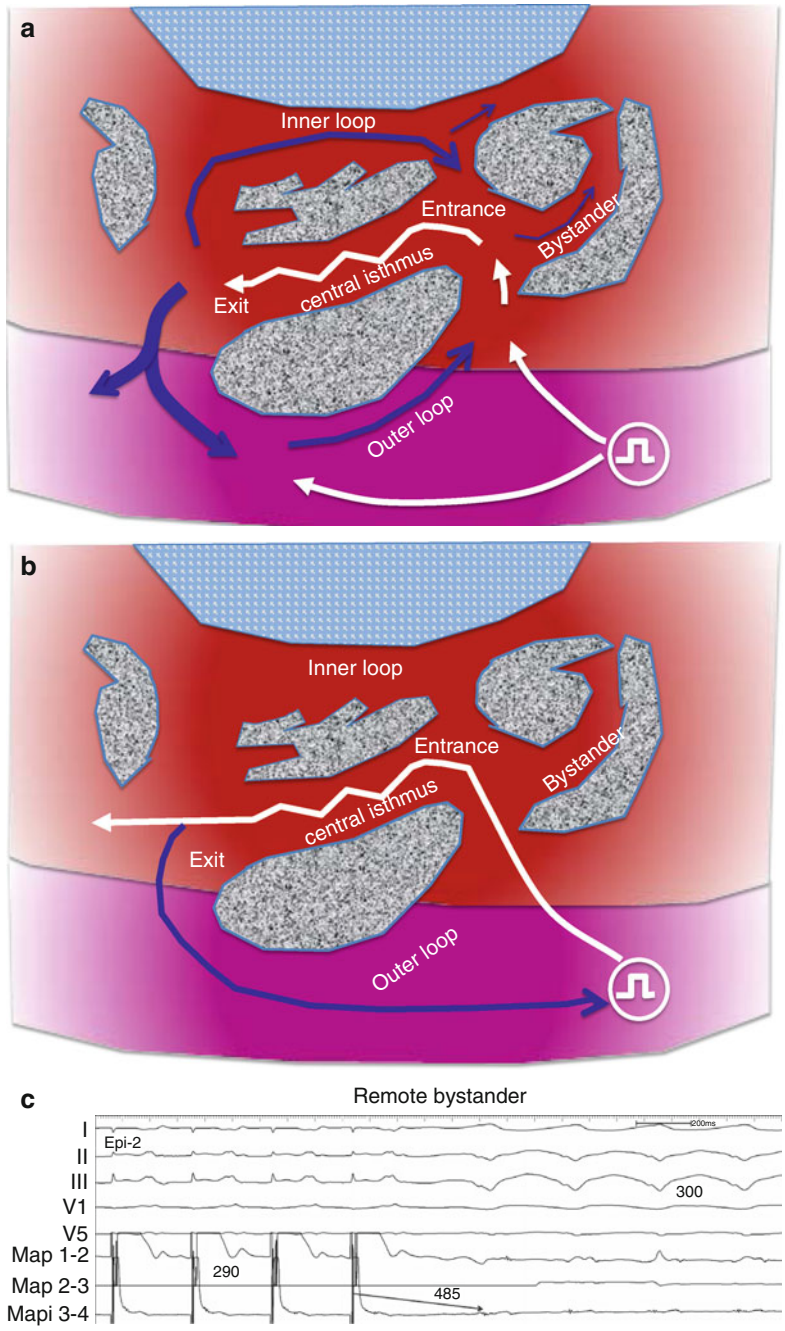


Figure 38–7. Entrainment of VT by pacing at a site remote from the reentry circuit. In panel (**a**), pacing produces a wavefront that propagates to the circuit and splits into two wavefronts. An anti-dromic wavefront collides with the orthodromic tachycardia wavefronts. An orthodromic wavefront propagates through the circuit, resetting the circuit. Panel (**b**) shows the post pacing interval (*PPI*) following the last stimulus. The final stimulated wavefront propagates to the circuit, through the circuit and back to the pacing site. Hence the PPI exceeds the revolution time through the circuit (tachycardia cycle length) by the conduction time from pacing site to circuit, and then back from circuit to pacing site. Panel (**c**) shows an example. VT with a cycle length of 300 ms is present. Pacing at a cycle length of 290 ms accelerates all electrograms and QRS complexes to the pacing rate. The PPI is 485 ms, substantially longer than the tachycardia cycle length of 300 ms. Note also that pacing produces QRS fusion

Even central isthmuses can be broad ranging from 6 to 36 mm and may require multiple lesions for abolition of VT [7]. Multiple lesions across the isthmus are often applied to prevent recurrence. When VT is related to prior inferior wall myocardial infarction, an isthmus is often present running parallel to the mitral annulus. Linear ablations from the annulus to the dense areas of the scar can often interrupt a submitral isthmus and abolish these VTs [43, 44]. Entrainment in bystander areas that may have electrograms suggestive of a central isthmus,

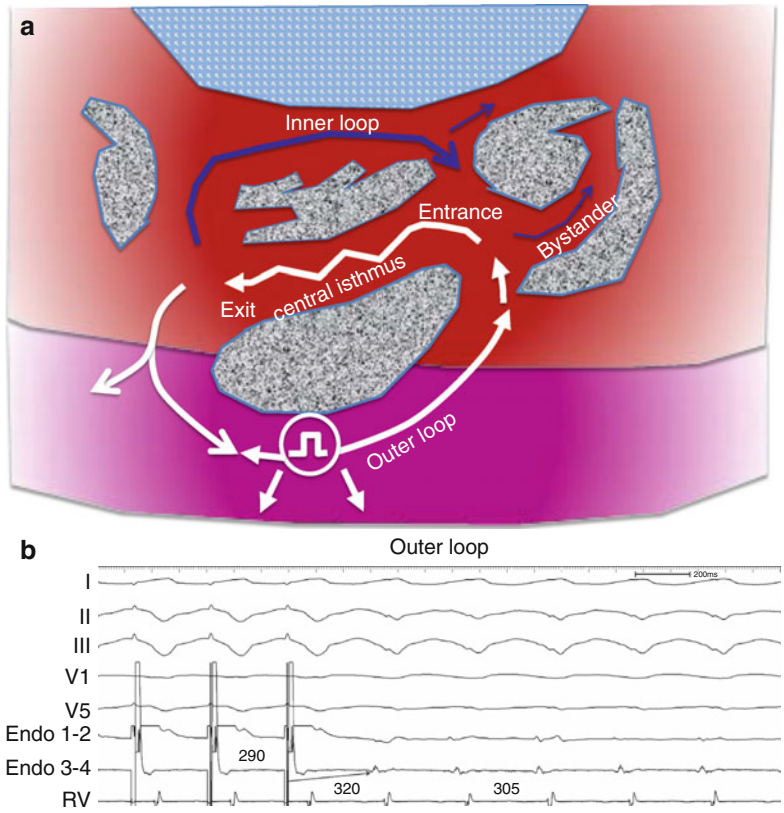


Figure 38–8. Entrainment of VT from an outer loop site. In panel (**a**), the antidromic wavefronts collide with the orthodromic tachycardia wavefronts near the pacing site, but also propagate directly away from the pacing site to produce QRS fusion. The stimulated orthodromic wavefront propagates through the circuit, resetting the circuit. The PPI matches, or only slightly exceeds the VT cycle length. Panel (**b**) shows an example. VT with a cycle length of 305 ms is present. Pacing at a cycle length of 290 ms accelerates all electrograms and QRS complexes to the pacing rate and alters the QRS morphology due to fusion. The PPI is 320 ms, only 15 ms longer than the tachycardia cycle length

usually return long post pacing intervals in excess of 30 ms of TCL.

Some caveats in measuring PPI are worth noting. During entrainment pacing, it is important to confirm that the pacing stimulus has captured the ventricle and accelerated it to the pacing cycle length. Specifically, the electrogram selected for PPI measurement should have been captured during pacing. Measurements to far-field components of the local electrogram can result in misleading data (Fig. 38.9). Typically, occurrence of PPI shorter than the TCL is an indication that far field signals are being measured or there has been loss of capture before termination of pacing. In addition, pacing at too short a cycle length can produce decremental conduction in the circuit and return long PPI. Entrainment for measurement of PPI usually employs pacing rates only slightly faster than TCL (10–20 ms) to avoid altering the circuit or terminating tachycardia [45].

A pacing stimulus that fails to capture the ventricle but results in termination of tachycardia is specific for the stimulus site being in or very close to a critical component of the reentrant circuit and is good site for ablation [46]. Local capture of the circuit followed by block of the propagating wavefront within the scar (non-global capture) is the likely mechanism. This observation while specific for VT termination with ablation is infrequent and time consuming to reproduce. It can also be mimicked by fortuitous VT termination. Occasionally, mechanical pressure with the catheter can render a circuit refractory; if the site that resulted in terminated with barotrauma is known, ablation at the site should be considered especially if the VT cannot be re-induced [47].

Epicardial Ablation

In approximately 10–15 % of patients with VT associated with structural heart disease, VT circuits are intramural or subepicardial and not

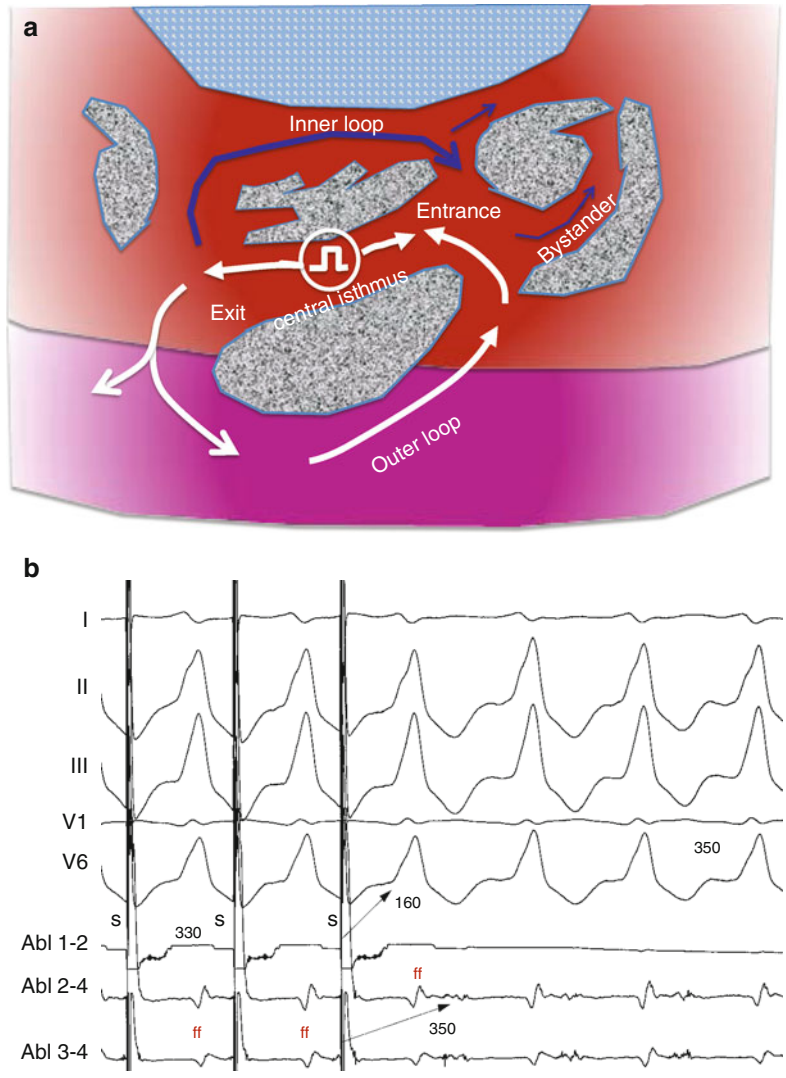


Figure 38–9. Entrainment of VT from a central isthmus site. In panel (**a**), the stimulated antidromic wavefronts collide with the orthodromic tachycardia wavefronts near the pacing site. The stimulated orthodromic wavefront propagates to the exit after and then through the circuit, resetting the circuit. The PPI matches the VT cycle length. Panel (**b**) shows an example. VT with a cycle length of 350 ms is present. Pacing at a cycle length of 330 ms accelerates all electrograms and QRS complexes to the pacing rate without altering the QRS morphology (fusion is concealed within the circuit where the antidromic and orthodromic wavefronts collide). The PPI is 350 ms, matching the tachycardia cycle length. Note the far-field electrograms (*ff*) that remain visible during pacing, and which are larger than the local potentials, to which the PPI is measured

accessible with an endocardial catheter. In one series, an epicardial approach was used in 13 % of 913 VT ablation procedures [48]. With increasing experience, the epicardial approach is being employed more frequently and as a first line approach when the ECG features are highly suggestive of epicardial exits for the VT [49]. Epicardial VT substrate is often encountered in NICM or ARVC (Fig. 38.10); it is less frequently required in patients with coronary disease. Once epicardial access is obtained as described above, methods of mapping and ablation are identical to those on the endocardium. Pacing thresholds tend to be higher on the epicardium. In general, epicardial scars tend to border a valve annulus especially in patients with NICM.

Assessing the Effects of Ablation

In patients with a stable VT, termination of VT with ablation is good evidence that the site is critical to the tachycardia circuit as long as the termination was not due to a premature beat that rendered the circuit refractory. With delivery of ablation energy at a critical isthmus, VT termination is usually abrupt within 19 s, but may be preceded by gradual slowing. When

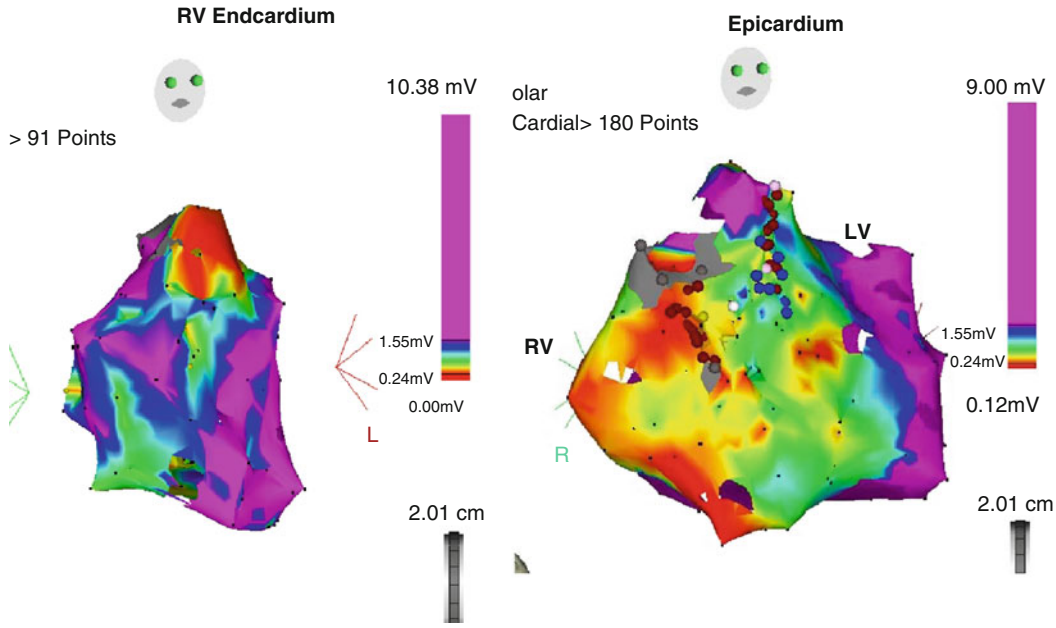


Figure 38–10. Right ventricular endocardial (*left panel*) and epicardial (*right panel*) voltage maps from a patient ARVC are shown. Purple areas indicate bipolar electrogram amplitude exceeding 1.5 mV representing normal myocardium. A small area of low voltage is present in the RV endocardial outflow tract and at the inferior wall. The epicardium, however, shows extensive low voltage across the RV. Maroon tags indicate ablation sites where VT was interrupted with a line of lesions between two regions of electrically unexcitable scar (*grey regions*)

prolonged periods of RF delivery are required for gradual slowing and termination of VT, there is a high likelihood that the area of effective heating is only influencing the margins of the circuit and VT recurrence is common. This scenario is particularly true of deep intramural circuits in septal or subepicardial being affected by ablation on the endocardium.

Following RF application, we typically pace the site at 10 mA at 2 ms pulse width to ensure that the area can no longer be captured. Non-excitability of the ablated tissue provides a fair indication of delivery of an adequate lesion [15]. During substrate based ablation, rendering sites of interest non-excitable is our immediate goal of ablation.

Programmed stimulation is repeated after creation of ablation lesions. While non-inducibility is the goal, rapid non-clinical VTs or non-sustained VT may be induced. Operators vary in their approach to dealing with non-clinical VTs. Slower VTs often lead to recurrent hospitalization and ICD shocks and we target them with additional ablation. Even when VT is rendered non-inducible, approximately 20 % of patients will experience recurrent VT [50]. Healing of RF lesions and withdrawal of antiarrhythmic drugs that may be suppressing VTs at the time of the procedure may be factors in some recurrences.

Transcoronary Ethanol Ablation

When catheter based ablation on the endocardial and epicardial surface fail to control VT or is precluded due to access issues, controlled infarction of the VT circuit maybe possible by ethanol injection into the branch of an epicardial coronary vessel that supplies the region of interest [51]. Once a suitable branch is identified, the relationship between the branch and a critical portion of the VT circuit is proven by observing that VT terminates with injection of iced saline or by occlusion of the branch by balloon inflation. If VT termination is not achieved, another branch is tested. Once a clear relationship is established, 1 ml of sterile absolute

alcohol is injected after balloon occlusion to prevent reflux into other branches. In a series from our center, acute clinical success was obtained in 56 % of patients [52]. The need for this approach is infrequent (1–2 %) and complications include heart block and extension of infarction with further deterioration of LV function. Unfavorable coronary anatomy is also a limitation. However, in patients with intractable VT unresponsive to traditional ablation techniques, this approach can be life saving.

Outcomes of VT Ablation

For VT associated with structural heart disease, ablation typically aims at palliation to reduce recurrent arrhythmias and prevent defibrillator shocks. Hence, interpretation of results of ablation is often clouded by the presence of inducible VTs that have not been seen to occur spontaneously and that are not targeted by ablation. The target VT is rendered acutely non-inducible in 70–90 % of patients [7, 13, 15, 24]. A recent meta-analysis of four randomized and one observational study of VT ablation for structural heart disease demonstrated a significant 38 % reduction in VT recurrence compared with medical therapy [53]. In addition, adjunctive catheter ablation showed a trend toward reduction in electrical storms provoking multiple ICD shocks. Ablation did not influence mortality in this patient population; over a mean follow up of approximately 2 years, 12 % in the ablation group and 14 % in medical therapy group died. In patients with monomorphic VT resulting from infarct scars, there is now substantial experience with VT ablation such that ablation should be considered early in the course of recurrent VT triggering ICD shocks [13].

Experience with VT ablations for non-ischemic dilated cardiomyopathy is more limited. VTs often originate from intramural or epicardial scars that are more difficult to ablate. Success is likely lower. There is increasing experience with ablation for primary right ventricular disease. Although a high incidence of recurrences has been observed in some studies, it is hoped that outcomes will be better with increasing use of epicardial ablation for these patients [54, 55]. It is important to recognize that cardiac sarcoidosis often causes scar related VT and can mimic ARVC [56]. Small series of catheter ablation for scar-related VTs have also been reported for valvular heart disease and hypertrophic cardiomyopathy [57, 58].

Ablation of VT late after surgical correction for congenital heart disease has been reported in relatively small case series. A substrate-guided approach can be taken, and anatomic isthmuses can often be predicted from the anatomy and the nature of surgical repair [59].

Avoiding Complications

Catheter ablation of VT can be challenging. Careful pre-procedural evaluation and anticipation of hemodynamic consequences in patients with severe LV dysfunction are important to minimize the risks of serious complications. Procedure related mortality in patients with structural heart disease approximates 2–3 % and is primarily related to uncontrollable VT when the procedure fails [13]. Other complications relate to left heart catheterization and include vascular complications, thromboemboli, cardiac perforation, and valve injury. Damage to the conduction system, and coronary arteries are risks particular to the VT locations being targeted. Episodes of induced VT can cause hypotension, myocardial ischemia and prolonged myocardial stunning. Exacerbation of heart failure may result from VT sustained for mapping and due to fluid administration through the use of externally irrigated ablation catheters.

Ventricular perforation and tamponade are reported in 1 % of procedures. Most perforations related to endocardial ablations occur in association with steam pops during ablation; tamponade is less likely in patients with prior cardiac surgery. RV perforation is most common but LV rupture can occur and emphasize the role of cardiac surgical back up during these procedures. Epicardial access is occasionally associated with cardiac perforation. Right ventricular perforation with the needle or guide wire is usually self limiting and in general, no acute intervention is required as long as a sheath

has not been advanced through the perforation. Cardiac tamponade was reported in 3.7 % in a recent survey with half of them occurring late [49]. Surgical intervention is rarely required for right ventricular tears some of which are caused by a sheath left in the pericardial space without a catheter; the sharp edges of a vacant sheath tip can lacerate the RV or coronary vessels. Intra-abdominal hemorrhage from laceration of diaphragmatic vessels has been reported [49]. A safe distance from epicardial coronary arteries and the phrenic nerve has to be established by angiography and high output pacing respectively, prior to ablation.

Patients who are being considered for catheter ablation should have a thorough pre-procedural evaluation including tests to exclude significant ischemia, and thrombus within the ventricular chambers. If significant vascular disease is suspected, a trans-septal approach should be considered. If atrial fibrillation is present, guidelines for anticoagulation should be followed because cardioversion is likely to occur during conversion of VT by external shock.

Summary

Catheter ablation is an important treatment option for patients with recurrent ventricular arrhythmias. The approach to ablation and the risks and likely efficacy are determined by the nature of the severity and type of underlying heart disease. Ablation successfully reduces VT recurrences and controls incessant VT or VT storm for the majority of patients with structural heart disease.

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39
The Implantable Cardioverter Defibrillator: Technical and Clinical Considerations

Bruce L. Wilkoff and Sergio G. Thal

Abstract

The implantable cardioverter defibrillator (ICD) has become the most common device implanted for the treatment of arrhythmia disorders. The enormous technological development of these devices is perhaps the most dramatic progression observed in medicine over the last 30 years. The initial experiments of Mirowski published in 1978 required an external unit developed into epicardial patches and a large abdominal human implantable device released in 1985 and this yielded to transvenous leads in the early 1990s and smaller pectoral and dual chamber devices in the late 1990s and ultimately to combine cardiac resynchronization devices with defibrillation in the first few years of the new millennium.

The aim of this chapter is to review the current ICD indications based on the results of the most recent published trials, comment about the technical aspects involved in the design, implant and testing of the devices and an overview of the follow up recommendations.

Keywords

Implantable Cardioverter Defibrillator • Sudden Cardiac Death • ICD • Defibrillation • Antitachycardia Pacing • Shock therapy • DFT • Telemetry

B.L. Wilkoff, MD (✉)
Department of Cardiovascular Medicine,
Heart and Vascular Institute, Cleveland Clinic,
9500 Euclid Avenue, Desk J2-2, Cleveland,
OH 44195, USA

Medicine Department,
Cleveland Clinic Lerner College of Medicine,
Case Western Reserve University,
Cleveland, OH, USA
e-mail: wilkofb@ccf.org

S.G. Thal, MD
Cardiology Department, Cardiac Electrophysiology,
Southern Arizona VA Health Care Center,
3601 South 6th Avenue, Tucson,
AZ 85723, USA

Medicine Department, University of Arizona,
Tucson, AZ, USA
e-mail: sergio.thal@va.gov

The implantable cardioverter defibrillator (ICD) has become the most common device implanted for the treatment of arrhythmia disorders. The enormous technological development of these devices is perhaps the most dramatic progression observed in medicine over the last 30 years. The initial experiments of Mirowski published in 1978 required an external unit developed into epicardial patches and a large abdominal human implantable device released in 1985 and this yielded to transvenous leads in the early 1990s and smaller pectoral and dual chamber devices in the late 1990s and ultimately to combine cardiac resynchronization devices with defibrillation in the first few years of the new millennium [1, 2].

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Table 39.1 United States Centers for Medicare and Medicaid Services (CMS) approved indications for primary prevention ICD implant

ICD is reasonable for:
1. Patients with ischemic dilated cardiomyopathy (IDCM), documented prior myocardial infarction (MI), New York Heart Association (NYHA) Class II and III heart failure, and measured left ventricular ejection fraction (LVEF) ≤ 35 %
2. Patients with nonischemic dilated cardiomyopathy (NIDCM) >9 months, NYHA Class II and III heart failure, and measured LVEF ≤35 %
3. Patients who meet all current CMS coverage requirements for a cardiac resynchronization therapy (CRT) device and have NYHA Class IV heart failure

ICD is reasonable for patients with NIDCM > 3 months, *NYHA Class II or III heart failure, and measured LVEF ≤35 %, only if the following additional criteria are also met*
1. Patient must not have
   Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm
   Had a CABG or PTCA within the past 3 months
   Had an acute MI within the past 40 days
   Clinical symptoms or findings that would make them a candidate for coronary revascularization
   Irreversible brain damage from preexisting cerebral disease
   Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year
2. Providers must be able to justify the medical necessity of devices other than single lead devices. This justification should be available in the patient medical record

Table 39.2 ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities

ICD is indicated in:
1. Survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes
2. Patients with structural heart disease and spontaneous sustained VT
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study
4. Patients with LVEF less than 35 % due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III
5. Patients with nonischemic DCM who have an LVEF less than or equal to 35 % and who are in NYHA functional Class II or III
6. Patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than 30 %, and are in NYHA functional Class I
7. Patients with nonsustained VT due to prior MI, LVEF less than 40 %, and inducible VF or sustained VT at electrophysiological study

The aim of this chapter is to review the current ICD indications based on the results of the most recent published trials, comment about the technical aspects involved in the design, implant and testing of the devices and an overview of the follow up recommendations.

Indications

In 2002, a task force from the North American Society of Pacing and Electrophysiology (NASPE, currently Heart Rhythm Society), the American College of Cardiology and the American Heart Association, delineated most of the current indications for ICD implants [3]. These indications were updated by the United States Centers for Medicare and Medicaid Services (CMS) guidelines of February 2005 and more recently by the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, which incorporated the results of randomized clinical trials and widely opened reimbursement as supported by the evidence base (Tables 39.1 and 39.2) [4]. Initially the use of these devices was restricted to secondary prevention, defined as patients that had experienced a cardiac arrest or who had evidence of sustained ventricular tachycardia. The evidence base has expanded over the last several years demonstrating its efficacy as a tool for primary prevention in targeted subgroups of patients at a higher future risk of developing sudden death.

Primary Prevention

The MADIT trial, published in 1996 was the first in demonstrate benefit of ICD's for primary prevention of sudden death in a high-risk group [5]. This trial included patients post myocardial infarction (at least 3 weeks), with a low left ventricular ejection fraction (LVEF < 30 %) and evidence of non-sustained ventricular tachycardia (NSVT). These patients were evaluated during an electrophysiologic study (EP) and demonstrated inducible monomorphic sustained ventricular tachycardia that was not suppressed with the use of antiarrhythmic medications. Those patients inducible but not suppressible by medications were then randomized to receive antiarrhythmic medications alone or antiarrhythmic medications plus an ICD implant. The study was terminated early due to the significant impact on reduction in sudden death among the patients treated with the ICD. On the same research path, the MUSTT trial investigators reported similar findings [6]. In this trial,

patients with coronary artery disease and a left ventricular ejection fraction of 40 % or less and asymptomatic, unsustained ventricular tachycardia were included. The patients underwent an EP testing and those with sustained, monomorphic ventricular tachycardia induced by any method of stimulation and those with sustained polymorphic ventricular tachycardia (including ventricular flutter and fibrillation) induced by one or two extrastimuli were randomized to either antiarrhythmic therapy guided by the results of electrophysiologic testing or no antiarrhythmic therapy. ICD therapy was not prespecified, but in 46 % of the patients randomized to EP guided therapy there was no effective antiarrhythmic medication identified and therefore received an ICD as their EP guided therapy. The investigators concluded that electrophysiologically guided antiarrhythmic therapy with implantable defibrillators, but not with antiarrhythmic drugs, reduces the risk of sudden death in this group. Finally, to complete the support for the current primary prevention indications, the results of the MADIT II trial were published in 2002 [7]. In this study patients with previous myocardial infarction and a left ventricular ejection fraction equal or less than 30 % were randomized to receive an ICD or medical treatment. Here, once again, the ICD decreased the risk of sudden death. It is important to have in mind that according to the inclusion/exclusion criteria of this study, patients were at least 3 month after any revascularization procedure or 1 month after being admitted for a MI. This is particularly important when we examine the results of the DINAMIT study published in 2004 [8]. In this trial, ICDs were implanted early after an acute myocardial infarction. The investigators included patient within 6–40 days after an acute MI, with low ventricular ejection fraction (<35 %) and abnormal heart rate variability measured during a holter monitoring. The results showed no difference in total mortality between patients treated with ICD compared with those not implanted. A significant reduction in arrhythmic death was observed in the ICD group, but at the same time a significant increase in non-arrhythmic death was observed in this group. We can at least initially conclude that a prudent waiting time after revascularization or MI would help to target a group that would more likely benefit from therapy with ICD therapy.

As been described here, most of the initial efforts to identify a target population at a higher sudden death risk were oriented mostly to the ischemic patients. But in 2004, the results of the DEFINITE trial opened the door to focus the physician community attention to the group of patient with a dilated cardiomyopathy of non-ischemic origin [9]. This study included patients with a non-ischemic dilated cardiomyopathy, symptomatic heart failure, spontaneous PVCs (>10/h or NSVT) and poor ventricular function (LVEF ≤35 %). Patients that met the inclusion criteria were randomized to receive optimal medical therapy (that included ACE inhibitors and beta blockers) or optimal medical therapy and single chamber ICD therapy. The primary end point of "all cause mortality" showed a trend towards ICD therapy benefit but did not achieve statistical significance. As a secondary end point, "arrhythmic death", was significantly reduced by ICD therapy. A second larger study of heart failure patients also provides support for ICD therapy of patients with non-ischemic dilated cardiomyopathy and evidence of decrease left ventricular function. This study was the SCD-HeFT trial published in May of 2005 [10]. It included 2,521 patients with New York Heart Association (NYHA) class II or III congestive heart failure (CHF) and a left ventricular ejection fraction of 35 % or less, and randomized them to receive treatment with optimal medical heart failure therapy alone or together either with Amiodarone or a single lead ICD. This trial concluded that amiodarone has no favorable effect on survival, whereas single-lead, shock-only ICD therapy reduces overall mortality by 23 %. This favorable mortality benefit was seen for patients with ischemic and non-ischemic cardiomyopathy. These mortality benefits have also been confirmed in the setting of combined ICDs with CRT functionality in patients with a wide QRS and NYHA class I, II, III and IV symptoms in the setting of ischemic cardiomyopathy and NYHA class II, III and IV symptoms in the setting of non-ischemic cardiomyopathy [11–13]. There is no data regarding the potential benefit of ICD therapy in patients with non-ischemic dilated cardiomyopathy and NYHA class I symptoms.

Secondary Prevention

The AVID trial was the first randomized trial that prospectively evaluated the use of ICD's in patients with documented spontaneous sustained ventricular tachycardia or after resuscitation from sudden cardiac death [14]. It included patients who had been resuscitated from near-fatal ventricular fibrillation or who had undergone cardioversion from sustained ventricular tachycardia and patients with ventricular tachycardia also had either syncope or other serious cardiac symptoms, along with a left ventricular ejection fraction of 40 % or less. It randomized this population to receive medical treatment with a class III antiarrhythmic agent (primarily Amiodarone) or an ICD implant. Its results showed that the ICD group had a significant decreased overall mortality compared with the medical treatment group at 1, 2 and 3 years of follow up. The Canadian Implantable Defibrillator Study (CIDS) addressed a similar target population as AVID for secondary prevention [15]. It included patients with resuscitated VF or VT but also included patients with unmonitored syncope if there was inducible sustained VT with programmed stimulation. The patients were randomly assigned to treatment with an ICD or with amiodarone. There was a trend towards reduction of all-cause mortality (20 % relative risk reduction) and a statistically significant 33 % reduction in arrhythmic mortality with ICD compared to amiodarone therapy. A subsequent sub-analysis, published a month after the main trial publication, showed a significant reduction in overall mortality in the highest risk subgroup of the CIDS trial patients. This highest risk group was defined as having at least 2 of the following: ≥70 years old, LVEF of ≤35 % or NYHA class III or IV [16]. Finally, the CASH study was published in the same year of the CIDS trial [17]. It included patients who survived a cardiac arrest secondary to documented ventricular arrhythmias, and randomized them to treatment with an ICD or antiarrhythmic drug therapy. It showed that therapy with an ICD was associated with a 23 % nonsignificant reduction of all-cause mortality when compared to treatment with amiodarone or metoprolol. The subgroup treated with propafenone was discontinued early in the study because it showed during an interim analysis a significant increased risk of mortality compared to ICDs.

Technical Aspects of ICDs

Hardware

The current ICDs, developed for thoracic subcutaneous implants, are the results of an amazing evolution since the first experimental implants at the beginning of the 1980s. Initially the size of these devices only allowed for abdominal implants. The defibrillation electrodes required patches to be surgically implanted either on the epicardial surface or on the external surface of the pericardium and sometimes a transvenous SVC or coronary sinus coil. Sensing electrodes were either epicardial or transvenous but did not provide bradycardia pacing support or antitachycardia pacing.

Today, the devices available are significantly smaller, 31.5 cc down from over 200 cc from the initial models and weigh approximately 40 g. The system implantation avoids open-chest placement of epicardial shocking patches and employs transvenous combined pacing/shocking leads and employs the ICD titanium can to provide programmable anti-bradycardia and anti-tachycardia pacing support, cardioversion and defibrillation therapy.

ICD Generator

The new generators combine the functions of defibrillation with single, dual or triple chamber pacemaker stimulation.

The device "case" is made out of titanium and serves to work as an active defibrillation electrode, which can be programmable off in some ICD models [18].

The most common battery used today is a silver vanadium cell, providing approximately 18,000 J. Most of the devices contain two of these batteries to power all of the ICD functions including antitachycardia and antibradycardia therapies. The battery voltage can be assessed along with the status of the rest of all ICD activities with a radiofrequency telemetry system that

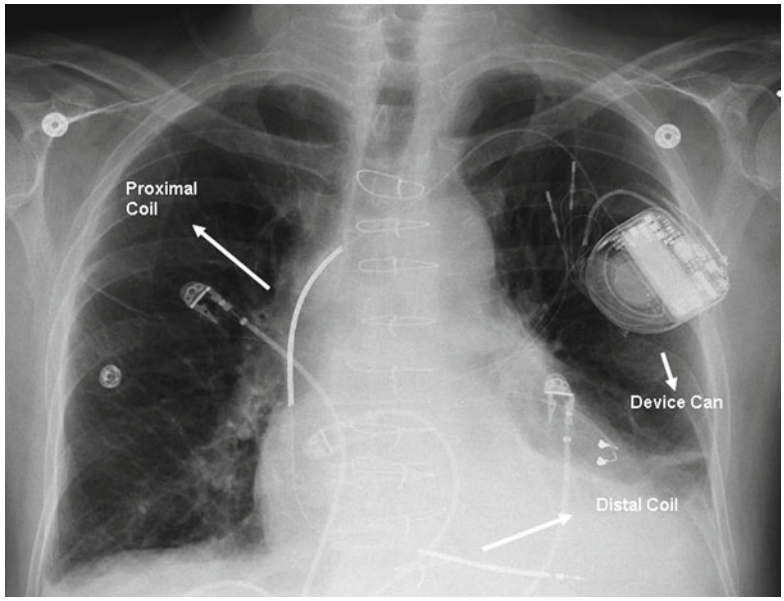

Figure 39–1. Chest X-ray of a VVI/ICD. The image corresponds to a chest x ray from a patient implanted with a VVI/ICD. The ICD lead was inserted through the left subclavian vein and the distal tip of the lead attached to the right ventricular apex. The *arrows* show the location of the proximal coil at the superior vena cava and the distal coil at the right ventricle

communicates the device data to the external programmer. Each ICD system has a voltage (approximately 2.6 V) at which the system continues to function precisely as it has been programmed but should be electively replaced before the battery is no longer able to guarantee adequate therapy. This voltage reduction sets the Elective Replacement Indicator (ERI), and means that the device would be able to function properly for approximately 3 months. If the battery voltage drops further, the End of Life (EOL) indicator is set (approximately 2.2 V) and full capacitor charge times will be prolonged and full shocking voltage may not be achieved. Either immediate device replacement is required at this time or provision for alternative protection through hospitalization or a wearable defibrillator therapy.

In order to delivery the high energy required for a DC shock, in an appropriate time frame, the devices are provided with capacitors, able to be rapidly charged to 750–800 V in less than 10 s. The capacitors are discharged over 5–20 ms and deliver up to approximately 41 J of energy less than 15 s after the tachycardia initiation. As the battery voltage declines over time and depending on the status of the capacitor (due to capacitor deformation) it may take up to 30 s to fully charge and deliver the defibrillation shock when the device is at EOL status.

The basic ICD lead provides for right ventricular electrogram detection and pacing through a conventional distal pacemaker electrode and high energy delivery through a right ventricular defibrillation coil. Sensing and capture is established by using the distal pacemaker electrode as the cathode and either the right ventricular coil as the anode, termed an integrated bipolar lead, or by providing an anodal ring electrode positioned in between the cathode and the shocking coil, termed a dedicated bipolar lead. The basic high energy shock delivery configuration employs the titanium can as one defibrillation electrode and the RV coil as the second electrode. Many ICD leads provide for a second defibrillation coil about 15 cm proximal from the distal electrode. This proximal shock coil is usually combined with the titanium can as a single electrode and the energy is delivered to and from this electrode to the right ventricular coil electrode. These are non thoracotomy leads that are inserted through venous access at the subclavian or cephalic vein (Fig. 39.1) [19, 20]. Fixation to the right ventricular myocardium is achieved either by an extendable/retractable helical screw or lodging small tines near the distal electrode the trabeculations of the muscle. The development of the device "active can" for ICD shocks allows in some occasions to use leads without a proximal coil and with this avoid future venous

complications due to increase venous fibrosis which could be a potential complication in the case of need of a future extraction [21]. However additional defibrillation coils or patches are sometimes required to provide consistent defibrillation efficacy. These electrodes have been placed in the superior vena cava, subclavian vein, azygous vein, subcutaneously or submuscularly in the axilla or posterior to the heart in the subcutaneous tissue [22–28].

Device Function

Ventricular tachyarrhythmia detection and discrimination from supraventricular tachyarrhythmias are essential aspects of ICD performance. It must be able to distinguish the absence of rhythm disturbances from the presence of tachycardia or bradycardia. The different models available today use a variety of complex algorithms to be able to differentiate rhythms that require or do not require therapy. These algorithms usually evaluate heart rate, the pattern of atrial and ventricular activation, cycle length stability, suddenness of rhythm initiation, mode of tachycardia initiation and various aspects of electrogram timing or morphology. The ability to correctly evaluate these variables is directly related to the quality of signals that the device will obtain for evaluation. For this reason the lead should be located at the implant time in a position that provides a good balance between electrogram detection, in the healthiest muscle, and defibrillation efficacy which has been demonstrated to be most often best at the right ventricular apex [29]. The amplitude of the signal during sinus rhythm should be able to assure as good as possible detection of an eventual ventricular fibrillation (VF). It is estimated that a ventricular activity sensing of at least 5 mV during sinus rhythm predicts that less than 10 % of the electrograms during VF events will be under sensed [30].

Tachyarrhythmia Therapies

Antitachycardia Pacing (ATP) is available in almost all current ICD models. It consists in the delivery of ventricular pacing at a faster rate than the tachycardia cycle length. This short burst of impulses will often interrupt the tachycardia circuit and stop the ventricular tachyarrhythmia without a high energy shock. This has the potential to have a significant impact on patient's quality of life and the device longevity. There are different ways in which this can be delivered including a short burst (constant cycle length of pacing impulses) or also ramp burst where each subsequent interval is incrementally shorter than the previous one.

One of the problems with this type of therapy is it potential for acceleration of ventricular tachycardia cycle length to the ventricular fibrillation detection zone. This is observed in approximately 5 % of the cases and this rhythm may be more hemodynamically compromising potentially causing syncope and may require a higher energy to be successfully terminated [31]. Besides this potential problem, antitachycardia-pacing therapy was shown to have a success rate of over 90 % for ventricular tachycardia rates of less than 200 bpm and over 70 % when applied to tachycardias with rates between 200 and 250 bpm when it is empirically programmed at the implantation time [32]. In the PREPARE Study a strategy of antitachycardia pacing in combination with supraventricular tachycardia discriminators, proved to be safe and effective in patients receiving ICD implants for primary prevention [33]. In all cases, if antitachycardia pacing fails, a shock therapy is programmed as the subsequent therapy.

Shock therapy is the electrical shock produced by delivery of 50–800 V stored on the ICD capacitors over 5–20 ms through the defibrillation coils, can or patches in an attempt to produce a uniform voltage gradient throughout the ventricular myocardium to permit reestablishment of normal ventricular activation and automaticity. The waveform currently in use by almost all the available ICDs is biphasic. This means that the capacitor discharge is divided in two phases. The anode and cathode is switched after several milliseconds to the opposite polarity (Fig. 39.2). The clear improvement in defibrillation efficacy of this technique is explained by the "cell membrane burping" theory [34]. This theory established that the function of the first phase of a biphasic shock depolarizes or extends the refractory periods of

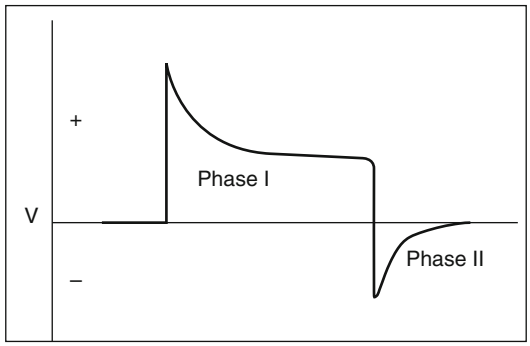

Figure 39–2. Biphasic wave shock. Scheme representing the two phases of the biphasic wave currently in use for ICD shocks. Phase I correspond to the initial positive portion and phase II to the final negative deflection. *V* voltage, "+" positive, "–" negative

virtually all ventricular myocytes, and the second phase with opposite polarity is to remove the excess charge from any cells where it remains [35]. Migration from the monophasic truncated exponential capacitor discharge to biphasic waveforms and use of the defibrillator can as an electrode in current devices has produced a simplified and more efficient device implantation.

Defibrillation Threshold

As mentioned before, the main objective of a correct device function implies the ability to accurately detect life threatening ventricular tachy-arrhythmias and then to terminate it with a shock. In order to assure this correct functioning, ventricular fibrillation detection and termination is tested during implantation.

The success of therapy is dependent upon several clinical variables which change with patient status such as electrolytes, metabolic decompensation, hemodynamic condition, antiarrhythmic medications and so on. Also, the success of a shock is exposed to a probabilistic variance. That is why reproducibility of a success defibrillation increases the certainty of a device performance and is a goal when testing is performed. There is variable data regarding the safety of DFT testing. Some studies suggested no adverse effects from multiple DFTs testings, while some others suggest that performing these tests could be deleterious or risky for patients. The risk appears to be greater if the baseline ejection fraction is low as is the case of the majority of the patients that receive this devices [36–39]. Despite the poor ventricular function in these patients, unless the patient's becomes compromised with either pulmonary or hemodynamic deterioration during the device implantation, fibrillation detection and termination testing can be safely performed and would result in approximately a 1 % incidence of an inadequate defibrillation system if omitted.

The initial step for DFT test is the induction of a VF, most commonly done by delivering a small shock on the T wave through the device. This is more efficient than rapid ventricular pacing and accomplished by administration of a 200 V shock around 10 ms before the peak of the T wave [40]. The next step is let the device detect the VF and shock cardiovert it. The main objective of the test is to assure that the implanted device has the ability to deliver a shock capable of terminate ventricular fibrillation, the most difficult rhythm to convert. There are many different protocol approaches to perform the test. The simplest one is the named "step down protocol", that is mainly the reduction of the energy of successives shocks until one fails. The opposite approach would be the "step up protocol" and the combination of them was one of the most popular classic approaches.

Since defibrillation efficacy is not most accurately expressed as an energy level, but as a percentage of episodes converted at each energy level, it is useful to demonstrate a safety margin. This has been done with multiple techniques but reproducibility is the most common tool to prove adequacy of the defibrillation configuration. Two successful conversions at 10 J below the maximum output of the device were shown by Strickberger et al. to predict a successful conversion in the clinical setting of about 99.5 % [41]. Gold and his colleagues demonstrated that a single successful defibrillation at 14 J stored (11 J delivered) in a 31 J device (27 J delivered) appears to be similarly efficient [42]. However, rarely a practical approach that demonstrates multiple successful conversions at maximal output is the only reasonable alternative, but only after testing of alternative defibrillation configurations, pulse durations or tilt values.

Telemetry, Diagnostics and Follow Up

The basic functional components of an ICD are the battery, capacitor, software and computer processor and the telemetry coil. Most of the technology of the ICD is in the logic algorithms but the window into the ICD function and the status of the patient comes through the telemetric link and the programmer. On the surface the need for long term surveillance of defibrillation function is similar to that of pacemakers. However because of the seriousness of the underlying condition, sudden cardiac death, the physically and emotionally painful defibrillation shocks and the increased complexity of the device increases the mandate for regular patient and device follow-up.

The original ICDs had no programmability and no telemetric communication with a programmer, but current device programmability also requires the ability to document the current parameters to interpret the behavior of the device. In addition, multiple self diagnostic measurements and maintenance behaviors are programmed into the device and provide a unique view into the fitness of the ICD system.

Radiofrequency telemetry uniquely identifies communication of an individual device and a programmer or communicator. Most devices can only transmit a signal over a few inches but there is now communication over several meters using the frequency spectrum previously dedicated to weather balloons. This extended range has been used to collect full interrogations of the programmed, measured and event data from the device's memory via home based interrogators and to transmit that data to an internet based data center or directly to a physician's office.

The standard for ICD follow-up requires full interrogation of the device at least every 6 months and evaluation of capture and sensing function at yearly intervals. However the need for more frequent evaluations is dependent on the patient's clinical condition, the age of the ICD, the battery voltage, condition and function of the leads and the frequency of ventricular and supraventricular arrhythmias. Remote interrogation of the device can augment formal programming sessions and substitute for situations when programming or formal threshold testing isn't required.

Evaluation of defibrillation efficacy is usually tested only at time of implantation. There is data that supports the concept that defibrillation remains relatively constant over time with biphasic shock wave configuration [43–45]. For this reason, there is no need for subsequent defibrillation threshold unless evidence of shock failure in the clinical scenario.

Summary

The implantable cardioverted defibrillator has experienced a tremendous evolution since its initial conception to the present reality. Today, ICD implants are a daily occurrence in the modern EP lab instead of a rarer and more complex open chest procedure. The available published data, the result of multiple multicenter clinical trials performed in the last several years and the ones that are currently ongoing, is pushing the manufacturers and the physician community to develop better and safer devices. The present is encouraging and the future is promising with improved technologies and therapy strategies, mostly for heart failure treatment, which will modify the duration and quality of life of our patients.

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Beyond Sudden Death Prevention: Minimizing ICD Shocks and Morbidity, and Optimizing Efficacy

Eyal Nof, Michael Glikson, David Luria, Joseph Gard, and Paul A. Friedman

Abstract

Implantable cardioverter defibrillators (ICDs) remain the de facto gold standard for sudden death prevention in high-risk populations. However, ICD therapy is associated with morbidity and resource utilization related to shock delivery, product advisories, and, in some cases, right ventricular pacing induced heart failure and atrial fibrillation. This chapter reviews how to optimize ICD therapy by minimizing these comorbidities.

Keywords

Implantable defibrillator • Shock reduction • Anti tachycardia pacing • Right ventricular pacing • Remote monitoring • Programming

Abbreviations

AAD	Anti arrhythmic drug
AAI	Atrial-based
ATP	Antitachycardia pacing
BiV	Biventricular
CRT-D	Cardiac resynchronization device
ICD	Implantable cardioverter defibrillator
NSVT	Non-sustained ventricular tachycardia
SVT	Supraventricular tachycardia
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VVI	Ventricular-based

E. Nof, MD • M. Glikson, MD • D. Luria, MD
Davidai Arrhythmia Center, Leviev Heart Center, Sheba Medical Center and Tel Aviv University, Tel Hashomer, Israel
e-mail: mglikson@post.tau.ac.il; dluria@sheba.health.gov.il

J. Gard, MD
Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA
e-mail: mglikson@post.tau.ac.il

P.A. Friedman, MD (✉)
Division of Cardiovascular Medicine, Mayo Clinic, Rochester, MN 55905, USA
e-mail: pfriedman@mayo.edu

Introduction

Implantable cardioverter defibrillators (ICDs) remain the de facto gold standard for sudden death prevention in high-risk populations. However, ICD therapy is associated with morbidity and resource utilization related to shock delivery, product advisories, and, in some cases, right ventricular pacing induced heart failure and atrial fibrillation. This chapter reviews how to optimize ICD therapy by minimizing these comorbidities.

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Managing Shock Morbidity

Implantable cardioverter defibrillator (ICD) shocks are the most effective way to immediately terminate life-threatening ventricular arrhythmias. Failed ICD shocks are rare with modern defibrillators. Large database analysis reveals that <2 % of appropriate ICD therapies fail to terminate ventricular tachycardia or fibrillation (VT/VF) episodes [1]. Even among ICD recipients who die suddenly, device interrogation demonstrates ineffective shocks as the cause of death in only a minority of cases [2, 3].

With the increasing use of ICDs for primary prevention of sudden death, 30–50 % of all delivered shocks are inappropriate, so that these remain the most important source of morbidity and suffering in contemporary ICD patients [4–6]. The most common causes of inappropriate shocks are atrial fibrillation, other supraventricular arrhythmias, sinus tachycardia and over sensing [7]. Among causes of over sensing, which constitute approximately 10 % of inappropriate shocks, T-wave over sensing, electrode failure, myopotentials, external noise, and double counting of QRS complexes are most common [8].

Morbidity and Mortality Associated with Shocks

Both appropriate and inappropriate ICD shocks are associated with significant suffering, pain, morbidity and mortality; both result in recurrent hospital admissions, anxiety, depression and post-traumatic stress disorders [9, 10]. In the AVID trial, patients who received ICD shocks had a lower quality-of-life score than those who did not, with reduced physical functioning and mental well being [11]. Moreover, recent evidence associates shock with worsening heart failure and mortality. In the SCD-Heft trial, one appropriate shock was associated with an almost fourfold increased risk of death, whereas an inappropriate shock was associated with a twofold increased risk [12]. Similar results were reported from the MADIT II trial [13]. However, whether shocks are an independent cause of mortality, or whether they serve as a marker of the severity of heart disease that in turn leads to atrial and ventricular arrhythmias is not clear. Evidence exists to support shocks as markers of disease severity. ICD shocks delivered during induced ventricular arrhythmias at the time of noninvasive programmed stimulation do not increase mortality [14]. Additionally, the ALTITUDE Study Group found that while both appropriate and inappropriate shocks were associated with an increased risk of death, there were significant differences in outcome based on the underlying rhythm during shock delivery. Compared to patients who received no shocks, those who received a shock for sustained monomorphic VT, VF, non-sustained VT (NSVT), and AF had a lower survival rate. However, patients who received inappropriate shocks for sinus tachycaradia, SVT, or over sensing of noise or artifact, had a survival similar to that of patients who received no shocks [15]. These data suggest that shocks themselves do not increase mortality, but rather are a marker for advanced disease that leads to arrhythmias that trigger device therapy.

When ICD shocks fail to terminate a supraventricular or ventricular arrhythmia, or an arrhythmia recurs immediately triggering another shock, patients may receive repetitive discharges, an event termed “electrical storm”. Electrical storm may occur in up to 10–20 % of ICD recipients. The efficacy of beta-adrenergic blockade and sedation in electrical storm therapy highlights the role of stress and the pro-arrhythmic effect of shocks themselves in promoting arrhythmia in this extremely stressful situation [16–20].

Due to the pain and morbidity associated with ICD discharge, minimizing shock delivery is paramount. There are several strategies for minimizing ICD shocks while preserving the ICDs ability to save lives. These include:

1. Avoiding detection of non-sustained VT by prolonging detection time, thus preserving battery and preventing therapy;
2. Using painless anti-tachycardia pacing (ATP) to terminate arrhythmias whenever possible;
3. Using SVT-VT discriminators to prevent inappropriate shocks for sustained supraventricular tachycardia (SVT);
4. Programming algorithms and parameter settings to minimize the risk of over sensing;

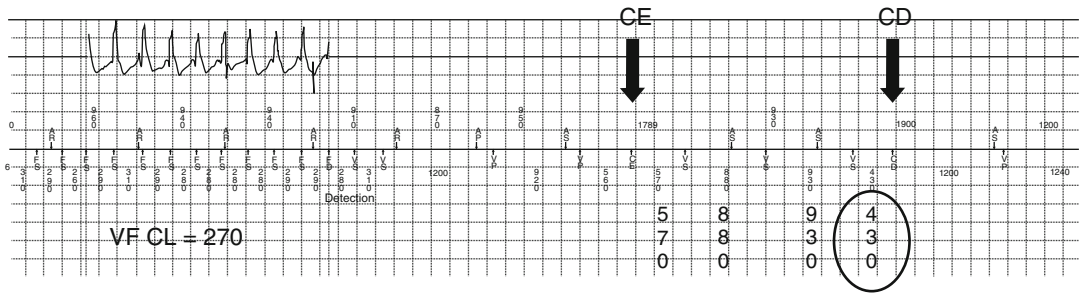

Figure 40–1. Shock for nonsustained V. The case involves a 60-year-old man with ischemic cardiomyopathy and recurrent NSVT who had a previous generation ICD (Medtronic GEM DR) implanted. The VT cutoff was programmed at 400 ms. On the night following implantation he received several shocks for nonsustained VTs at a cycle length of 270. Interrogation of one of the episodes is shown here. In old Medtronic devices there is no reconfirmation during charging, only upon charge end. When the charge ends (*CE + arrow*) there is a 300 ms blanking period; following this even one out of the next four beats that falls within the VTCL + 60 ms range (= 460 in this case) is considered a reconfirmation of ongoing tachycardia. Unfortunately, the fourth interval here was 430, therefore a shock was delivered (*CD + arrow*)

5. Deploying remote monitoring to detect incipient lead failure or increasing arrhythmia burden;
6. Preventing VT/VF by means of adjuvant therapies (drugs and/or ablation).

While traditionally shocks are categorized as "inappropriate" when delivered during SVT or NSR, and appropriate when delivered during VT, we prefer the terminology "necessary" and "unnecessary." Unnecessary shocks are those delivered during SVT, NSR, or VT that would have spontaneously terminated had the time from detection to shock been prolonged. Necessary shocks are those delivered sustained ventricular arrhythmias. This nomenclature recognizes that not all shocks delivered for VT are appropriate [21].

Shock Reduction Strategies

Minimizing Shocks for Non-sustained Ventricular Arrhythmias

NSVT is a self-terminating arrhythmia that is usually well tolerated and should not be shocked. In early ICDs, shocks were committed after initial arrhythmia detection, irrespective of arrhythmia termination before charge end ("committed" shocks). In subsequent devices, programmable reconfirmation features enabled abortion of shock delivery if the arrhythmia terminated prior to the end of charging. Reconfirmation is "trigger happy" so that even a few intervals shorter (faster) than the slowest VT interval Boston Scientific or 60 ms > VT interval (Medtronic before the Protecta series) result in shock delivery. Thus, a single ventricular premature complex or over sensed complex during the reconfirmation period could result in a shock (Fig. 40.1) [22–24]. Furthermore, this results in a hidden interaction in that the first ventricular fibrillation (VF) shock is functionally committed when a long VT interval is programmed. In order to minimize the risk of slow intervals forcing shock delivery, in the Medtronic Protecta series, reconfirmation requires a cycle length within 60 ms of the *detected* tachycardia rate (as opposed to programmed VT rate) if the tachycardia is regular, making it less trigger-happy; for irregular tachycardias in the VF zone, reconfirmation requires a cycle length of the VF detection interval + 60 ms. In new SJM devices the reconfirmation rate is programmable to an operator-selected zone. The reconfirmation algorithm applies to the first shock only in Medtronic devices, making all redetected tachyarrhythmias committed. In Boston Scientific devices every other shock is committed (i.e. two consecutive shocks cannot be diverted), whereas in SJM devices all shocks can be non-committed.

In current ICDs, the sensing channel continues to monitor the rhythm during device charging and is able to recognize arrhythmia termination at any point before discharges prevent unnecessary shocks. In older generation Boston Scientific and Biotronik devices, the absence of a signal on the ventricular channel (i.e. asystole) after VT

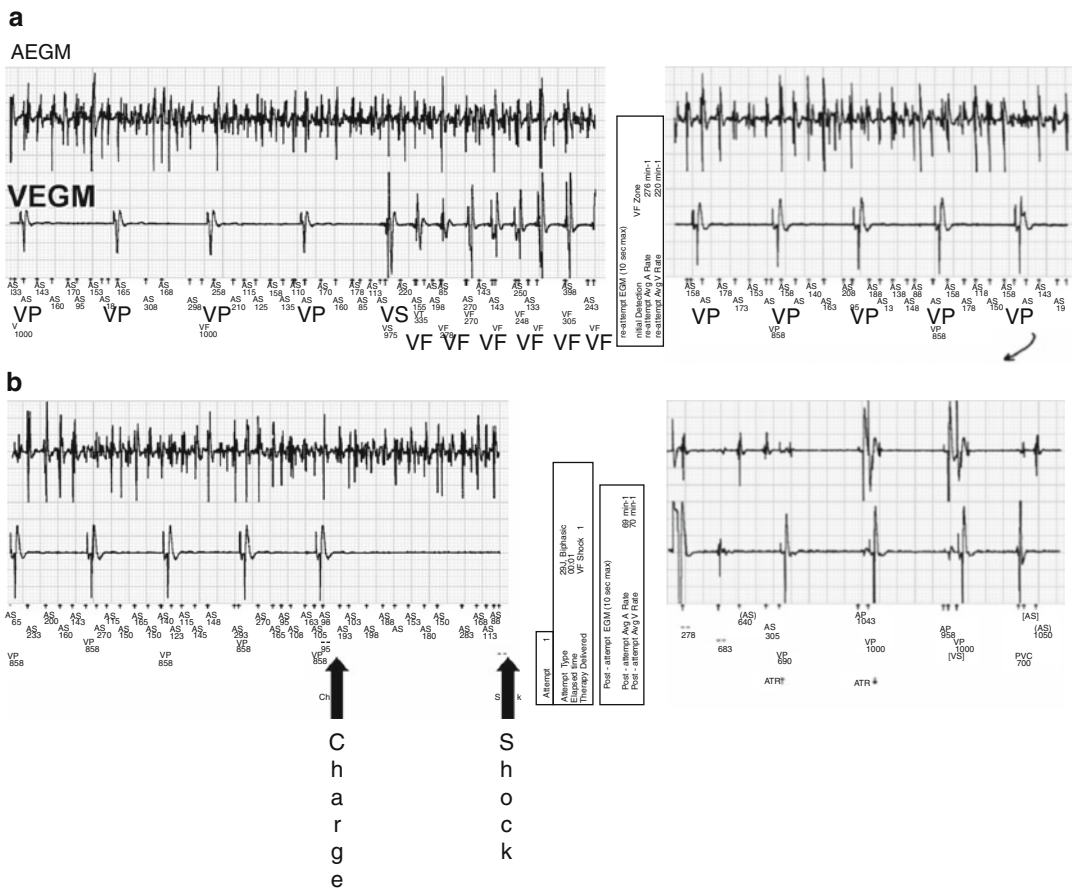

Figure 40–2. Shock for nonsustained VT in an Boston Scientific Prizm DR ICD. The case involves a 72-year-old man with SSS + VTs admitted with recurrent shocks. The patient is pacemaker dependent. (**a**, **b**) Figures are taken from interrogation of one of the episodes, with an atrial electrogram (*EGM*) (in AF) on the top channel, a ventricular channel in the middle, and EGMs on the bottom channel. Figure (a) demonstrates a run of nonsustained fast VT detected in the VF zone; thus charging is initiated. Figure (b) demonstrates the end of charging (*first arrow*); the device then attempts to reconfirm VF. When there is no underlying ventricular activity, this device delivers a shock (*second arrow*) to avoid undersensing of ventricular fibrillation, making shocks functionally committed in pacemaker dependent patients. Due to repeated similar episodes the device had to be replaced with a newer model. Current generation pulse generators pace rather than shock in the absence of sensed ventricular activity

termination or charge-end did not abort device therapy in order to avoid non-detection of fine VF. This necessarily led to an inappropriate shock after termination of NSVT in pacemaker-dependent patients. In newer Biotronik devices, programming of the "fine VF" feature overcomes this limitation; Boston Scientific devices from Prizm 2 on longer shock during asystole, but rather pace. While not an issue with current generation pulse generators, in older models recurrent intractable shocks due to NSVT in a pacing-dependent patient may require pulse generator change out (Fig. 40.2). NSVT that triggers ICD therapy is common [25].

The first line of defense against inappropriate therapy for NSVT or SVT is an appropriately long detection interval [26]. Use of a relatively long fast VT detection time (18 of 24 intervals) results in high frequency of fast VT episode termination (34 %) before shock delivery without significant detection delay [27]. In the PREPARE [28] and RELEVANT [29] trials, an even longer detection time (30 of 40 intervals, or 7–9 s) resulted in excellent overall safety as measured by arrhythmic syncope or untreated VT. In primary prevention patients or in patients with frequent and long episodes of non-sustained VT/VF such as long QT syndrome, longer detection

is favored. While excessive delays in detection may result in syncope, increased defibrillation threshold or the under sensing of VF, these rarely occur for VF lasting <30 s.

Using Anti-tachycardia Pacing to Terminate Arrhythmias

Painless ATP terminates up to 90 % of VT episodes [30–32], with a risk of VT acceleration requiring a shock of 1–5 % [33]. Routine electrophysiologic testing to tailor ATP is no longer considered necessary [33–37]. Lack of VT induction with programmed stimulation does not exclude subsequent clinical episodes that are often successfully terminated by ATP. Furthermore, empiric ATP is more successful than physician tailored programming in preventing ICD shocks [28, 36]. ATP can be delivered as "bursts" (sequences of pacing pulses delivered at the same cycle length) or "ramps" (the cycle length shortens within the pulse train). The efficacy and safety profile of various ATP schema have been studied extensively [30, 33, 35, 38] and can be summarized as follows:

1. Burst is generally more effective than ramp, and carries a lower risk of acceleration [39]. This is true for vast VT (roughly above 190 bpm) and slower VTs.
2. The coupling interval and rate of ATP within the commonly used clinical range of 69–88 % of tachycardia cycle length, does not significantly affect efficacy;
3. The first ATP attempt is the most effective (up to 80 %); up to 6 ATPs may be programmed when treating slow, relatively stable VTs; ATP is limited to 1–2 sequences of 8 pulses when treating faster VTs (HR > 188 bpm). Of note, in the PainFree Rx trial [40] a single ATP burst of 8 cycles terminated 72 % of fast VT.

Patient and arrhythmia characteristics determine ATP outcomes. The lower the ejection fraction and the faster the VT, the lower the likelihood of arrhythmia termination and the higher the risk of acceleration [27, 33, 41, 42]. Sinus tachycardia before VT is associated with diminished ATP efficacy [43]. Medical therapy (beta blockers, anti-arrhythmic drugs (AADs)) has a synergistic effect with ATP, probably by slowing the VT rate in the case of membrane active drugs. ATP is equally effective in ischemic and non-ischemic cardiomyopathy [27, 43]. Clinical data show that 90 % of fast VT (up to 250 bpm) can be successfully terminated by two ATP bursts (8 pulses, 88 % of VT cycle length), with a low risk of acceleration (4 %) or syncope (2 %) [27, 42]. We routinely program one or two empiric ATP bursts in a fast VT zone (between 182 and 250 bpm), and use additional bursts in slower VT zones only in patients with known slow VTs. Current generation ICDs deliver ATP therapy either before or during charge, and this feature is routinely programmed on with minimal or no effect on the timing of the first shock.

ATP is also effective in chronic heart failure patients implanted with a cardiac re-synchronization device (CRT-D). In the ADVANCE CRT-D trial [44], there were no significant differences regarding efficacy of VT termination between biventricular (BiV) and right ventricular ATP. However, BiV ATP appeared to be safer in those with coronary artery disease. Therefore, in ischemic cardiomyopathy patients implanted with CRT, it may be reasonable to program biventricular as opposed to right ventricular ATP delivery.

The ongoing MADIT RIT study (clinicaltrials.com no NCT00947310 sponsored by Boston Scientific Co.) compares standard MADIT II ICD programming vs. high-rate cutoff (therapy >200 bpm only), or long detection time in all three zones. In the latter branch, therapies in all three zones will be programmed as follows: zone I: 170–200 60 s delay; ATP + rhythm ID + shocks; zone II: 200–250 12 s delay; ATP + Rhythm ID + shocks; zone III: >250 2.5 s delay; quick convert ATP + shock.

In secondary prevention patients we program a VT zone 10–20 bpm slower than the slowest clinical arrhythmia, or 150–162 if the clinical rate is unknown with 6–8 ATP bursts of 81–88 % burst cycle length, followed by maximum output shocks. The VF zone is programmed above 200–220 bpm. ATP before and during charge minimizes shock delivery.

Review of care of patients with inherited channelopathies is beyond the scope of this chapter. In general, due to their relatively young age, and the frequency of atrial arrhythmias and non-sustained ventricular arrhythmias, a high cutoff VT/VF zone with long detection times is programmed. The addition of an atrial lead to enhance SVT-VT discrimination is weighed

against the increased risk lead-related complications in a younger population. Patients with primary electrical diseases have a high rate of inappropriate therapies [45–47].

Programming SVT-VT Discriminators

Inappropriate therapies delivered for non-ventricular arrhythmias are the Achilles' heel of ICD therapy [11, 27]. The problem affects 8–40 % of ICD recipients [48–52], has a deleterious effect on quality-of-life, and has the potential for pro-arrhythmia [53, 54]. Supraventricular rhythms, particularly sinus tachycardia and atrial fibrillation, are the most common cause of inappropriate shocks. SVT-VT discriminators are algorithms that are applied to differentiate VT from SVT for tachycardias occurring in the heart range at which both VT and SVT may be present. Ideally, these algorithms reject supraventricular arrhythmias (i.e. increase the specificity of detection) without affecting the ability to detect VT (sensitivity). In general, these algorithms are most commonly applied to the "slower VTs" (heart rates of 140–190 bpm), for which a small delay in detection to enhance specificity is often acceptable. Manufacturers differ in their approach to SVT-VT discriminator application. SJM and newer Boston Scientific ICDs allow SVT-VT discriminators to be programmed in either or both VT zones. Medtronic devices restrict some discriminators (onset and stability) to VT zones, but permit others (PR Logic and wavelet) to overlap the VF zone. Approximately 25 % of SVTs receive ventricular therapy since their cycle length falls within the VF zone and detection enhancements are not applied. Therefore, appropriate zone programming is crucial to insure that SVT-VT discriminators are applied [55]. High rate time outs override discrimination algorithms to force therapy delivery if arrhythmia persists longer than the programmed time limit, at the expense of specificity. Therefore this feature [56] is not nominally "on" in Medtronic (dual chamber), Biotronik and the newer St. Jude ICDs.

While detection enhancement specifics vary among manufacturers, in general terms they are divided into single chamber and dual chamber algorithms.

Single-Chamber Algorithms

In single-chamber ICDs, algorithms use only ventricular information to distinguish SVT from VT. They do so by analyzing the patterns of detected ventricular intervals (onset and stability) or by comparison of tachycardia electrogram characteristics to a baseline template (morphology).

Onset

The onset algorithm differentiates sinus tachycardia from VT by the abruptness of arrhythmia onset. A tachycardia with a gradual onset is classified as sinus tachycardia, whereas one with an abrupt onset is defined as VT. Sinus tachycardia is always detected at the sinus-VT rate boundary. Limitations include misdiagnosis of exercise-induced VT (that evolves from sinus tachycardia and thus appears "gradual" in onset), and of SVTs with abrupt onset such as atrial fibrillation/atrial tachycardia that are classified as VT. Furthermore, since this algorithm makes its determination based on a single event (arrhythmia onset), it does not get a second chance to correct a classification error. Onset has been extensively studied and found to provide a relatively high sensitivity and acceptable specificity [57, 58] but is best used in combination with other discriminators due to its limitations [59–61].

Stability

The stability algorithm differentiates ventricular tachycardia (stable, regular R-R intervals) from atrial fibrillation (unstable, variable R-R intervals). Figure 40.3 depicts stability algorithm function. In contrast to onset, stability continually reassesses a tachycardia initially defined as atrial fibrillation (due to interval variability) and re-diagnoses it as VT, should it become regular. As with the onset algorithm, it is best used in combination with other detection enhancements [57–60]. VTs with variable cycle length (irregular monomorphic VT or polymorphic VT) and SVTs with stable intervals defeat this algorithm. Importantly, since R-R intervals in atrial fibrillation are more regular at faster rates, interval stability cannot reliably discrimi-

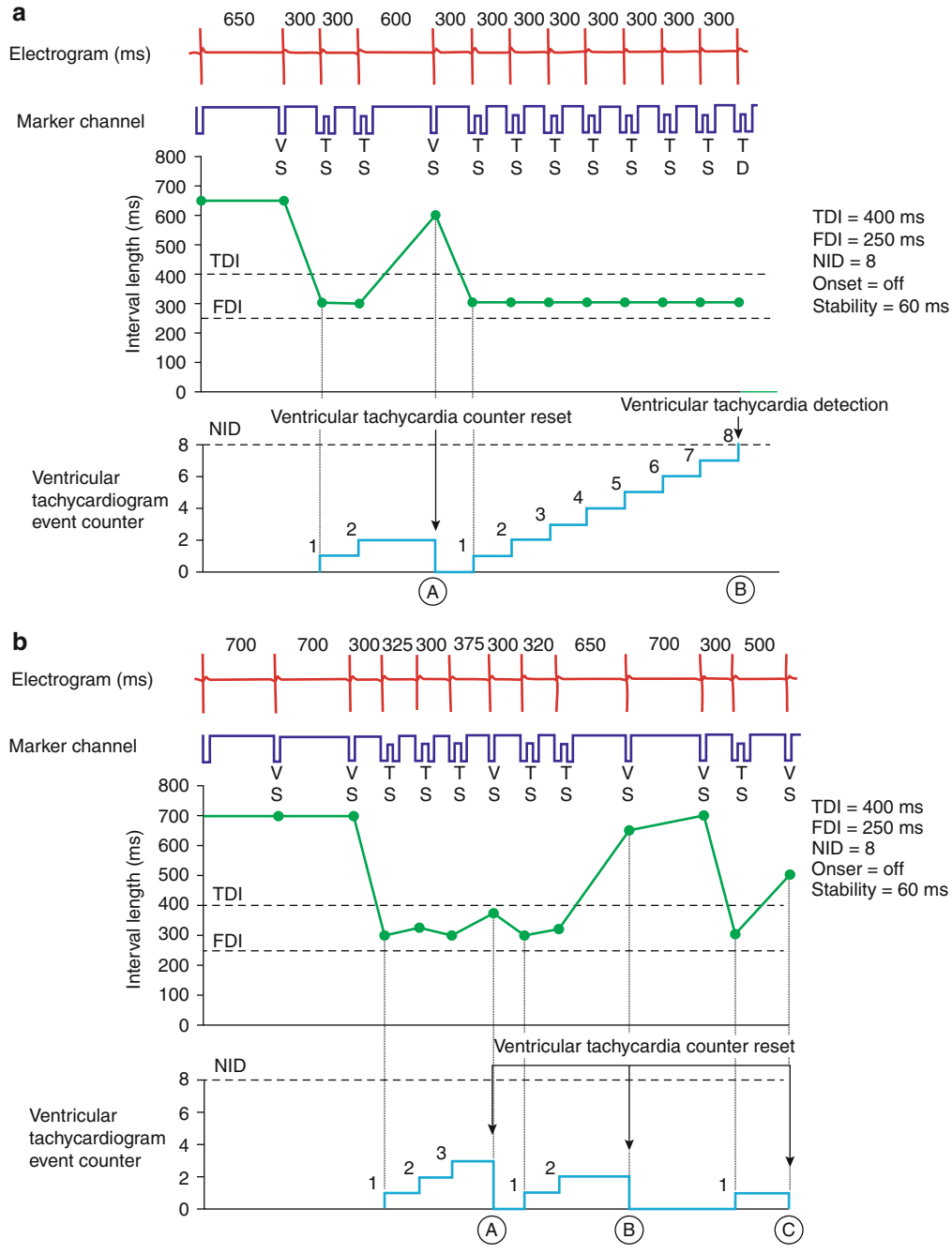

Figure 40–3. Ventricular tachycardia detection and stability enhancement. (**a**) Detection of an episode of tachycardia. *Dashed lines* show tachycardia detection interval (*TDI*) and fibrillation detection interval (*FDI*). Intervals are labeled as VS in the normal heart rate zone and TS, when they are shorter than the TDI. The third electrogram occurs at a cycle length of 300 ms, which is less (faster) than the programmed TDI of 400 ms, incrementing the counter to 1. At *A*, the counter is reset to zero by a sensed interval of 600 ms, which is longer than the TDI. At *B*, tachycardia is detected, since the eight consecutive intervals that are faster than the TDI mean that the counter reaches the programmed number of intervals to detect tachycardia (*NID*). Depending upon the type of treatment programmed, antitachycardia pacing or shock delivery would begin at this point. (**b**) The stability criterion to prevent inappropriate detection of tachycardia for fast atrial fibrillation. Tachycardia counting begins with the first fast interval (300 ms). At point A the counter is reset to zero since the cycle length of 375 ms, although less (faster) than the TDI, is more than 60 ms greater. At points *B* and *C* the counter is again reset due to a long interval. (From Glikson and Friedman [170]. Reprinted with permission from Elsevier Limited)

Table 40–1. Modes of morphology algorithm failure

Type of morphology failure	Mechanism	Correction
Inaccurate template	Change in baseline electrogram due to lead maturation or intermittent bundle branch block, or recording of template during abnormal rhythm	Apply automatic template updates or use new template
Electrogram truncation (clipping)	Recorded electrogram signal exceeds sense amplifier range, altering its morphology	Adjust amplitude scale (Medtronic and SJM) so electrograms are 25–75 % of dynamic range available
Alignment errors	Misalignment between tachycardia electrogram and template lead to miscalculation of "match" score	Eliminate clipping and/or change electrogram source (Medtronic), atrially pace at rapid rate to assess sensing (SJM)
Oversensing of pectoral myopotentials	Myopotentials distort the electrogram, altering its morphology	Change the electrogram source. Only affects algorithms utilizing far-field electrograms (Medtonic, SJM)
Rate related aberrancy	Morphology of electrograms change during SVT due to refractoriness (non-excitability) of part of the conduction system	If reproducible, record template during rapid atrial pacing (while aberrancy present) and turn off autotemplate update; adjust match score to allow greater variability before defining VT; turn off morphology
SVT immediately following shocks	Shocks lead to transient distortion of morphology	Morphology is not used for redection

nate atrial fibrillation from VT at rates >170 bpm [58, 62]. With the use of class IC antiarrhythmic drugs and amiodarone, true VT acquires irregular intervals [63].

Morphology

Morphology algorithms compare the intracardiac electrogram recorded during tachycardia to a stored template acquired during sinus rhythm. Tachycardia morphology sufficiently different from the sinus template indicates VT. This algorithm emulates the clinical approach of ECG arrhythmia diagnosis by visual analysis of the QRS morphology. Algorithms can be programmed to automatically acquire and update the templates periodically. Used in combination with onset and stability, morphology further improves discrimination function.

Morphology algorithms have known failure modes [26]. Morphology necessarily misclassifies rate related bundle branch block during SVT as VT. Small changes in electrograms may cause misalignment of the tachycardia electrogram with the template leading to misclassification misclassification. Due to electrogram distortion following a delivered shock, morphology is not applied during redirection… The modes of morphology algorithm failure are listed in Table 40.1.

Manufacturers have adopted different approaches to morphology algorithms. The Medtronic Wavelet ™ [64] algorithm is based on a wavelet transformation of the ECG at baseline and during arrhythmia, which are mathematically compared for fit. Its sensitivity and specificity at nominal settings have been reported as 100 and 78 % respectively [64]. It replaced an older QRS width-based algorithm that was less reliable [65]. Morphology-based algorithms continue to evolve [66].

The Boston Scientific Rhythm ID ™ algorithm is based on the comparison between the timing and correlation of rate and shock channel electrograms during arrhythmia and in sinus rhythm. The far-field electrogram, which by its nature has more morphology information due its use of a wider "antenna" for signal acquisition, is used for morphometric comparison. The sharper near-field rate sensing signal, with its greater slew, is used to insure appropriate electrogram alignment. It has been shown to have 99 % sensitivity and 97 % specificity when used in single-chamber settings in the laboratory [67]. Its "real life" results were 100 % sensitivity for VT/VF, and 92 % specificity for SVT [68]. The Rhythm ID Going Head to Head Trial (RIGHT) the first head-to-head comparison study between Boston Scientific Rhythm ID and Medtronic ICDs using the Wavelet discrimination algorithms on a large scale [69]. It demonstrated equivalence of the two manufacturers' algorithms with dual chamber ICDs, but a greater number of inappropriate therapies with single chamber ICDs. Importantly, many inappropriate therapies were for slower VTs (<175 bpm) [70].

The St Jude Morphology Discrimination (MD™) algorithm generates a match score by comparing tachycardia and baseline near-field

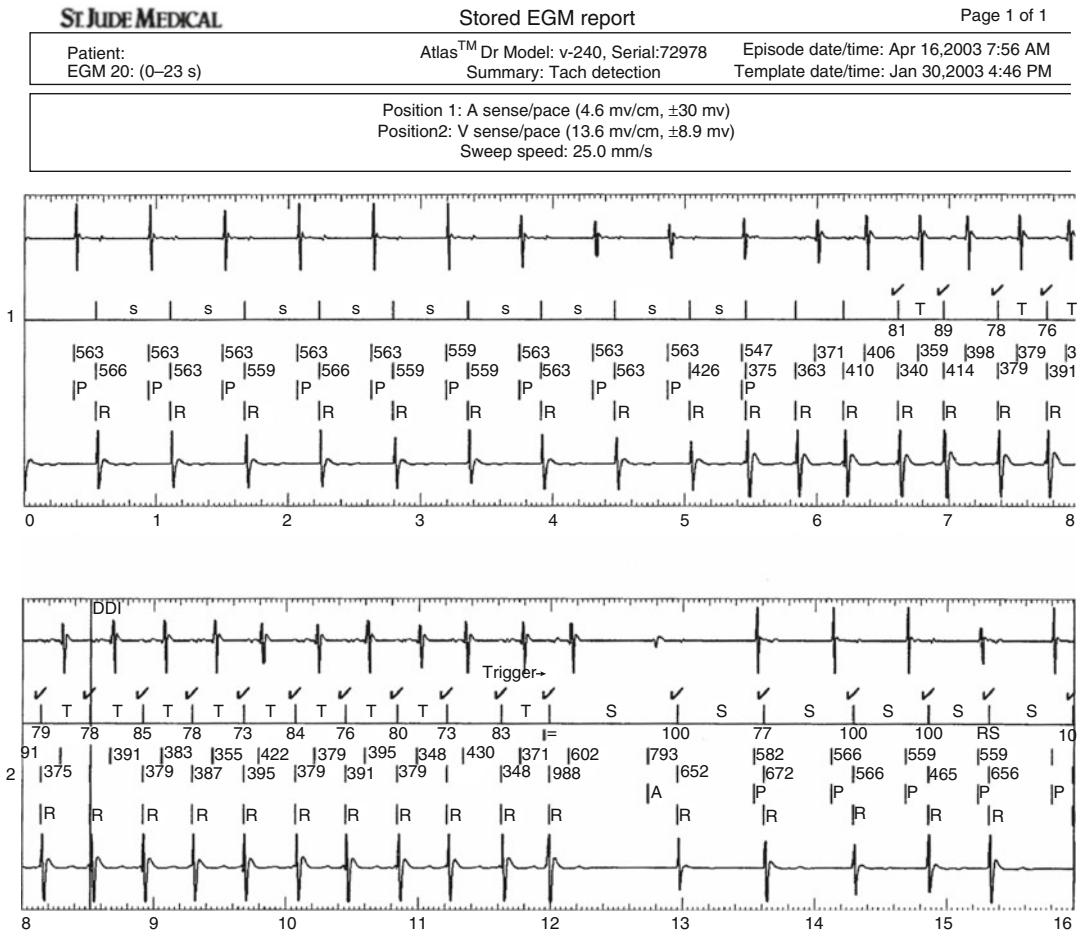

Figure 40–4. Morphology algorithm error. An electrogram of an episode of VT. There are two consecutive recordings marked *1* and *2*. Each one shows the atrial channel on the *top*, markers in the *middle*, and ventricular channel on the *bottom*. At the end of recording 1 VT starts (VT is clearly diagnosed by its initiation in the ventricle on the top recording). There is a wrong template match that suggests SVT, (marked by the *check mark signs* above the complexes), therefore therapy is withheld until the episode terminated spontaneously in the middle of recording 2

electrograms, with the score derived from differences in the direction and amplitude of the electrogram deflections. Electrograms are modeled using polygons, facilitating computations. We [59,71,72] and others [73,74] found that it improves the specificity of VT detection, but is best used in combination with other algorithms to avoid degradation in sensitivity (Fig. 40.4) [59, 70, 72, 73].

Dual-Chamber Algorithms

Dual-chamber algorithms utilize information collected simultaneously from the atria and ventricles, with the goal of using atrial information to improve specificity. They add atrial rate information to standard ventricular only algorithms, or compare the relative timing of atrial and ventricular events during arrhythmia. For example, stability is applied only after the atria are confirmed to be in atrial fibrillation (Guidant) or only when the atrial rate is faster than the ventricular rate (St Jude). In St Jude devices, stability has also been fortified by the addition of the AV association criteria for dual-chamber devices. The AV association algorithm differentiates VT from regular SVT with 2:1 conduction (such as atrial flutter) by recognition of a constant AV interval in the case of regular SVT. When AV association is operational, stable tachycardias with constant AV interval will not be detected as VT despite their cycle length regularity. Proper atrial and ventricular sensing is essential for correct diagnosis. Thus, it is important

to prevent far-field R wave over sensing as well as the under sensing of small fibrillation waves on the atrial channel.

Specific Dual-Chamber SVT-VT Discriminators

Boston Scientific devices can be programmed to use stability and onset, or RhythmID, an "on/of" algorithm that includes morphology (Vector Timing and Correlation [VTC], as used in single chamber devices). The dual chamber RhythmID initially compares atrial and ventricular rates, defining an arrhythmia with ventricular rate greater than atrial rate as VT. If V > A is not true, morphology analysis (VTC) is applied. If VTC does not reject the rhythm SVT, the interval stability is assessed if the atrial rate is above the mode switch rate. Alternatively, the operator may choose to use only stability and onset as enhancements, in which case morphology (the nominal setting) is not applied.

The Medtronic algorithm (PR logic, enhanced PR logic, and adaptive PR Logic) is based on analyzing the pattern of the timing of atrial and ventricular events to define arrhythmia mechanism. In the first generation algorithm, a fixed VT-sinus tachycardia boundary differentiated retrograde P waves (defined as occurring in the first 50 % of the R-R interval) from anterograde P waves. This resulted in misclassification of sinus tachycardia with a long PR interval as VT. Enhanced PR logic added VT-sinus boundary programmability, and adaptive PR Logic (Entrust and newer) eliminated use of a fixed VT-sinus tachycardia boundary. It rather assesses PR and RR intervals and expected variation rates; abrupt changes define VT. PR Logic's sensitivity for VT has been reported as 100 % with a positive predictive accuracy and specificity for VT just below 80 % [55, 75]. In the Protecta™ series ICDs, wavelet has been added to PR logic, increasing its specificity in the VF zone (since both VF and AF are irregular). If PR logic classifies a tachycardia as possible VT confirmation by the wavelet algorithm is required before therapy delivery. This algorithm is undergoing evaluation in the Painfree SST trial [76].

St Jude ICDs assign tachycardias into one of three branches based on the relative rates in the atrium and in the ventricle (V = A, V > A, V < A), and then selectively applies detection enhancements (morphology, stability and onset) in the V = A and V < A branches. On the V > A rate branch, SVT-VT discriminators are not applied and therapy is immediately delivered, eliminating up to 80 % of tachycardias from evaluation and possible algorithm errors. Different combinations of discriminators and logic are programmably applied depending on branch assignment, significantly influencing device performance, resulting in a wide range of sensitivity and specificity results [70, 73, 74]. We found a sensitivity of 99 % and a specificity approaching 80 % with the "best" nominal combination; performance may be improved when tailored to the individual patient. Similar results were reported with the use of Biotronik SMART [77] and the ELA Parad + algorithms [78].

Single- vs Dual-Chamber Algorithms

In patients who are not in permanent atrial fibrillation who do not have a requirement for dual chamber pacing to treat bradycardia or to provide resynchronization, the choice between a single- or dual-chamber ICD remains controversial. Intuitively, dual-chamber algorithms, which use atrial and ventricular intracardiac information for rhythm classification, should be superior to single-chamber, ventricular only detection enhancements. However, early non-randomized studies and subsequent small randomized trials failed to show any superiority of dual-chamber over single-chamber diagnosis [48–50]. Some studies employed early algorithms, which have since been refined; however, the single most common failure mode for dual-chamber algorithms is atrial sensing malfunction [48].

We compared dual-chamber to single-chamber detection in 400 recipients of St Jude dual-chamber ICDs and found that dual-chamber programming of study-specified nominal values significantly reduced inappropriate detection of SVT as VT (Fig. 40.5) [79]. Careful attention was paid to atrial lead function at implant and during follow-up. In a meta-analysis by Theuns et al. [80] dual chambers were associated with a reduction in the number shock episodes but not in the number of patients treated with shocks. Thus, patients with a propensity towards shocks received fewer shocks, but an individual's likelihood of getting any shocks was unchanged.

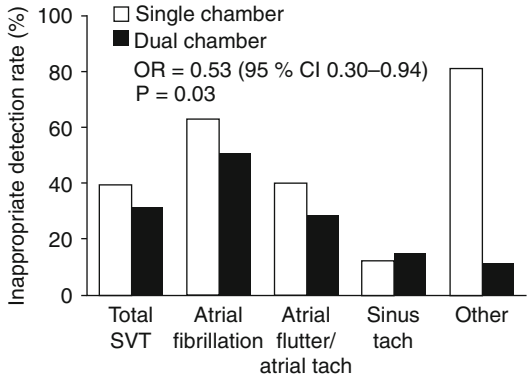

Figure 40–5. Results of the detect SVT trial. Rate of inappropriate detection of SVT demonstrating the advantage of dual-chamber over single-chamber detection, with breakdown by arrhythmia subtype [atrial fibrillation, atrial flutter/atrial tachycardia (tach), sinus tachycardia, or other], for subjects with single- or dual-chamber detection. "Other" arrhythmias include atrial tachycardia, junctional tachycardia, AV nodal reentrant tachycardia, and AV reentrant tachycardia. Subtype classification was based on a blinded episode reviewer. The odds ratio (*OR*) and probability value refer only to the overall comparison of inappropriate detection of SVT (From Friedman et al. [79]. Reprinted with permission from Wolters Kluwer Health)

In contrast, the DATAS study [81] showed that although two or more inappropriate shocks in an individual patient is relatively rare, there were fewer shocks with dual-chamber ICDs compared with single ones. Dual-chamber ICDs also reduce atrial fibrillation related events, likely due to the effects of atrial ATP and better classification of SVT [82]. The RAPTURE study (Clinical Trials.Gov. Identifier: NCT00787800) will hopefully further define the role of dual- vs. single-chamber ICDs in reducing inappropriate shocks and prevention/termination of atrial arrhythmias.

In summary, while ICD rhythm classification has substantially improved, false positive detection of ventricular arrhythmia remains the Achilles' heel of ICD therapy. Newer approaches including algorithms based on the response to electrophysiological maneuvers hemodynamic sensors will improve ICD therapy [83, 84].

Putting it All Together

Based on the PREPARE trial [28] and the accumulating data summarized above, an approach to nominal programming of ICDs has been developed to minimize the risk of unnecessary shocks. This includes:

1. Use of a prolonged detection time to avoid detection of self-terminating episodes (up to 9 s);
2. Use of detection zones above 180 bpm for prophylactic device;
3. Consistent application of SVT-VT discriminators;
4. Application of ATP even in fast detection zones.

The general recommendations (that apply to patients with primary prevention indication for implantation with devices of all companies with some variations) are listed in Table 40.2. Figure 40.6 demonstrates the advantage of this new approach as used in the PREPARE trial to decrease appropriate and inappropriate shocks.

We recently analyzed our experience with these settings in patients implanted for primary prevention indications. We programmed ICDs in160 patients based on these principles, and retrospectively compared them to 140 similar patients programmed at the treating physician's discretion, prior to our adoption of this strategy. With a mean follow up of 3.5 years, the rate of appropriate and inappropriate shocks decreased from 7.9 to 3.8 % and from 10 to 1.9 % in the physician vs. strategy driven programming (unpublished observation).

Algorithms and Techniques to Reduce Over Sensing

Over sensing causes up to10% of inappropriate shocks, most commonly due to over sensing T-waves, myopotentials, external noise, make-break potentials consequent to lead failure, and double counting of QRS. Several new tools have been added to devices to minimize over sensing.

ICDs must accurately sense relatively large amplitude R waves and potentially very low amplitude fibrillation electrograms, while avoiding T waves, the sensing of which leads to double counting. To accomplish this, ICDs use dynamic sensing, which becomes less sensitive with the R-wave, and subsequently increasingly sensitive over time to permit VF detection while avoiding the T-wave. Prominent or elevated T-waves (Brugada syndrome) or delayed T-wave (long

Table 40–2. Primary prevention ICD programming

			Detection			Discriminators				
PG	Zone	Rate	Detect	Redetect	Therapy	Single Chamber		Dual Chamber & CRT-D		
Med	VF	330 ms (182 bpm)	30/40 int	12/16 int	35Jx6, ATP during charge R-R≥230	Wavelet: ON	Other enhancements	PR logic	Other enhancements	
						SVT V. Limit: 300 ms	Stability: OFF	AF/Afl: ON (Protecta: Wavelet ON)	Stability: OFF	
							Onset: OFF	Sinus tach: ON	Onset: OFF	
	FVT via VF	240 ms (250 bpm)			ATPx1, 35Jx5		High rate timeout: OFF	Other 1:1 SVT: OFF	High rate timeout: OFF	
	Monitor	360 ms (167 bpm)	32 int		None			SVT V. Limit: 300 ms		
BS	VF	200 bpm (300 ms)	7 s	1 s	Quick convert ATP ON, Shocks 41Jx8	Enhancements (apply to VT and VT-1)		Enhancements (apply to VT and VT-1)		
						Rhythm ID		Rhythm ID		
	VT	180 bpm (333 ms)	7 s	1 s	ATP1 Burst, Shocks 41Jx8	VT detection enhancements ON		VT detection enhancements ON		
	VT-1	160 bpm (375 ms)	9 s	1 s	ATP1&2 OFF, Shocks OFF	Sustained rate duration OFF		Sustained rate duration OFF		
SJM	VF	240 bpm / 250 ms	30 int	6 int	35J, 40Jx5, ATP while charging	SVT Discrimination		SVT Discrimination		
						SVT discrimination: ventricle only		SVT discrimination: dual chamber		
						SVT discrimination timeout: OFF		SVT discrimination timeout: OFF		
						SVT upper limit: 200 bpm/ 300 ms		SVT upper limit: 200 bpm/ 300 msec		
	VT-2	181 bpm / 330 ms	30 int	6 int	ATPx1, 40Jx4	Morph: ON	Int Stab: 40 ms If 2 of 3	V<A Morph: ON	Int stability: passive	
	VT-1	166 bpm / 360 ms	30 int		Monitor only	Sudden onset: ON 100 ms		V=A Morph: ON	Sudn onset: ON	If Any

ATP therapy	Rx
Burst	
Initial pulses	8
# of sequences	1
%RR	88%
Interval decrement	10
V-V Min inerval	200 msec
Chambers paced BiV Devices for ATP	
Medtronic	Program RV+LV
BS	Default BiV
SJM	Default RV only

Dependent patients: Turn all SVT discriminators OFF

Chronic atrial fib with atrial port of BiV plugged: Use single chamber discriminators

Acquiring morphology template:

1. Pace AAI >100 bpm to see if bundle branch block aberrancy develops. If so, do not use morphology discriminators.
2. If no aberrancy with rapid pacing, manually acquire template at implant or at device check for Wavelet, Morphology, and Rhythm ID

(Bos Sci will try to auto acquire template with lower rate of 60 bpm, Med will not alter brady params for auto collection, and SJM will not auto acquire with BiV)

Acknowledgement: Brian Powell, MD, Marj Martin, RN, Tracy Webster, RN, Jim Ryan, RN

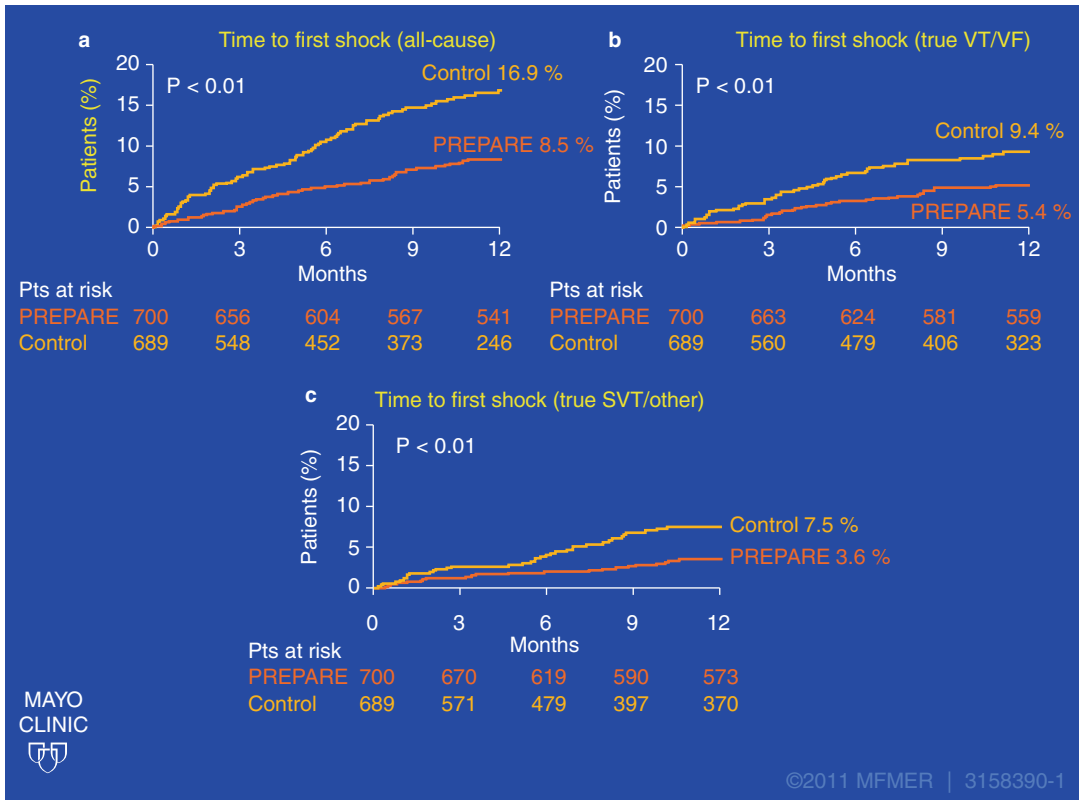

Figure 40–6. Role of shock reduction programming in primary prevention patients. The PREPARE study cohort underwent programming that included prolonged detection, use of detection enhancement, and ATP. Kaplan-Meier curves show the percentage of patients in each study cohort receiving a first shock during the first 12 months of follow-up due to: (**a**) all-cause; (**b**) true VT/VF; (**c**) true SVT/other. For each case, the p value shows the results of a log-rank test comparing the PREPARE study cohort and control (From Wilkoff et al. [28]. Reprinted with permission from Elsevier Limited)

QT syndrome) increase the risk of T-wave over sensing. Traditional programming solutions have included programmable maximum sensitivity, and in SJM devices, programmable sensing attack and delay rates. Recently improvements have been introduced by several manufacturers including the use of an arrow band pass filter in Boston Scientific devices [85], the use of frequency as well as pattern analysis to discriminate T-waves from QRS in Medtronic devices, and programmable attack patterns and filtering frequencies in Biotronik devices. The potential risk of any T-wave rejection processing is VF underdetection. In patients at risk for T-wave over sensing, VF induction at implant with the algorithm on assesses device VF detection. The clinical value of these algorithms is currently being evaluated.

To prevent shock due to noise from lead fracture, Medtronic Protect series devices cross check sensed events on the near-field electrogram with the far-field electrogram, exploiting the principal that VF should be present on both electrograms, whereas over sensing due to conductor fracture is more likely to present only on the near field signal. The sensing integrity counter (SIC) utilizes non-physiological very short R-R intervals to identify lead fracture. Lead integrity alerts combining both impedance and short R-R intervals, were found to have a positive predictive value 83 (95 %, CI 59–96 %) for a lead fracture. These positive alerts resulted in a 46 % reduction in inappropriate shocks [93]. Boston Scientific's Dynamic Noise Algorithm DNA® also aims to reduce over sensing due to high frequency external noises. These algorithms work

synergistically with remote monitoring and recognition of advisory leads (discussed below) to minimize shock risk.

Remote Monitoring and Shock Reduction

ICD malfunction due to over- or under sensing, lead fracture, lead dislodgment, loose set screw or other mechanisms may lead to inappropriate shocks, which in some cases may be the first and only manifestation of the malfunction. In one study, 76 % of lead malfunction came to clinical attention because of inappropriate shocks [86]. Prospective randomized trials have shown that automated remote monitoring effectively permits early detection of system malfunction and "preventative" intervention [87–91], and some data suggest a survival benefit [92]. With automated daily assessments, the treating physician is able to detect trends and changes in lead impedance, the development of ventricular or atrial arrhythmias, recorded but asymptomatic T-wave over sensing, and generator-related issues, such as low battery voltage or prolonged charge time. Values that exceed a threshold automatically trigger patient alerts and/or internet based warnings. Remote monitoring facilitates the management of device advisories, discussed below.

Adjunctive Therapies to Prevent Ventricular Arrhythmias

In addition to device-based therapies, other strategies may lower the risk of ICD shock.

Antiarrhythmic Drug Therapy

AADs are used in up to 50 % of ICD recipients to alleviate arrhythmia symptoms and minimize device shocks [94, 95]. The efficacy and safety of membrane active drugs in preventing ICD shocks has been the subject of prospective randomized trials [94, 96, 97]. In one study, sotalol resulted in a 44 % relative risk reduction of death or first ICD shock for any reason compared to placebo. The efficacy of sotalol was similar in patients with moderate and severe left ventricle dysfunction. The mean frequency of ICD shocks was reduced from 3.9 ± 10.7 in the placebo group to 1.4 ± 3.5 in the sotalol group [94]. However, when compared "head to head" with amiodarone and beta-blockers in the OPTIC study, sotalol was less effective in preventing ICD shocks than amiodarone, and had only a borderline advantage over beta-blockers alone. After a 1-year follow-up, shocks occurred in 38.5 % of patients treated with beta-blockers alone, 24.3 % in those treated with sotalol and 10 % in those receiving amiodarone plus beta-blockers. However, frequent shocks (>10 shocks during 1 year or >2 shocks within 24 h) occurred five times less frequently in both the sotalol and amiodarone groups compared to beta-blocker therapy alone [96]. A new agent, azimilide, with potassium channel blocking properties (I_{Kr} and I_{Ks}), was tested in the SHIELD (SHock Inhibition Evaluation with AzimiLiDe) trial [97]. Azimilide reduced total symptomatic ventricular arrhythmia by 50 % and substantially reduced the number of emergency department visits and hospitalizations. However, the total number of all-cause ICD shocks was not affected [97]. The Shield II trial will further evaluate the effect of azimilide.

The benefit of membrane active drugs in preventing shocks must be carefully balanced against the risk of adverse effects. Since most ICD recipients have significant left ventricle dysfunction, they are prone to pro-arrhythmia and heart failure exacerbation. Indeed, controlled studies demonstrate a high frequency of AAD discontinuation due to side effects: at 1-year follow-up, sotalol was stopped in 25 % of patients, amiodarone in 18 %, and azimilide in 35 % [92, 96, 97]. Of note, torsade de pointes occurred only rarely in these studies and when present was successfully treated by the ICD. Although class I AADs (flecainide, propafenone) have not been well studied in ICD patients, they are avoided in the setting of left ventricular dysfunction due to their negative inotropy and increased risk of pro-arrhythmia in that setting.

Drug-device interactions occur when AADs affect ICD function, and may be positive or adverse. Drugs may slow VT below the programmed detection rate [98, 99] or may facilitate arrhythmia termination by painless ATP,

minimizing shock risk [100]. AADs may also modify the defibrillation threshold and thus may either facilitate (sotalol) or jeopardize (amiodarone) successful defibrillation [101,102]. While this issue has been the focus of extensive attention in the past, current defibrillators provide a sufficiently large safety margin such that it has become of little importance except for a minority of patients with borderline defibrillation function [103, 104].

In summary, the potential complexity of membrane active drug use in ICD recipients precludes their *routine* use for primary shock prevention in patients with prophylactic ICDs. Membrane active drugs are commonly used in patients with clinical arrhythmia, especially those with recurrent sustained monomorphic VT, which carries a high risk of recurrence and shock [95,96]. When membrane active drugs are added, the VT detection interval is lengthened by 30–40 ms and defibrillation threshold testing is often performed. Importantly, other commonly used cardiovascular drugs (beta-blockers, angiotensin-receptor antagonists, statins, diuretics) have little or no effect on ICD function, and are routinely used due to their demonstrated mortality benefit across broad populations of cardiovascular disease patients.

Radiofrequency Catheter Ablation of VT

Percutaneous transcatheter ablation of VT/VF has become an important adjuvant therapy in the management of ICD recipients by decreasing the shock burden in patients with recurrent VT [105–110]. Using an irrigated tip catheter, VT ablation has a 3 % procedure-related mortality and a 7.3 % risk of significant non-fatal complications [111, 112]. While originally limited to targeting sustained hemodynamically stable VT [111, 112], innovations in ablation technology have enabled successful ablation of even rapid "unmappable" arrhythmias, resulting in an over 90 % reduction of appropriate ICD therapies [113–115]. This progress has been facilitated by the development of advanced three-dimensional mapping systems that permit localization of scar tissue and ablation during sinus rhythm and percutaneous ventricular assist devices to provide hemodynamic support during VT. Consequently, the role of VT ablation has expanded from limited use in very symptomatic multi-drug resistant arrhythmias treated to a larger population. Indeed, the role of prophylactic ablation has been assessed in two prospective studies (SMASH VT study [116] and VTACH [117]). These trials randomized patients with pre-existing myocardial infarction and an ICD implanted for VT/VF to "prophylactic" VT ablation or no therapy. The VTACH study enrolled only patients with a first episode of a stable VT, while the SMASH VT enrolled patients with unstable VT or syncope and inducible VT during an electrophysiological study. In both studies there was a significant reduction in appropriate ICD shocks. Of note, in the VTACH trial the difference in VT recurrence rates between treatment groups was seen mainly in those with left ventricular ejection fraction >30 %. A novel approach proposed by Haissaguerre et al. applied ablation to prevent polymorphic VT and VF by targeting the foci within Purkinje system that gives rise to triggering premature contractions [104]. These foci are responsible for the initiation of life-threatening arrhythmia after myocardial infarction [103] and in patients with Brugada and long QT syndromes [118, 119]. Although most studies of VT ablation in ICD recipients enrolled patients with ischemic cardiomyopathy, there are now several reports of successful ablation with diminution of ICD therapies in patients with dilated cardiomyopathy and arrhythmogenic right ventricular dysplasia [115, 120–122]. In these clinical situations, however, ablation procedures are more challenging and more likely to require right ventricular and/or epicardial mapping and ablation.

It should be emphasized, that most studies on the efficacy and safety of VT ablation in ICD recipients reflect the experience of a handful of high volume centers. The broad applicability to clinical practice requires further evaluation via randomized controlled multicenter trials. A relatively recent consensus expert opinion report [123] recommended that VT ablation should be offered for symptomatic sustained monomorphic VT that recurs despite AAD therapy. VT ablation can be considered in patients with left ventricular ejection fraction >35 % who had

haemodynamically-tolerated monomorphic VT due to a prior myocardial infarction even prior to AAD therapy. Ablation techniques have been used successfully to treat electrical storm, albeit at a higher risk of complications and mortality [20, 124, 125]. The role of ablation is discussed further in Chap. 37. Rarely, when drugs and ablation fail to prevent multiple ICD discharges during intractable VT/VF storm, cardiac assist devices can be life saving, providing a "bridge" to cardiac transplantation [126–128].

Management of Advisory Devices and Leads

Despite their overall high level of reliability, over the years there have been periodic safety alerts, advisories, and "recalls" of ICDs and ICD leads affecting thousands of patients. The number of pacemakers and ICDs affected has increased dramatically since 1995, probably due to increased awareness, greater enforcement of reporting policy, reports by the lay press, and increased device complexity. According to a multi-registry meta analysis [129], ICD malfunction rates peaked at 36 replacements per 1,000 patient years during 2001 [130]. Lead advisories, affected 250,000 patients worldwide.

Defective system components and recalls affect patient well being, and therefore have become a significant cause of morbidity via several mechanisms:

1. Advisories increase patient concern and anxiety, thus affecting quality-of-life [131]. It is important to realize that somewhat counter intuitively, some studies have failed to demonstrate a significant psychological effect of recalls, probably due to an understanding of the situation by well-informed patients and good physician-patient communication [132–134].
2. Advisories lead to complications related to interventions, such as infections following surgical replacement of defective devices or leads, or surgical complications associated with extraction. In fact, complications are more common during replacements than during initial implantation, and even more common if lead revision is involved [135–137]. When deciding whether to intervene surgically following an advisory, one should bear in mind that the risk of corrective action may exceed that of complications consequent to the defective hardware. A striking example of this phenomenon occurred with the Accufix atrial J lead recall, which resulted in more deaths due to extraction than due to the lead malfunction itself [138].
3. Defective components may directly cause morbidity such as inappropriate shocks due to lead fracture. A prominent example is the Fidelis lead, which with fracture may present with an abrupt onset of multiple inappropriate shocks caused by lead fracture noise. The rate of Fidelis lead fracture appears to be accelerating and has recently been estimated at nearly 3 % per year [139]. A software algorithm (Lead Integrity Alert, LIA ®) can be loaded into Medtronic ICDs to identify lead malfunction prior to inappropriate shock delivery. When the algorithm detects lead fracture based on changes in impedance and over sensing of non-physiologic short R-R intervals, it modifies detection parameters to decrease the likelihood of shock delivery, and generates a patient alert (audible tone) and caregiver alert (internet based alert) [93]. Limitations of the LIA algorithm include a short interval from alert to first shock in some patients. Its use lowers the percentage of patients with lead fracture presenting with inappropriate shock from approximately 65–30 % [140]. Whether prophylactic lead replacement should be performed during pulse generator replacement remains controversial, and may be favored in younger patients [141].
4. Defective components may lead to failure of arrhythmia detection or therapy and consequent morbidity or death. However, this phenomenon appears to be quite rare.

Documents published by professional societies provide guidance for the management of device and lead advisories. The documents emphasize early detection of hardware malfunction, clear and timely communication to minimize patient confusion, and avoidance of unnecessary interventions to minimize surgical complications. The recommendations emphasize the need to balance the risk caused by defective hardware with the risk associated with intervention, and the need to balance the need for patient monitoring

with the need to minimize his or her level of anxiety [142–144]. The following guidelines are suggested for patient management:

1. More frequent follow-up of advisory hardware.
2. Use of automatic alerts and home monitoring systems for early detection of malfunctions in patients with advisory hardware.
3. Efficient, rapid and responsible communication between manufacturers, physicians and patients to ensure that relevant information will reach patients through their care givers rather than via mass media.
4. Individual risk assessment to take into account not only the probability of intrinsic device failure but also potential consequences of failure should it occur. For instance, a pacemaker-dependent ICD patient with recurrent life-threatening arrhythmias is at a much higher risk in the event of device failure than a patient implanted for primary prevention of sudden death. The concept of *current* device indication (as opposed to original indication for implantation) is important as the clinical condition may have changed since implantation.
5. Assessment of individualized replacement operation risk while considering the remaining time to elective device replacement [139]. Overall, a risk of malfunction below 1/1,000 is considered low when contemplating replacement in a patient who is not at particular high risk should the device malfunction [142].
6. Use of noninvasive management measures, such as reprogramming, frequent monitoring, or daily magnet application when applicable.

Given the low risk of device malfunctions in most circumstances, the physician must allay patient anxiety and confusion, and objectively balance the risk of operation with continued observation.

Pacing Morbidity: Minimizing Right Ventricular Pacing

The detrimental role of right ventricular pacing was initially suggested by trials comparing ventricular-based (VVI) and atrial-based (AAI) pacing systems [145, 146]. Long-term follow-up demonstrated less atrial fibrillation, less heart failure and improved survival with atrial compared to ventricular pacing. Subsequently, the DAVID study demonstrated an increase in the composite end point of mortality and hospitalization for heart failure in ICD recipients with dual-chamber pacing at 70 bpm compared to VVI 40 back-up pacing [147]. The frequency of right ventricular pacing directly correlated to a worse outcome [148]. These findings have been corroborated by analysis of the MADIT II trial [149], the MOSTT trial [150] and other studies [151]. Patients with depressed ventricular function are at greater risk for right ventricular apical (RVA) pacing-related deterioration. Right ventricular pacing induces cardiac dys-synchrony, ventricular remodeling (pacemaker induced cardiomyopathy), and increased heart failure symptoms [152, 153].

Most ICD recipients have impaired left ventricular function and some degree of heart failure, and are therefore at risk for clinical deterioration caused by right ventricular pacing. In the MADIT II study, patients who were paced >50 % of the time had a similar long-term outcome to that of non-ICD recipients, but a worse outcome than ICD recipients paced <50 % of the time. In fact, in patients with left bundle branch block at enrollment, right ventricular pacing was associated with a higher mortality at 8-years follow-up than not receiving an ICD and or receiving an ICD with infrequent right ventricular pacing [154]. Based on these results, right ventricular pacing should be minimized in this population. In patients without an indication for pacing, programming the ICD to back-up low rate pacing at 40 bpm (VVI 40) seems to be a reasonable solution [147]. In a small subset of patients, chronotropic incompetence and sinus bradycardia, aggravated by the use of beta blockers and AADs, necessitate antibradycardia support. Use of a dual chamber pacing mode with a long AV delay prevents ventricular pacing when atrioventricular conduction is preserved. In this situation, potential side effects of pacing with long AV delay need to be considered. These include:

1. retrograde ventriculoatrial conduction facilitated by the long AV delay may increase the risk of pacemaker mediated tachycardia (due to recovery of AV nodal refractoriness);

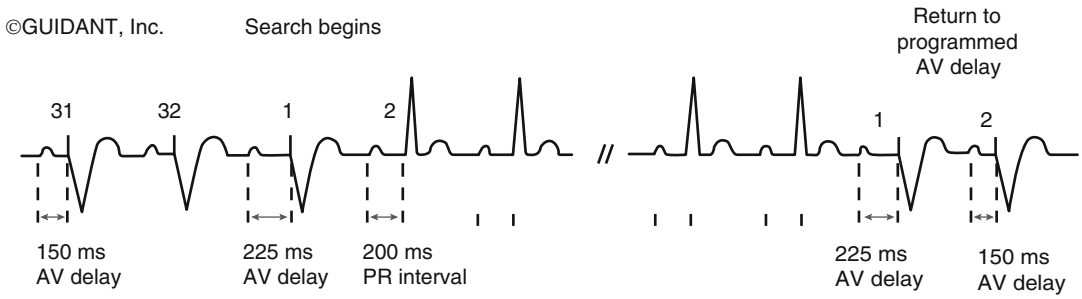

Figure 40–7. Atrioventricular search hysteresis. See text for explanation (From Olshansky et al. [156]. Reprinted with permission from John Wiley and Sons)

2. under sensing of atrial fibrillation or flutter caused by prolonged atrial blanking may adversely affect mode switch;
3. lower upper pacing and tracking rate ceilings caused by the lengthened AV delay, and
4. negative hemodynamic consequences caused by prolonged AV conduction.

In fact, the recent Danpace trial demonstrated that total avoidance of right ventricular pacing by AAI with very long AV, was associated with higher morbidity than DDD pacing with AV delays, that were usually long enough to allow intrinsic conduction, but never longer than 220 ms [155].

Algorithms have been developed that promote intrinsic AV conduction while providing ventricular pacing support when needed. The AV Search Hysteresis (Boston Scientific Inc) [156] and Autointrinsic Conduction Search (St. Jude Medical) algorithms are aimed to minimize ventricular pacing by automatic periodic prolongation of AV interval to search for intrinsic AV conduction (Fig. 40.7). When intrinsic conduction is detected, the AV delay remains prolonged. When a ventricular paced event occurs at the prolonged AV delay, the AV delay is returned to a shorter physiological AV delay. The limitations of these algorithms are related to their intermittent activation and restriction of maximal AV interval to pre-defined maximal values. In addition, all of the potential side effects of DDD programming with long AV interval can occur, albeit less frequently. AV search hysteresis can significantly decrease the number of ventricular paced events [156] and the development of persistent atrial fibrillation [157]. However, in terms of mortality or hospitalization for heart failure, DDDR pacing with the AV search hysteresis algorithm was neither inferior nor superior to VVI-40 backup pacing in the INTRINSIC RV (Inhibition of Unnecessary RV Pacing with AVSH in ICDs Study) study [6].

Another approach to minimize unnecessary ventricular pacing is the use of an AAI pacing mode. In some ICD models it can be combined with post shock dual-chamber pacing to allay the concern about post-shock conduction abnormalities. However, the risk of unpredictable AV-conduction deterioration in ICD patients, who frequently required drugs with negative chronothropic effects, needs to be considered.

For this reason, an algorithm (Managed Ventricular Pacing mode, Medtronic) was developed to minimize ventricular pacing. This algorithm combines the AAI pacing mode with the safety dual-chamber ventricular pacing backup, when transient or persistent AV block occurs. During AAI pacing, loss of AV conduction in 2 of 4 A-A intervals initiates a switch to DDD mode with physiological AV delay (Fig. 40.8). Subsequent "conduction check" by inhibition of tracking for one beat allows the detection of return of intrinsic AV conduction, with switch back of pacing mode to AAI. Initial clinical experience has demonstrated high efficacy of this algorithm in decreasing ventricular pacing by ICD [158]. Nevertheless, several cases of inappropriate bradycardia, severe AV dys-synchrony and pro-arrhythmia due to long short sequences, have been described with Managed Ventricular Pacing [159–161]. Alternatives that do not allow such long pauses are being investigated, such as the previously mentioned conduction search algorithms. The reverse mode switch developed by Boston Scientific also allows AAI pacing, but

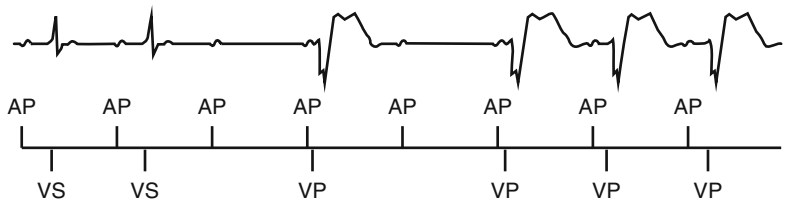

Figure 40–8. Managed ventricular pacing (MVP) mode. Loss of AV conduction following the third p wave lead to a ventricular support complex (after the fourth P-wave) with a characteristically short AV delay. After the second nonconducted P-wave (4th P-wave in the figure) the AAI(R) mode switched to a DDD(R) mode, with consistent AV pacing. The short AV delays in the two complexes that immediately follow the nonconducted P-wave identify the algorithm. See text for explanation (Courtesy Medtronic, Inc.)

does not permit pauses as long as those seen with the managed ventricular pacing algorithm.

In patients with LV dysfunction in whom high frequency of ventricular pacing cannot be avoided, consideration is given to implanting a CRT defibrillator [162, 163]. By pacing both ventricles, CRT mitigates or eliminates the deleterious effects of right ventricular pacing. The Pacing to Avoid Cardiac Enlargement (PACE) study [164] showed that right ventricular apical pacing resulted in a decrease in left ventricular ejection fraction and an increase in LV end systolic volumes in patients with normal ejection fractions. These deleterious changes were avoided in those randomized to CRT. Despite several studies addressing the issue of CRT in patients who need pacing support but who lack a currently accepted CRT indication [165–167], device selection in this population has not yet been resolved. The ongoing BioPace (Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization) trial will demonstrate whether CRT actually provides benefit in morbidity and mortality over right ventricular apical pacing [168]. Recent guidelines have already recommended the use of biventricular rather than right ventricular pacing in patients with left ventricular ejection fraction <35 % and New York Heart Association class ≥ III who need pacing [169].

In summary, we consider CRT as the pacing method of choice in patients with ventricular dysfunction who will require significant ventricular pacing. Whether biventricular pacing is superior to right ventricular pacing in patients with AV block and preserved LV function remains unresolved. Chapter 41 discusses the subject of CRT in more detail.

Conclusion

Implantable defibrillators have become the gold standard therapy for preventing death in patients at high risk for sudden death. With careful attention to device programming, device selection, use of adjunctive therapies and post implant care, both quality and length of life are improved.

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41
Pacing and Cardiac Resynchronization

Robert F. Rea

Abstract

Pacemaker therapy for antibradycardia support and cardiac resynchronization for amelioration of congestive heart failure have evolved technologically and application these therapies in different patient populations has been studied extensively. This chapter reviews new indications for cardiac resynchronization therapy (CRT), and application of CRT in patients with atrial fibrillation and patients with right bundle branch block. Strategies to improve response to CRT by echocardiographic screening of candidates as well as schemes to improve response to CRT by alteration of atrioventricular and interventricular timing sequences as well as newer lead and pulse generator technology are reviewed. New information on the potentially deleterious effect of right ventricular pacing and strategies to minimize this are reviewed.

Keywords

Cardiac resynchronization • Biventricular pacing • Tissue Doppler • Pacemaker • Implantable defibrillator • Congestive heart failure

Introduction

Current guidelines for cardiac resynchronization therapy identify candidate patients as those with class III/IV symptomatology, ejection fraction (EF) ≤35 %, and a broadened QRS complex ≥120 ms. Recently published studies and focused guideline updates, however, have both extended these indications to patients with less severe symptoms and narrowed their application by identifying subgroups less likely to respond.

R.F. Rea, MD
Internal Medicine, Cardiovascular Diseases,
Mayo Clinic, 200 First Street SW,
Rochester, MN 55905, USA
e-mail: rfrea@mayo.edu

Cardiac Resynchronization Therapy in Class I/II Heart Failure

Three recent studies are of interest.

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) [1] enrolled 1,820 patients with ischemic or non-ischemic cardiomyopathy, EF ≤ 30 %, QRS duration ≥130 ms, and class I or II symptoms. Patients with ischemic cardiomyopathy were eligible if they had class I or II symptoms while those with nonischemic cardiomyopathy were eligible only if they had class II symptoms. Patients were randomized in a 3:2 ratio to receive a cardiac resynchronization therapy defibrillator (CRT-D) or implantable cardioverter defibrillator (ICD). The primary

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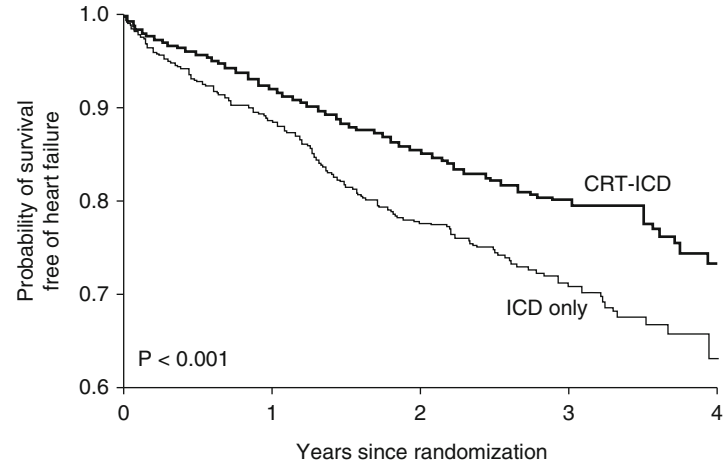
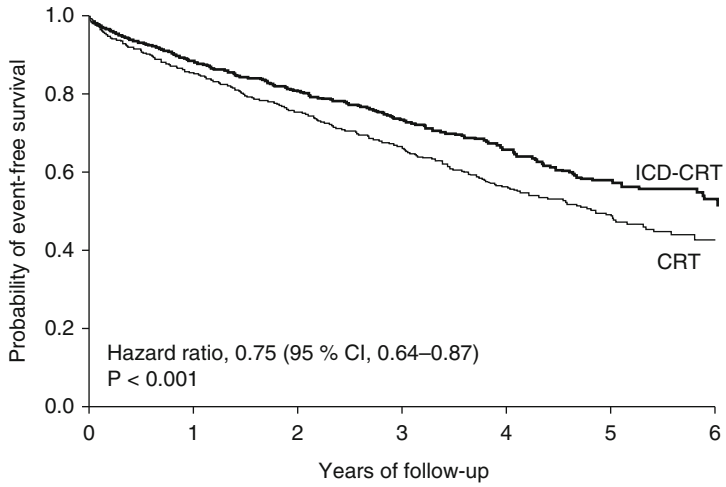


No.at risk (probability of survival)

ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT-ICD	1,089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

Figure 41–1. Comparison of survival free from heart failure in ICD and CRT-D recipients in MADIT-CRT (Adapted from Moss et al. [1]. With permission from The Massachusetts Medical Society)



No. at risk

ICD-CRT	894	790	615	429	278	130	41
ICD	904	770	572	384	214	101	19

Figure 41–2. Comparison of event free survival in RAFT. See text for explanation (Adapted from Tang et al. [2]. With permission from The Massachusetts Medical Society)

endpoint was death from any cause or a nonfatal heart failure event.

Over 2.4 years the primary endpoint occurred in 17.2 % in the CRT-D group and 25.3 % in the ICD group (Fig. 41.1). The dominant effect was a reduction in heart-failure events that was seen primarily in patients with QRS duration ≥150 ms (prespecified subgroup analysis).

The Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) [2] randomly assigned 1,798 patients with class II-III heart failure due to ischemic or nonischemic cardiomyopathy, QRS duration 120 ms (or paced QRS ≥ 200 ms) to receive ICD or CRT-D. The primary endpoint was death or hospitalization for heart failure.

Over 40 months the primary endpoint occurred in 33.2 % of CRT-D recipients and 40.3 % of ICD recipients ($p < 0.001$). Death occurred in 20.8 % of CRT-D recipients and 26.1 % of ICD recipients and hospitalization for heart failure occurred in 19.4 % of CRT-D recipients and 26.1 % of ICD recipients ($p < 0.001$). Adverse events related to the procedure were more common with CRT-D (17.2 %) than ICD (6.4 %) ($p < 0.001$) (Fig. 41.2).

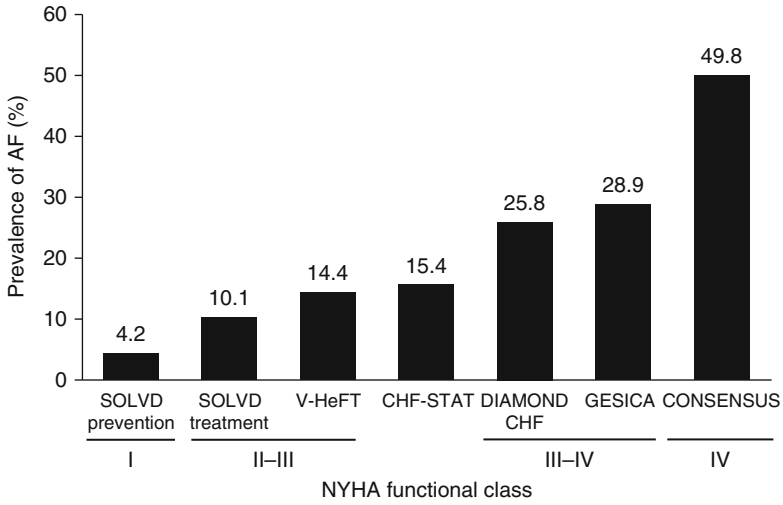


Figure 41–3. Prevalence of atrial fibrillation (*AF*) across seven heart failure trials (Adapted from Maisel and Stevenson [7]. With permission from Elsevier Limited)

The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) [3] assigned 610 patients with NYHA functional class I or II heart failure, QRS duration ≥120 ms, EF ≤40 %, and left ventricular end diastolic dimension (LVEDD) ≥55 mm to receive a CRT device (pacemaker or ICD) with CRT randomly assigned on or off (2:1 ratio) for 12 months with all patients crossing over to active CRT thereafter. In Europe patients remained in their assigned groups for 24 months and did not cross over.

A composite heart failure (HF) clinical response score that incorporated NYHA functional class, HF morbidity and mortality was the primary endpoint and the left ventricular end systolic volume index (LVESVI) was the secondary endpoint.

Of 419 patients assigned to CRT-on, 16 % had worsened HF composite score at 1 year compared to 21 % of 191 patients assigned to CRT-off ($p = 0.10$). However, left ventricular systolic volume index (LVESVI) improved in the CRT-on group compared to the CRT-off group ($p < 0.001$). Of the 262 European patients followed for 24 months, 19 % of patients assigned to CRT-on had worsened HF composite score compared to 34 % assigned to CRT-off ($p < 0.01$).

On the strength of MADIT-CRT, the United States Food and Drug Administration (FDA) approved new CRT-D indications covering NYHA class II or ischemic class I heart failure patients with QRS duration ≥130 ms, EF ≤30 % and left bundle branch block (LBBB) [4, 5]. Close reading of the FDA's approval shows that the new indication lengthens the required QRS duration to 130 ms from 120 ms, and requires the presence of left bundle branch block.

What are clinicians to make of this new evidence, especially as it pertains to asymptomatic (class I) patients? MADIT–CRT and REVERSE enrolled a small proportion of such patients (15 and 18 % respectively) and subgroup analysis showed limited efficacy. Owing to these limitations, the European Society of Cardiology has not endorsed use of CRT in asymptomatic patients and has limited its recommendations in class II patients to those with QRS duration ≥150 ms [6]. Data from device registries that follow implanted patients over time will clarify whether or not CRT is helpful in the asymptomatic patient with ventricular dysfunction and a broadened QRS complex.

Cardiac Resynchronization Therapy in Patients with Atrial Fibrillation

Atrial fibrillation is common in patients with heart failure and systolic dysfunction and the incidence increases with the severity of heart failure symptoms [7] (Fig. 41.3) and up to 27 % of CRT candidates may have permanent atrial fibrillation [8]. Despite this commonly encountered coupling, randomized controlled studies of CRT have enrolled few patients with atrial fibrillation with the exception of the Multisite Stimulation in Cardiomyopathy Trial

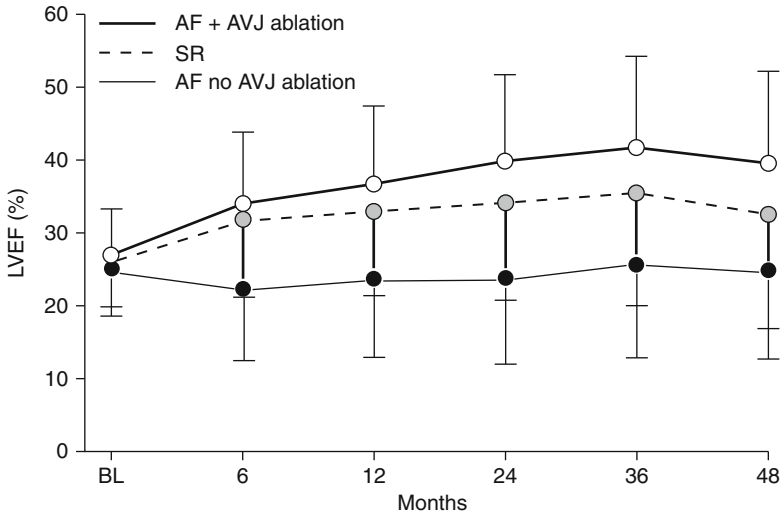


Figure 41–4. Effects of atrioventricular junction (*AVJ*) ablation on left ventricular ejection fraction (*LVEF*) responses to cardiac resynchonization therapy in patients with atrial fibrillation compared to those with sinus rhythm (*SR*) (Adapted from Hsu et al. [14]. With permission from Elsevier)

(MUSTIC-AF) [9]. Two recent meta-analyses have attempted to address this shortcoming in the evidence base [10, 11]. Each has shown a beneficial effect of CRT in these patients but with reduced efficacy compared to those in sinus rhythm.

Two physiological problems are generated by the presence of atrial fibrillation in CRT recipients; (1) inability to optimize AV delay owing to the non-contractility of the atria, and (2) difficulty in effecting a high percentage of left ventricular pacing owing to ventricular capture by conducted beats.

Problem 1 is inescapable in patients with permanent atrial fibrillation.

Problem 2 has been addressed by device manufacturers with algorithms that attempt to "resynchronize" conducted beats by initiating left ventricular pacing upon sensing of conducted complexes. During follow-up, a goal of ≥90 % left ventricular pacing is sought and device event counters are commonly used for this assessment. However, long term ambulatory ECG recordings have shown that event counters may overestimate left ventricular capture efficiency owing to pseudofusion and fusion with conducted impulses [12].

The definitive answer to the problem of competition for capture with conducted complexes in ablation of the atrioventricular (AV) conduction system [13]. Five small studies reviewed in one recent meta-analysis [10] indicated, in the aggregate, a favorable effect of AV conduction system ablation. Figure 41.4 shows the effect of AV conduction system ablation on functional capacity in patients with CRT in sinus rhythm, and atrial fibrillation with or without AV conduction system ablation in one study.

An additional consideration in the patient presenting with atrial fibrillation and systolic heart failure is the possibility that ventricular dysfunction was caused or exacerbated by rapidly conducted atrial fibrillation. In this setting, aggressive attempt to restore sinus rhythm including left atrial catheter ablation [14] may improve ventricular function sufficiently to avoid the need for CRT (Fig. 41.5).

Cardiac Resynchronization Therapy in Patients with Right Bundle Branch Block

Right bundle branch block prolongs the QRS complex to a sufficient degree to satisfy the CRT implant guideline criterion of 120 or 130 ms QRS duration. Yet the consequences of right and left bundle branch block are very different and the effects of left ventricular pacing would not be expected *a priori* to have any effect on the electromechanical disturbance caused by right bundle branch block. This has been emphasized in a recent editorial commentary [15].

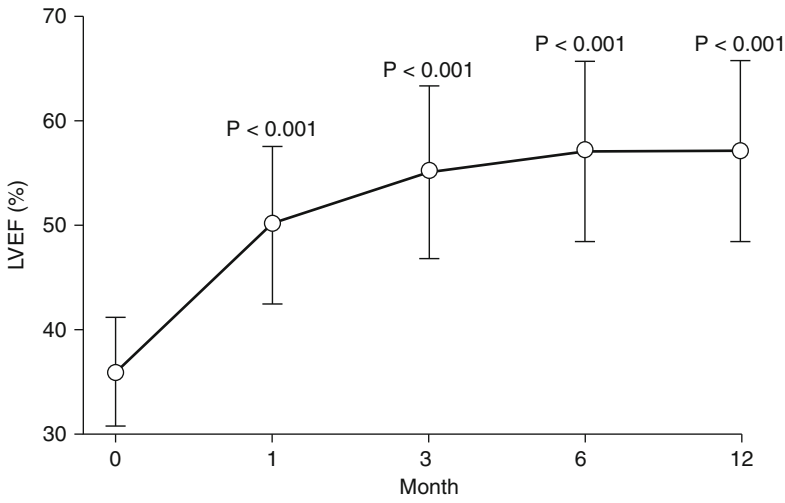
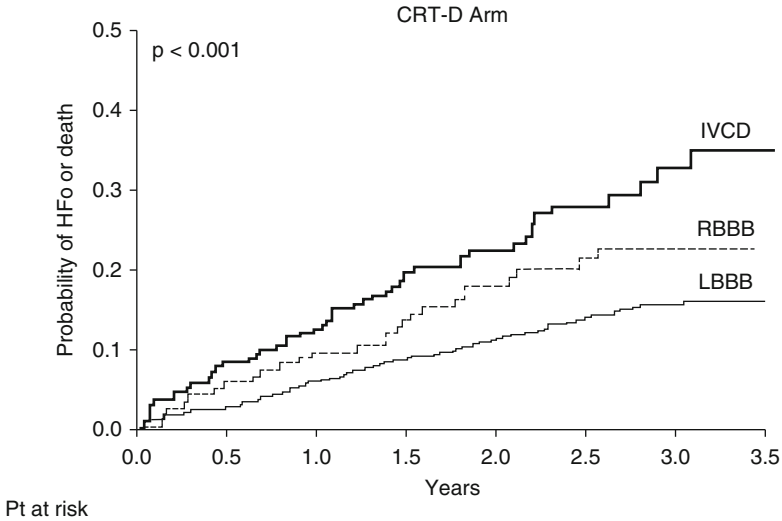


Figure 41–5. Effects of catheter ablation of atrial fibrillation on LVEF over 12 months. See text (Adapted from Zareba et al. [16]. With permission from The Massachusetts Medical Society)



Pt at risk				
LBBB	761	700 (0.06)	491 (0.12)	220 (0.16)
RBBB	136	119 (0.10)	86 (0.18)	42 (0.23)
IVCD	191	166 (0.13)	94 (0.23)	35 (0.33)

Figure 41–6. Influence of conduction system abnormalities on response to CRT. *IVCD* nonspecific intraventricular conduction delay, *RBBB* right bundle branch block, *LBBB* left bundle branch block. See text (Adapted from Zareba et al. [16]. With permission from Wolters Kluwer Health)

In RAFT, described above, patients with right bundle branch block were a predefined subgroup and comprised 161 of 1,798 patients enrolled in the overall study. Sixty-eight received CRT and 93 standard ICD. There was no effect of CRT on the composite primary outcome of death or hospitalization for heart failure [2].

In a post-hoc analysis of MADIT-CRT [16], 228 of 1,817 patients with available sinus rhythm ECGs manifested right bundle branch block. As shown in Fig. 41.6, there was no effect of CRT in patients with either nonspecific intraventricular conduction delay or right bundle branch block. This included effects on both clinical and echocardiographic endpoints.

In a single center retrospective study of the effects of CRT in patients with varying QRS morphologies, right bundle branch block, present in 36 of 338 patients, was an independent predictor of death [17].

Thus, there is evidence, albeit dominantly post-hoc, that patients with right bundle branch block derive scant benefit from CRT. Whether the presence of right bundle branch block implies

an adverse underlying physiological substrate or that epicardial left ventricular pacing is destined to fail remains unclear.

The Role of Echocardiographic Estimates of Dyssynchrony in Selecting CRT Candidates

While CRT may improve symptoms and promote favorable ventricular remodeling in a significant proportion of patients with heart failure, up to 1/3 of patients who satisfy implant criteria are non-responders. In an attempt to further identify predictors of response, multiple echocardiographic parameters of dyssynchronous ventricular contraction were explored in a small single center studies and showed promise. As detailed below, larger, multicenter centers, however, failed to corroborate these observations.

The Predictors of Response to CRT Trial (PROSPECT) was the first multicenter study to evaluate systematically the value of various echocardiographic parameters of dyssynchrony in predicting clinical and echocardiographic responses to CRT [18].

Twelve echocardiographic measures (7 using tissue Doppler imaging, 5 using M-mode or pulsed Doppler imaging) were employed in 498 patients across 53 centers in the United States, Europe and Hong Kong. A combined clinical composite score and reduction in left ventricular end-systolic volume were pre-specified endpoints and were assessed at approximately 6 months after device implant.

There was modest sensitivity and specificity of any echocardiographic parameter in predicting clinical or echocardiographic response. In addition, there was substantial intraobserver and interobserver variability in parameter measures and significant difficulty in interpreting the measures by the core laboratory. It was concluded that no single echocardiographic parameter could be recommended to improve patient selection for CRT. A single center study of 184 patients receiving CRT in which a single echocardiography laboratory performed all analyses came to essentially the same conclusion [19].

Other imaging modalities, notably magnetic resonance imaging with scar quantification are being explored in an attempt to better characterize potential CRT responders [20]. Single center studies have demonstrated a correlation between dyssynchrony measured by radial strain and response to CRT. Multicenter studies are ongoing to confirm these initial findings.

Optimization of Programmed Atrioventricular and Interventricular Delays to Improve Response to CRT

Since up to one-third of CRT recipients may not realize adequate clinical response, attempts have been made to optimize the electromechanical atrioventricular (A-V) and interventricular (V-V) timing in these devices to provide the best loading conditions and maximize cardiac output [21, 22]. Small cohort studies suggested benefit of these optimization schemes that commonly involved use of echocardiography as the programmed timing sequences were altered. While echocardiography-based optimization is logistically cumbersome and expensive it is justifiable if proved clinically useful. Two recent studies addressed this question.

The SMART-AV Trial was a double-blinded randomized trial in which 1,014 CRT-D recipients were assigned to a fixed empirical A-V delay of 120 ms, an echocardiographically optimized A-V delay, or A-V delay dictated by a proprietary (Boston Scientific, Inc) electrogram-based algorithm [23]. The primary end point was left ventricular end-systolic volume and secondary end points included NYHA functional class, quality-of-life score, 6-min walk distance, left ventricular end-diastolic volume and LVEF.

Neither the electrogram-based algorithm nor echocardiography guided A-V optimization was superior to a fixed A-V delay of 120 ms.

The RHYTHM II ICD study was a single-blinded trial of 121 CRT-D recipients randomized to simultaneous right and left ventricular pacing (n = 30) or echocardiography guided V-V timing to achieve maximal stroke volume. End points included changes between pre-implant and 6-months post implant in NYHA functional class, 6-min walk, and quality-of-life score [24].

CRT-D implant was associated with significant clinical improvement but there was no demonstrable effect of V-V timing optimization.

These two studies suggest that routine optimization of A-V and V-V intervals is of little utility in the aggregate. In the clinical non-responder to CRT, however, a subgroup that was not specially addressed in either study, it is reasonable to manipulate these easily programmable timing intervals with the use of intra-device electrogram-based algorithms or echocardiography.

New CRT Technologies

Optimal placement of coronary vein left ventricular (LV) pacing leads can be frustrating and time consuming owing to the vagaries of anatomy, delivery tools and lead shapes. In addition, the proximity of the left phrenic nerve to the obtuse margin of the heart often interferes with lead positioning.

To circumvent some of these problems manufacturers have developed leads and pulse generators with a variety of left ventricular pacing configurations ranging from LV bipolar, LV lead (tip or ring) coupled to the RV coil or ring electrode, LV lead (tip or ring) coupled to the pulse generator among others.

A new CRT pulse generator coupled to a new quadripolar left ventricular pacing lead is available offer ten programmable left ventricular pacing vectors (Fig. 41.7). Preliminary studies have indicated that the new pacing vector options can obviate phrenic nerve stimulation in some patients [25].

Pacing

It is increasingly appreciated that pacing the right ventricle is some patients can have deleterious effects on left ventricular function. Some investigators have advocated alternative right ventricular pacing sites [26], or biventricular pacing even in patients with relatively normal LVEF to avoid adverse remodeling when ventricular pacing is obligatory. When atrioventricular block is intermittent, use of a pacemaker with an algorithm that minimizes right ventricular pacing may be beneficial [27].

The Pacing to Avoid Cardiac Enlargement (PACE) trial was a double-blinded, randomized trial of right ventricular versus biventricular pacing in patients with normal LVEF [28]. Patients (n = 177) received a biventricular pacemaker and were randomly assigned to right ventricular apical (n = 88) or biventricular (n = 89) stimulation.

At 1-year follow up the mean LVEF was lower and the left ventricular end-systolic volume higher in patients receiving right-ventricular pacing than in those receiving biventricular pacing (Fig. 41.8) though there was no difference in clinical end-points such as 6-min walk distance or development of heart failure.

Patients with congenital atrioventricular block are a unique group typically without associated structural heart disease who often come to clinical attention in adolescence or early adulthood. As such, when they receive pacemakers, they are destined to be exposed to the effects of pacing for an extended period of time.

In a natural history study of pacing in such patients over some 20 years, the development of clinical heart failure and left ventricular dysfunction was more likely than in a matched population. Interestingly, however, the worse outcome was seen only in patients with antinuclear antibodies, an immunological marker found patients with congenital heart block born to mothers with similar autoimmune markers [29]. This raises the intriguing possibility that obligatory right ventricular pacing may permit expression of otherwise subtle abnormalities of cardiac function.

Summary

Significant progress has been achieved in pacing to treat congestive heart failure. Recent studies have expanded the indications for CRT in patients with NYHA class I-II heart failure. We now have a better understanding of patients less likely to respond to CRT (those with RBBB, nonspecific intraventricular conduction delay, or QRS < 150 ms). Patients with atrial fibrillation and biventricular pacing less than 90 % may benefit from AV node ablation. Techniques to better select patients for CRT are still in devel-

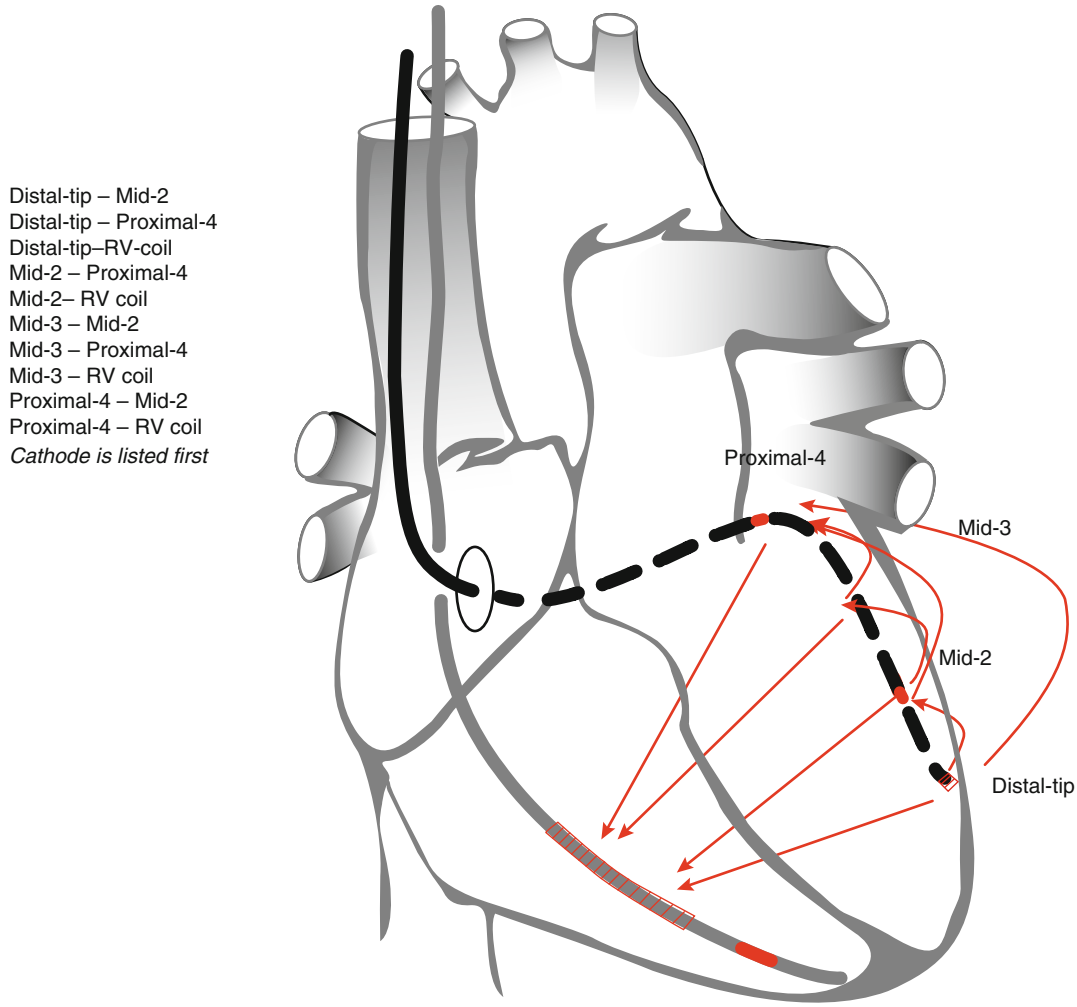


Figure 41–7. St. Jude Medical quadripolar left ventricular pacing lead that allows selection of ten different pacing vectors in cardiac resynchronization device (Courtesy of and copyrighted by St. Jude Medical)

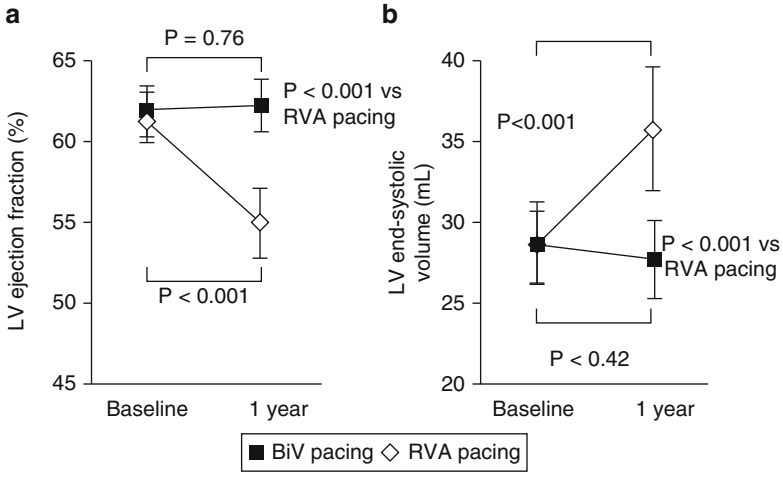


Figure 41–8. Comparison of effects if right ventricular apical versus versus biventricular pacing on LVEF (panel **a**) and left ventricular end-systolic volume (panel **b**) in the Pacing to Avoid Cardiac Enlargement Trial (Adapted from Yu et al. [28]. With permission from the Massachusetts Medical Society)

opment, while LV lead technology continues to improve. With all of these advancements, CRT can be better targeted to patients most likely to benefit from the therapy.

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