Cardiovascular Medicine

Peter Kowey
Jonathan P. Piccini
Gerald Naccarelli
James A. Reiffel *Editors*

Cardiac Arrhythmias, Pacing and Sudden Death

Springer

Cardiovascular Medicine

Series Editor

James T. Willerson
MC 3-116
Texas Heart Institute
Houston, Texas, USA

Cardiovascular Medicine will offer today's most up-to-date, user-friendly guidance on the evaluation, diagnosis, and medical and surgical treatment of heart and vascular disease and will be on the wish list for every trainee and practising cardiologist, cardiac surgeon, vascular surgeon, diabetologist, cardiac radiologist and any physician who manages cardiac patients. The book and online package is dedicated to providing comprehensive coverage of every aspect of cardiovascular medicine from cardiac signs and symptoms through peripheral vascular disease and the genetic basis for cardiovascular disease to preventive cardiology. The Editors – and over 150 world authorities – will offer their decades of scientific and clinical experience. A major selling point will be the consistent chapter organization, clear design, and engaging text that includes user-friendly features such as tables, lists and treatment boxes. The reader will have all the guidance to diagnose and manage a full range of conditions in a series of textbook resources, while also having access to additional video material. More than 1600 illustrations over the eight volumes – including a wealth of color Doppler, nuclear imaging, surgical and pathological images – clarify complex principles and help in the understanding of the subtleties of technique and their application, so that they can be implemented in your practice. The eight volumes of Cardiovascular Medicine, 4th Edition will be the premier resource of its kind, which will advance readers' knowledge and stimulate further study in cardiovascular medicine. Each volume is designed as firstly as a standalone reference in its subject, breaking the field of cardiology down into logical learning modules.

More information about this series at http://www.springer.com/series/10474

Peter Kowey • Jonathan P. Piccini
Gerald Naccarelli • James A. Reiffel
Editors

Cardiac Arrhythmias, Pacing and Sudden Death

Springer

Editors
Peter Kowey, MD
Lankenau Heart Institute and Jefferson Medical College
Philadelphia
PA
USA

Gerald Naccarelli, MD
Bernard Trabin Chair in Cardiology
Professor of Medicine
Chief, Division of Cardiology
Associate Clinical Director
Heart and Vascular Institute
Penn State University College of Medicine
Hershey
Pennsylvania
USA

Jonathan P. Piccini, MD, MHS, FACC, FAHA, FHRS
Associate Professor of Medicine
Duke University Medical Center
Duke Clinical Research Institute
Durham
NC
USA

James A. Reiffel, MD
Professor Emeritus of Medicine
Department of Medicine, Division of Cardiology, Section of Electrophysiology
Columbia University
New York
USA

ISSN 2363-5053 ISSN 2363-5061 (electronic)
Cardiovascular Medicine
ISBN 978-3-319-57998-6 ISBN 978-3-319-58000-5 (eBook)
DOI 10.1007/978-3-319-58000-5

Library of Congress Control Number: 2017951647

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

The editors would like to dedicate this book to our families, who patiently endure our absence and our distractions on a daily basis, and our patients, whose courage and perseverance inspire us to find ever better ways to diagnose and treat the difficult diseases that afflict them.

Foreword

When Dr. Willerson contacted us to assess our interest in editing an electrophysiology book for his highly successful cardiology series, we will admit that we were in a quandary. On one hand, we were flattered to have been asked, and eager to join an assembly of renowned contributors enlisted by Dr. Willerson in other areas of cardiovascular medicine. And how to say no to one of the most distinguished cardiology educators of all time? On the other hand, of textbooks there may never be an end, and in this modern day, what value might another tome have over data sources that are continuously streamed and updated?

After some serious reflection, we decided to go forward but only if we could attract what we deemed to be the most knowledgeable and accomplished faculty on the planet. The conundrum, or course, was that these people are enormously busy and overworked, and so the idea of taking on another task, no matter how dear the friendship of the editors, would not be especially appealing. Thus, we were astounded when every one of our first choices for each chapter agreed to contribute. As you can see, the table of contents is literally a *Who's Who* of modern electrophysiology and arrhythmology. As an added feature, several of the authors elected to enlist a junior faculty member or senior fellow to co-author, providing the richest of learning opportunities for those fortunate trainees.

The book itself was carefully structured to allow an individual, at virtually any level of training, to find information to their needs and liking. We start with topics in basic electrophysiology and move through diagnostic and treatment methods, finally focusing on specific arrhythmia syndromes before concluding with the particularly thorny issue of special populations. In each chapter, the authors have provided conceptual material, followed by practical information upon which treatment decisions can be firmly based. We know that the book's organization has introduced a certain element of duplication, but as the Latin proverb proclaims, *repetition est mater studiorum*. Plus, garnering diverse opinions about important topics provides an added and unique perspective for the reader.

We were also concerned that the time it might take to produce a conventional textbook might render some portion of its contents obsolete, especially given the warp speed at which our specialty evolves. We needn't have worried. Our authors, sitting at the very cutting edge of science, nicely anticipated trends and advances and have, in each chapter, provided a perspective that is topical and enduring.

Thus, our decision to move ahead with this textbook was, in retrospect, a sound one. We believe that the information provided herein will be of immense benefit to those who seek to learn the craft of caring for patients with any form of cardiac arrhythmia. We thank Dr. Willerson and the publisher's staff for their help in bringing forward a textbook of which we are quite proud.

Contents

Contributors

Dean M. Abtahi, M.D. Division of Cardiology, Medical University of South Carolina, Charleston, SC, USA

Michael J. Ackerman, M.D., Ph.D. Division of Heart Rhythm Services, Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Division of Pediatric Cardiology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA

Department of Molecular Pharmacology and Experimental Therapeutics, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA

Juan Acosta, M.D. Arrhythmia Section, Cardiology Department, Thorax Institute, Hospital Clinic, Barcelona, Spain

Wayne O. Adkisson, M.D. Department of Medicine, University of Minnesota School of Medicine, Minneapolis, MN, USA

Charles Antzelevitch, Ph.D. Lankenau Institute for Medical Research, Wynnewood, PA, USA

Samuel H. Baldinger, M.D. Cardiovascular Department, Brigham and Women's Hospital, Boston, MA, USA

David G. Benditt, B.Sc., E.E., M.D. University of Minnesota Medical Center, Minneapolis, MN, USA

Matthew Bennett, M.D. UBC Division of Cardiology, Vancouver General Hospital, Vancouver, BC, Canada

J. Martijn Bos, M.D., Ph.D. Division of Pediatric Cardiology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA

Department of Molecular Pharmacology and Experimental, Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA

Josep Brugada, M.D., Ph.D. Arrhythmia Section, Cardiology Department, Thorax Institute, Hospital Clínic, Barcelona, Spain

Alexander Burashnikov, Ph.D. Lankenau Institute for Medical Research, Cardiovascular Research, Wynnewood, PA, USA

David J. Callans, M.D. Electrophysiology Section, Division of Cardiovascular Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Alan John Camm, M.D., F.R.C.P. Clinical Sciences Division, St George's University of London, Cranmer Terrace, London, UK

Abhishek Deshmuhk, M.D. Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic—St. Mary's Campus, Rochester, MN, USA

Paul Dorian, M.D., M.Sc., F.R.C.P.C. Division of Cardiology, Department of Medicine, St. Michael's Hospital, Toronto, ON, Canada

Kenneth A. Ellenbogen, M.D. Division of Cardiology, VCU School of Medicine, Richmond, VA, USA

N.A. Mark Estes III, M.D. New England Cardiac Arrhythmia Center, Tufts University School of Medicine, Boston, MA, USA

Bernard J. Gersh, M.B., Ch.B. Mayo Clinic, Rochester, MN, USA

Michael R. Gold, M.D., Ph.D. Medical University of South Carolina, Charleston, SC, USA

E. Kevin Heist, M.D., Ph.D. Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Jose F. Huizar, M.D. Virginia Commonwealth University/Pauley Heart Center, Virginia Commonwealth University, Richmond, VA, USA

Arrhythmia and Device Clinic, Hunter Holmes McGuire VA Medical Center, Richmond, VA, USA

Winston B. Joe School of Medicine, Stanford University, Stanford, CA, USA

John Alvin Kpaeyeh Jr, M.D. Medical University of South Carolina, Charleston, SC, USA

Andrew Krahn, M.D. UBC Division of Cardiology, Department of Medicine, Vancouver General Hospital, Vancouver, BC, Canada

Balaji Krishnan, M.D., M.S. Division of Cardiology, University of Minnesota Medical Center, Minneapolis, MN, USA

Ramanan Kumareswaran, M.D. Medicine/Cardiology, St. Michael's Hospital, Toronto, ON, Canada

Jackson J. Liang, D.O. Clinical Cardiac Electrophysiology Fellow Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Gregory Y.H. Lip, M.D. Institute of Cardiovascular Sciences, City Hospital, University of Birmingham, Birmingham, UK

Department of Clinical Medicine, Aalborg Thrombosis Research Unit, Aalborg University, Aalborg, Denmark

Moussa Mansour, M.D. Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

L. Brent Mitchell, M.D., F.R.C.P.C. Department of Cardiac Sciences, Calgary Zone, Alberta Health Services and Libin Cardiovascular Institute of Alberta, Calgary, AB, Canada

Raul D. Mitrani, M.D. Division of Cardiology, Department of Medicine, University of Miami, Miller School of Medicine, Miami, FL, USA

Robert J. Myerburg, M.D. Division of Cardiology, Department of Medicine, University of Miami, Miller School of Medicine, Miami, FL, USA

Stanley Nattel, M.D. Department of Medicine and Research Center, Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada

Department of Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada

Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Duisburg, Germany

Douglas L. Packer, M.D. Mayo Clinic—St Mary's Campus, Rochester, MN, USA

Victoria M. Robinson, M.B.Ch.B., B.Med.Sci. (Hons.) Lankenau Institute of Medical Research, Philadelphia, PA, USA

The University of Manchester, Manchester, UK

Dan M. Roden, M.D. Oates Institute for Experimental Therapeutics, Vanderbilt University School of Medicine, Nashville, TN, USA

Jeremy N. Ruskin, M.D. Massachusetts General Hospital, Boston, MA, USA

Samir Saba, M.D. University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Irina Savelieva Clinical Sciences Division, St George's University of London, Cranmer Terrace, London, UK

Keitaro Senoo, M.D. Institute of Cardiovascular Sciences, City Hospital, University of Birmingham, Birmingham, UK

M. Benjamin Shoemaker, M.D. Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Christian Steinberg, M.D. University of British Columbia, Vancouver, BC, Canada

William G. Stevenson, M.D. Cardiovascular Department, Brigham and Women's Hospital, Boston, MA, USA

Usha B. Tedrow, M.D., M.Sc. Cardiovascular Department, Brigham and Women's Hospital, Boston, MA, USA

Edward P. Walsh Cardiac Electrophysiology Division, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Paul J. Wang, M.D. Stanford University, Stanford, CA, USA

Basic Electrophysiology

1

Victoria M. Robinson and Stanley Nattel

Abstract

Basic electrophysiology is a rapidly evolving field, rich in detail. This introductory chapter provides a succinct and essential overview of key concepts in basic electrophysiology covering: The stages of the cardiac action potential and their generation; Excitation-contraction coupling; Cardiac automaticity; The cardiac conduction system and Arrhythmogenesis, including abnormal automaticity, afterdepolarizations, triggered activity and re-entry.

Keywords

Ion channels • Action potential • Electro-mechanical coupling • Automaticity • Cardiac conduction • Arrhythmogenesis • Afterdepolarisations • Triggered activity • Re-entry • Rotors

Introduction

Basic electrophysiology is a broad and fascinating discipline. To discuss this topic in depth is beyond the scope of a single book chapter. This chapter therefore serves as an introduction to the major areas of basic electrophysiology relevant to the practicing clinician. It is designed to be suitable for a wide range of readers from senior medical students to general physicians and cardiologists. It broadly covers key concepts in action potential formation, automaticity, cardiac conduction and arrhythmogenesis. Note, more detailed discussion into the mechanisms of specific arrhythmias will be addressed in later chapters pertaining to those individual arrhythmias.

V.M. Robinson, M.B.Ch.B. (✉)
Lankenau Institute of Medical Research, Philadelphia, PA, USA

The University of Manchester, Manchester, UK
e-mail: v.m.robinson@icloud.com

S. Nattel, M.D.
Department of Medicine and Research Center, Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada

Department of Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada

Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Duisburg, Germany
e-mail: stanley.nattel@icm-mhi.org

The Cardiac Action Potential

What Is an Action Potential? (AP)

The cardiac action potential (AP) is the time course of voltage change across a cardiac cell membrane, during one cardiac cycle. It is the basis for the electrical impulse that spreads through the heart and initiates organised contraction [1]. The cardiac AP has a specific shape, which varies among different areas in the heart. The ventricular AP, depicted in Fig. 1.1, will be used as the standard exemplar for this chapter.

How Is the Cardiac AP Generated?

Membrane Potential, Equilibrium Potential and Driving Force

To appreciate how the AP is generated, it is important to first understand the concepts of membrane potential (E_m) and equilibrium potential. The membrane potential is the potential difference, or voltage between the cell interior and

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_1

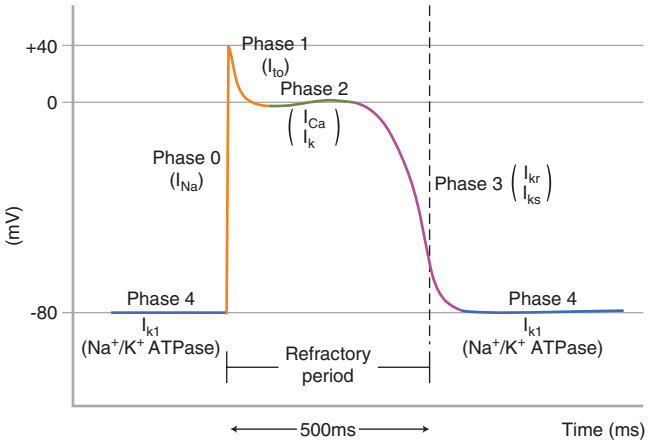


Fig. 1.1 Representative diagram of a ventricular AP, depicting the change in transmembrane voltage over time, as seen from the inside of the cell. The different phases of the AP are labelled along with the principal currents flowing during each phase. See text for details

exterior, and is formed by the unequal separation of charge across the cell membrane.

When a cell is selectively permeable to a specific ion and a concentration gradient is present, that ion species will diffuse down its concentration gradient, leaving behind a charge opposite to that of the permeable ion. The charge will attract the permeable ion back, and when enough charge has built up the electrical force holding the ion back becomes equal and opposite to the chemical force pushing the ion out. The transmembrane voltage at which the electrical and chemical forces exactly oppose each other, so that the ion stops moving, is called the "equilibrium potential". Each ion has a specific equilibrium potential (E_{ion}), calculated by the Nernst equation (Fig. 1.2). The driving force on an ion before the equilibrium potential is reached is equal to the membrane potential minus the equilibrium potential:

Driving Force = ($E_m - E_{ion}$).

In cardiac myocytes, the resting membrane potential is the potential during electrical quiescence between APs, i.e. phase 4 (Fig. 1.1) [2]. During phase 4, the membrane has the highest permeability to K^+ ions, with only slight permeability to other ions, therefore the resting membrane potential of roughly −80 mV lies close to the equilibrium potential for K^+. When the permeability to another ion increases, such as when channels carrying that ion open, e.g. the opening of Na^+ channels during phase 0, the membrane potential moves towards the equilibrium potential for that ion. Cellular depolarization, the cell interior becoming less negative, is due to increased permeability to inward-moving ions like Na^+ and Ca^{2+} with positive equilibrium potentials, whereas repolarization, the cell interior becoming more negative and returning towards the resting potential, is due to increased permeability to outward-moving ions like K^+.

During each AP, Na^+ and Ca^{2+} enter the cell, and K^+ leaves the cell. Since there are about 100,000 APs per day, the small net ion movement in each AP would result in loss of the ionic gradients if not compensated. Therefore, cells have active pumps and transporters, like the Na^+/K^+ ATPase pump, with a respective stoichiometry of 3:2 (3 Na^+ ions pumped out of cells, for every 2 K^+ ions pumped in), which maintain ionic homeostasis.

Channel Gating

Central to the generation of the AP is the opening and closure of specific ion-channels, which regulate the membrane permeability to different ions and shape the AP. For example, phase 0 is generated by the opening of Na^+ channels, which allow the cell to depolarize rapidly towards the Na^+ equilibrium potential. Phase 1 repolarization is caused by the opening and rapid closure of "transient outward" K^+ channels, phase 2 (the plateau) is formed by the opening of Ca^{2+} channels balanced by the maintained opening of several K^+ channels, and phase 3 repolarization is generated by the progressive opening of rapid (I_{Kr}) and slow (I_{Ks}) delayed rectifier K^+-currents (Figs. 1.1 and 1.3). The appropriate opening and closure of the various channels involved is determined by voltage and time dependent "gating".

A detailed discussion of the structure of various ion channels and their exact gating mechanisms is beyond the scope of this overview chapter, but some essential elements will be summarised. Ion channels can be classified according to their gating mechanism: voltage-dependent, ligand-dependent or mechano-sensitive (stretch activated) channels [3]. The majority of cardiac ion channels, including all of the key channels shown in Fig. 1.1, are voltage-gated, meaning that their conductance varies with a change in membrane potential. Changes in membrane potential rearrange the alignment of charged amino acids within the channel, causing conformational changes that allow the channels to open [4]. Opening is time-dependent, varying widely from micro-(10^{-6})-seconds for Na^+ channels to hundreds of milli-(10^{-3})-seconds for delayed-rectifier K^+ channels.

Figure 1.4 shows recordings of Na^+ current, obtained by depolarizing the cell membrane to various voltage steps to mimic different degrees of depolarization. The amount of current gradually increases to a peak and then tails off after about 20 mV, since the step potential at this stage is slowly reaching the equilibrium potential for Na^+ ions, therefore the driving force lessens. All voltage-gated ion channels in the AP activate upon depolarization, with the exception of the "funny" current (I_f), which contributes to pacing in the sinoatrial (SAN) and atrioventricular (AVN) nodes, and activates in response to membrane repolarization (which is one of the reasons it is "funny"). The other "funny" aspect of I_f is its relatively poor selectivity for Na^+ versus K^+,

$$E_{ion} = \frac{RT}{zF} \log_e \frac{[ion]_o}{[ion]_i}$$

Ion	Extracellular Concentration (mM)	Intracellular Concentration (mM)	E_{ion} (mV)	Permeability ratio to K^+ ions at resting potential (P_X/P_K)
K^+	4	120	-90	1.00
Na^+	140	10	+70	0.04
Ca^{2+}	2	0.1-0.5	+131	0.20
Cl^-	100	22	-40	0.11

Fig. 1.2 *Top panel:* The Nernst Equation, where E = equilibrium potential of the ion species in question (mV), R = gas constant (8.314 J K^{-1} mol^{-1}), T = absolute temperature in Kelvin, *z* = valence of ion, F = Faraday constant (96,485 C mol^{-1}), $[ion]_o$ = concentration of the ion on the *outside* of the cell membrane, $[ion]_i$ = concentration of the ion on the *inside* of the cell. *Bottom panel*: Table showing relevant properties of the most important ions in cardiac myocytes [2]

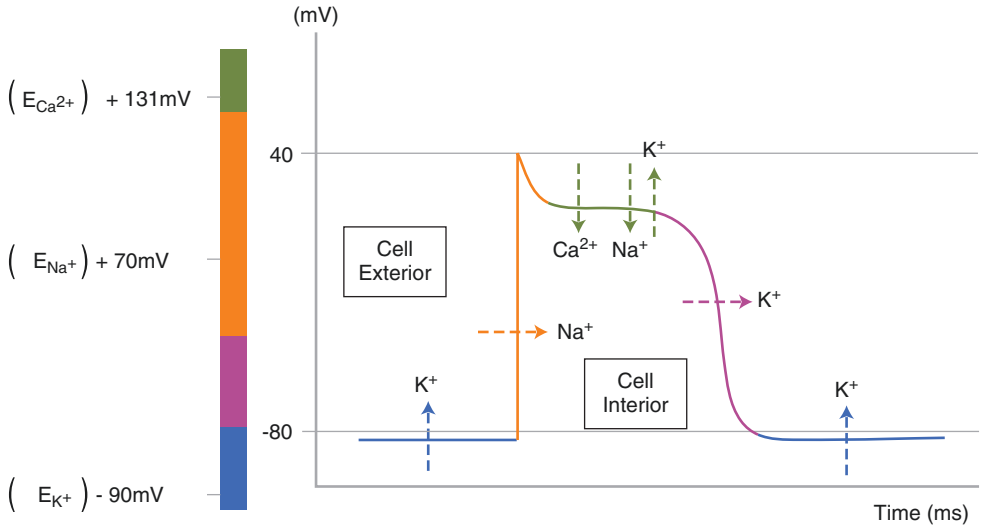


Fig. 1.3 A diagram showing the ventricular AP with the ions able to permeate the membrane during the various AP phases. The colour coding used is identical to that used to show the AP phases in Fig. 1.1 for ease of comparison. The colour bar on the *left* of the panel gives a linear representation of the various equilibrium potentials of the key ion species. Once a membrane is permeable to an ion through channel gating, it is subject to a driving force and diffuses either into or out of the cell down its concentration gradient in an attempt to reach its equilibrium potential. The labels of "cell interior" and "cell exterior" indicate the direction of travel of the different ion species during AP phases

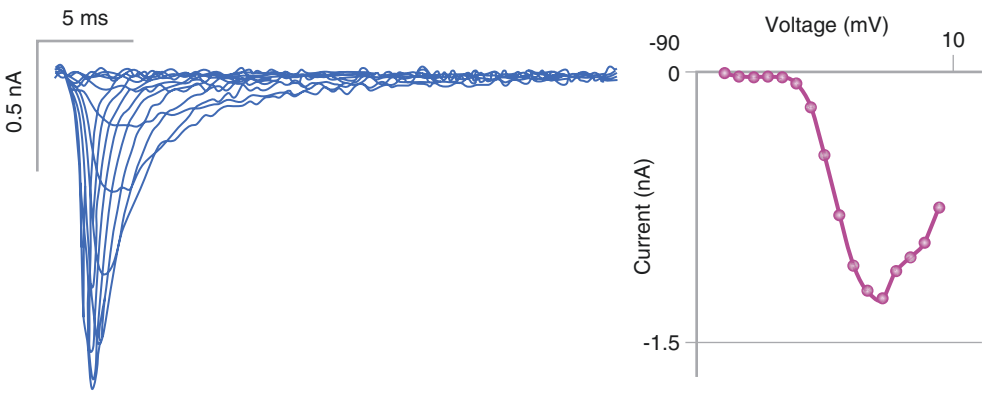


Fig. 1.4 *Left panel* (**a**): Na^+ currents during successive depolarizing voltage steps (test potentials). *Right panel* (**b**): Plot of Na^+ current recorded in nA (y-axis) at each test potential (mV), producing a current-voltage (I-V) curve

resulting in an equilibrium potential between those of Na^+ and K^+, at about −20 mV.

Voltage can also govern the closure of ion channels. Some channels, such as Na^+, transient outward K^+, and Ca^{2+} channels, switch to an inactive state with sustained depolarization (channel inactivation), which stops ion flux through the channel. Currents carried by these channels typically increase and then spontaneously decrease. In order for these channels to be "re-set" so they can be activated again by depolarization, they must first be returned to their resting closed state (recovery from inactivation). Channels that do not manifest inactivation (like the delayed rectifier channels) open in a time-dependent way, and do not close until the cell repolarizes to voltages at which opening is reversed back to the resting potential (deactivation) [3].

Another valuable concept is the phenomenon of rectification. Inward rectifiers conduct inward currents at voltages negative to their equilibrium potential more easily than outward currents at voltages positive to their equilibrium potential. Therefore, with progressive depolarization of the cell membrane, ion flow decreases through inward rectifiers. The most important inward rectifier in the heart is I_{K1}. The inwardly rectifying properties of I_{K1} are particularly important in preventing highly wasteful loss of K^+ from the cell interior during phases 0–2, when positive potentials produce a strong driving force for K^+ egress that would drive large amounts of K^+ out of the cell if I_{K1} permeability remained high.

Stages of the Cardiac AP

Phase 4: the Resting Membrane Potential

When the cardiac myocyte is resting, the outward I_{K1} current is most active, and K^+ ions slowly leak out of the cell in order to drive the membrane down to E_K (−90mv). The high I_{K1} conductance, along with the action of Na^+/K^+ ATPase to prevent the dissipation of the K^+ concentration gradient, keep the resting membrane potential stable at about −80 mV, unless a depolarization event occurs.

Phase 0: The Rapid Upstroke

The arrival of a depolarizing pulse, via propagation initiated by the cardiac pacemaker in the SAN, causes Na^+ channels to open. If the depolarization is large enough, i.e. reaches a threshold potential, Na^+ channels open and Na^+ ions flow down their concentration gradient into the cell, moving the membrane potential to more positive values. Rapid depolarization continues until the equilibrium potential for Na^+ is almost reached. After initial very rapid activation, Na^+-channels inactivate rapidly, contributing to termination of the AP upstroke. Na^+-channels then remain inactive until the membrane is repolarized, towards the end of phase 3, producing the absolute refractory period (Fig. 1.1).

The depolarization of the cell during phase 0 provides the large amount of energy needed for rapid conduction. The reduction of Na^+-current by antiarrhythmic drugs or Na^+-channel mutations leads to conduction slowing [5]. The electrocardiographic QRS duration reflects the time for the ventricles to be electrically activated, therefore ventricular conduction slowing is reflected by QRS prolongation.

Phase 1: Early Repolarization

The repolarizing notch that forms phase 1 of the AP is largely mediated by the transient outward current (I_{to}), primarily carried by a rapidly activating and inactivating K^+-channel. Phase 1 sets the membrane potential level for phase 2, thereby governing the degree of Ca^{2+} entry during the AP plateau [3]. Excessive dominance of I_{to} over opposing inward currents (especially residual I_{Na}) is important in the pathogenesis of J wave syndromes like the Brugada Syndrome [6], as detailed in Chap. 4.

Phase 2: The AP Plateau

A balance between inward current (mainly L-type Ca^{2+} current, I_{CaL}) and outward current (mainly I_{K1}, but also the delayed rectifiers I_{Kr} and I_{Ks} in the later stages of phase 2) maintains the AP plateau. The major role of the phase-2 inward Ca^{2+}-current is to produce Ca^{2+}-induced- Ca^{2+} release from the sarcoplasmic reticulum, i.e. the Ca^{2+} transient that leads to muscle contraction (see section "Contraction of Cardiac Myocytes"). Other inward currents include the late Na^+ current (INa_{-L}), which is believed to be a composite of delayed inactivation and re-opening of some Na^+ channels [2]. The Na^+-Ca^{2+} exchanger (NCX) contributes secondarily to the inward plateau current [7] since it is electrogenic: 3 Na^+ ions are transported into the cell, for every 1 Ca^{2+} ion exported out, leaving one net positive charge inside the cell. This is termed the "forward" mode of the NCX and is the usual direction of ion transport. Towards the end of phase 2, the inward currents begin to inactivate and the outward delayed rectifier currents, which are activated more slowly by depolarization become more prominent.

The QT interval on an ECG indicates the time from ventricular activation (QRS) to repolarization (T wave), and is an index of AP duration (APD). Imbalances between inward and outward currents during phase 2, can lead to pathological lengthening or shortening of the QT interval [8–11]. The pathophysiology of such syndromes is discussed in Chap. 4.

Phase 3: Repolarization

I_{Kr} is the major current directing repolarization during phase 3. I_{Ks} activates too slowly to play a major role during normal APs and its main role is as a "safety valve", increasing appreciably to prevent excessive AP-prolongation when repolarization is challenged (e.g. by APD-prolonging drugs or when I_{CaL} is enhanced by adrenergic stimulation). As the membrane potential repolarizes to below −20 mV, I_{K1} increases and contributes to late phase 3 as inward rectification is removed.

Contraction of Cardiac Myocytes

Ca^{2+}-Induced Ca^{2+} Release

The L-type Ca^{2+} channels are primarily located in the transverse tubules (T tubules), which are deep invaginations of the cardiomyocyte membrane (Fig. 1.5) [12]. T tubules are in close physical proximity to the sarcoplasmic reticulum (SR), the organelle that stores and releases intracellular Ca^{2+}. The SR has outpouchings, called junctional SR cisternae, which resemble flattened sacks reaching out towards the T-tubule extensions, in which are located clusters of ryanodine receptor Ca^{2+} release channels (RyRs) [13]. Ca^{2+} ions entering the cell can therefore quickly activate RyRs, causing a large release of Ca^{2+} from the SR into the cytoplasm, a process called "Ca^{2+}-induced- Ca^{2+} release" (CICR). The area of cytoplasm in which the T tubules and the SR come into close proximity is called the dyadic cleft.

Excitation-Contraction Coupling

The Ca^{2+} released into the cytosol by CICR binds to the myofilament protein regulator troponin-C [13]. Ca^{2+} binding to troponin-C causes a conformational change [14], followed by complex interactions with troponin-I, troponin-T and tropomyosin, exposing the myosin binding sites on actin and allowing cross-bridge cycling to take place [15].

The intracellular Ca^{2+} released during systole is removed from the cytoplasm during diastole, causing cardiac relaxation. The principal removal mechanisms are the Sarcoendoplasmic Reticulum Calcium ATPase (SERCA), which pumps Ca^{2+} back into the SR, and the NCX, which exports Ca^{2+} across the cell-membrane, Fig. 1.5).

Automaticity: The Cardiac Pacemakers

Cells with pacemaker activity spontaneously generate electrical signals. To do this, they depolarize automatically during phase 4 to the threshold potential required to initiate an AP (Fig. 1.6).

The intrinsic firing rate of roughly 60–75/min in the sinoatrial node (SAN) is faster than the other pacemaker regions (His-Purkinje system: 30–40/min, atrioventricular node (AVN) 40–50/min). The SAN is therefore the predominant pacemaker in the heart. The other regions possessing spontaneous automaticity act as back-up pacemakers, taking over if pacing fails in the SAN. There

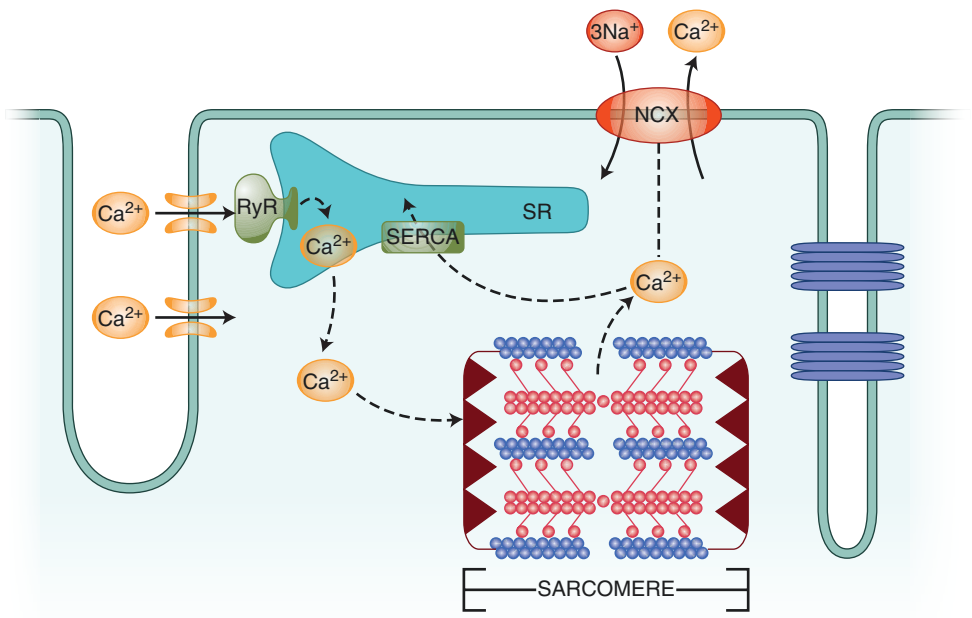


Fig. 1.5 Diagram of Ca^{2+}-induced Ca^{2+} release. L-type Ca^{2+} channels allow Ca^{2+} to activate ryanodine receptors in the dyadic cleft, triggering a larger release of Ca^{2+} into the cytoplasm. This Ca^{2+} causes contraction of the sarcomere. Ca^{2+} removal from the cytoplasm during diastole (via uptake into the SR by the SERCA pump and export from the cell via NCX) causes cardiac relaxation

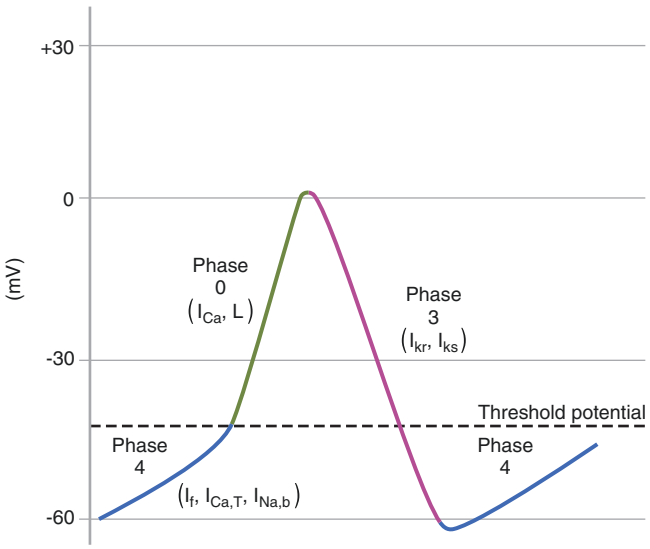


Fig. 1.6 Representative diagram of a spontaneous AP in the SAN

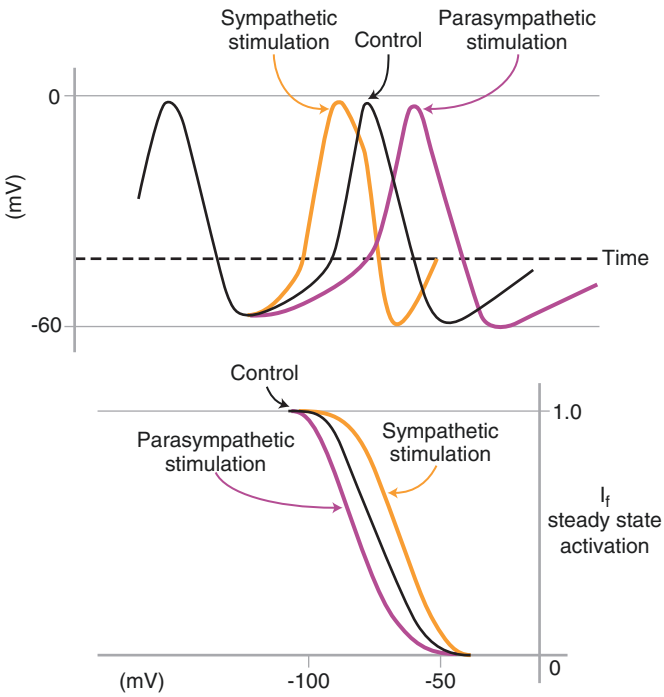


Fig. 1.7 *Top panel*: diagram showing the effect of the autonomic nervous system on the rate of phase 4 diastolic depolarization and therefore heart rate. *Bottom panel*: diagram showing the effect of the autonomic nervous system on the activation curves and therefore channel availability of HCN4 channels (I_f current). Adapted from [18]

are two principal mechanisms contributing to phase-4 diastolic depolarization, the membrane clock and the Ca^{2+} clock.

The Membrane Clock Model

The membrane clock involves a set of inward currents working together to depolarize the membrane to threshold. The best-known ion-channels involved in pacemaker activity are the hyperpolarization-activated cyclic nucleotide-gated channels (HCN channels), which underlie I_f [16]. Although these channels structurally resemble the K^+ channel superfamily, they are also permeable to Na^+ and to a lesser extent, Ca^{2+} [17]. At physiological voltages, Na^+ influx is greater than the outward K^+ current through HCN4 channels, which acts to gradually depolarize the cardiomyocyte to threshold as the I_f current.

The autonomic nervous system strongly regulates I_f. Sympathetic activation increases intracellular levels of cyclic AMP (cAMP), which binds to the cyclic-nucleotide binding domain at the C-terminus of the channel. Binding of cAMP to HCN4 causes a "rightward-shift" in the I_f activation curve, increasing the current flowing through the channel, and consequently the rate of phase-4 depolarization, at any given voltage (Fig. 1.7, *bottom*) which causes an increase in heart rate in response to sympathetic agonists (Fig. 1.7, *top*). The parasympathetic nervous system reduces the concentration of intracellular cAMP, causing a "leftward-shift" in the voltage-dependence of activation for I_f and a reduced phase-4 slope (Fig. 1.7).

Pathological loss of function of HCN4 can lead to the sick sinus syndrome [17]. Another poorly selective inward current has been described in rabbit, rat and guinea pig SAN cells, and flows despite I_f blockade with cesium [19]. This cation channel has its greatest permeability to Na^+ ions and has therefore been labeled as carrying the "background Na current" ($I_{Na,b}$) [17]. $I_{Na,b}$ is activated at −60 to −70 mV and has a peak current at about −50 mV, therefore is thought to work in synergy with the I*f* to achieve diastolic depolarization as part of the membrane clock [17]. Ca^{2+} channels also contribute to the membrane clock. L-type Ca^{2+} (Ca_v 1.2) channels activate at about −30 mV and therefore do not contribute to phase 4 of the SAN AP. However, another subfamily of voltage gated Ca^{2+} channels, T-type Ca^{2+} channels (Ca_v 3.1 and 3.2) are activated at roughly −60 mV [17] and therefore contribute to diastolic depolarization. The L-type Ca^{2+} channels present in SAN cells are primarily responsible for the phase 0 upstroke of the AP, therefore they determine SAN-cell threshold and automatic rate.

Additional ion channels are involved in regulating the membrane clock and diastolic depolarization under particular circumstances. I_{KACh} and I_{KATP} are inward-rectifier K^+ currents expressed in the SAN [17]. I_{KACh} channels open in response to acetylcholine release from vagal nerves, which activates muscarinic receptors in the SAN [20, 21]. The hyperpolarizing effect of acetylcholine reduces SAN pacing rate by moving diastolic potentials further from threshold [22]. I_{KATP} similarly hyperpolarizes the myocyte

membrane and is activated in response to reduced intracellular ATP levels, as occurs in myocardial ischaemia and hypoxia [23].

The Ca^{2+} Clock Model

Spontaneous SR Ca^{2+} release produces Ca^{2+} sparks or waves [24], which can propagate throughout the cell. Such Ca^{2+} sparks and waves near the edge of rabbit SAN myocytes produce Ca^{2+} transients that precede the SAN AP (Fig. 1.8). The released Ca^{2+} is extruded through the NCX, which carries a depolarizing inward current when removing Ca^{2+} from the cell. This inward current depolarizes the cell and contributes to SAN phase 4 depolarization. Suppressing Ca^{2+} sparks and waves decreases the slope of diastolic depolarization, particularly later in phase 4, and inhibits spontaneous SAN firing [25]. The automatic mechanism resulting from inward NCX-current resulting from spontaneous SAN Ca^{2+} release is called the "Ca^{2+} clock".

While Ca^{2+} sparks and resultant inward current oscillations via NCX can occur in the absence of APs, they dissipate over time without APs, which act to cyclically regulate cellular Ca^{2+} stores needed to maintain the Ca^{2+} clock. Thus, the membrane clock and the Ca^{2+} clock act co-dependently to achieve spontaneous diastolic depolarization and maintain automaticity.

Other Currents

Other currents may also contribute to SAN function. For example, there is evidence that the intermediate-conductance Ca^{2+}-activated K^+ channel ($K_{Ca}3.1$) may be important for SAN membrane depolarization upon initial Ca^{2+} entry/release [17]. This effect might contribute to maintaining membrane-voltage cycling between negative values (in the absence of significant SAN I_{K1}) and more positive values due to membrane and/or Ca^{2+} clock-induced depolarization.

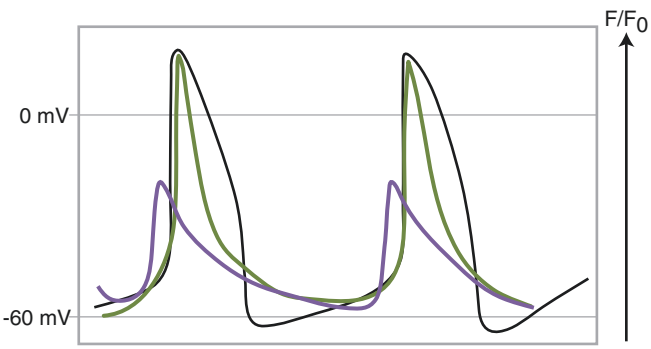


Fig. 1.8 Superimposed AP plots (*black line*) upon Ca^{2+} fluorescence transients measured by confocal microscopy in rabbit sinoatrial nodal cells. The *purple line* indicates the Ca^{2+} transient measured towards the edge of the cells, which precedes the major Ca^{2+} transient produced during phase 2 of the AP (green line). Adapted from [25]

Cardiac Conduction

SAN pacemaker activity initiates the cardiac impulse. The wave of depolarization travels through the atria, likely via organized strands of cardiomyocytes called the internodal pathways, since the three bundles track anteriorly, medially and posteriorly to the atrioventricular node (AVN). The anterior internodal pathway branches to form Bachmann's bundle, which crosses to the left atrium [26]. From these preferential conduction pathways, myocardial depolarization spreads more slowly through the remainder of the atrium. Atrial activation corresponds to the electrocardiographic P-wave.

Once the depolarizing impulse reaches the AVN, the wave of depolarization traverses slowly to reach the cable-like His-Purkinje system (Fig. 1.9) before spreading to the ventricles. This delay allows adequate time for ventricular filling after atrial contraction, before ventricular systole begins. The P-R interval represents the time for conduction to spread between the SAN and the ventricles.

After the depolarizing impulse has passed through the AVN, it travels via the bundle of His in the interventricular septum to the bundle branches and the Purkinje network, and from there spreads to activate the ventricles and produce the QRS complex. Finally, ventricular repolarization occurs, corresponding to the T-wave on the ECG.

Unlike APs in the working atria and ventricles/His-Purkinje system, the APs of the SAN and AVN have depolarized resting potentials; slow phase-0 upstrokes mediated by Ca^{2+} currents and delayed recovery of excitability governed by slow Ca^{2+} current recovery kinetics. Accordingly, the 2 types of APs are referred to as "fast-channel" (in working atria-ventricles/His-Purkinje system) and "slow-channel" (in SAN and AVN). The slower recovery kinetics of the Ca^{2+} channel and the resultant prolonged refractory period in the AVN allows the AVN to protect the ventricles against rapid conduction of supraventricular tachyarrhythmias. The main differences between fast and slow-channel APs are summarized in Table 1.1.

The AVN has a complex 3-dimensional structure. The core of the AVN is composed of pure slow-channel tissue ("N"-cells), while towards the atrial and ventricular ends, transitions are seen towards more "atrial-like" (AN) and "ventricular-like" (NH) APs. Mutations in SCN5A, the principal gene encoding Na^+ channels, can slow AVN conduction in humans by virtue of transitional AVN cells that possess significant Na^+ current [27].

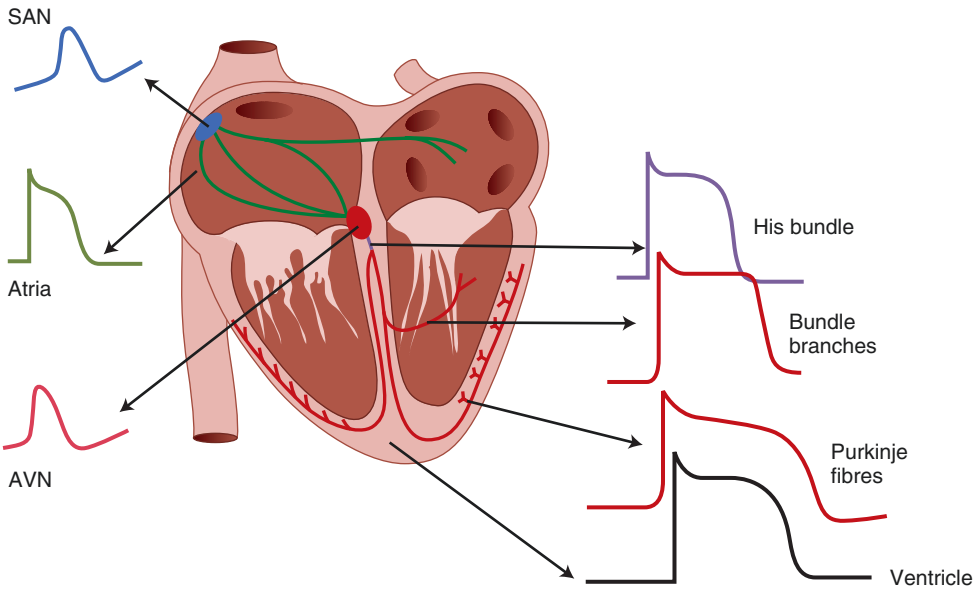


Fig. 1.9 Diagram of the principal components of the cardiac conduction system and their corresponding APs. Sinoatrial node (*blue*), internodal pathways and Bachmann's bundle (*green*), atrioventricular node (*red*), bundle of His (*purple*), bundle branches and purkinje fibres (*red*)

Table 1.1 Summary of the key differences between fast and slow-type APs.

	Fast-channel AP	Slow-channel AP
Phase 0 Conduction mediated by	Na^+ channels	Ca^{2+} channels
Activation	Fast	Fast
Recovery	Slow	Slow
Refractoriness determined by	AP Duration	Ca^{2+} channel recovery time

The N cells are the principal pacemaker cells within the AVN, and exhibit typical slow-channel AP morphology. N cells have a relatively positive diastolic membrane potential due to a very low density of I_{K1} [28], favoring pacemaker activity that allows the AVN to act as an "escape" pacemaker if the SAN fails. N cells also possess significant expression of a second isoform of L-type Ca^{2+} channels, Ca_v 1.3 channels, as opposed to the Ca_v 1.2 isoform found in atrial and ventricular myocytes [29, 30]. Ca_v 1.3 channels have a more negative activation potential than Cav 1.2 channels, and can activate towards the end of phase 4 to facilitate AVN automaticity. Ca_v 3.1, encoding the alpha-subunit of T-type Ca^{2+} channels, is also highly expressed in the AVN and contributes to automaticity [30].

Cell-Cell Coupling

The atrial and ventricular myocytes are connected to each other so that the wave of depolarization can rapidly spread throughout the myocardium as a functional syncytium and allow the heart to contract in a coordinated manner. The specialised area connecting myocytes electrically is called the intercalated disc. Three principal structures make up the intercalated disc: (1) adherins junctions, which provide anchoring sites for actin/sarcomeres, (2) desmosomes, structural proteins that bind cells together and (3) gap junctions; conduits between cells that contain cylindrical connexons joining cells, each connexon being composed of six interlinked connexin molecules [31]. Each connexin molecule is a hemichannel that connects to another connexin molecule in an adjacent cell, to form a low-resistance water-filled pore between the cells through which a propagating cardiac impulse can easily travel.

There are different isoforms of connexins within the myocardium. The ventricles primarily contain Cx43; the atria, a combination of Cx40 and Cx43; the AVN contains Cx45 and possibly Cx31.9; the Purkinje system Cx40, Cx43 and Cx45. Connexons can form with the same isoform (homotypic) or a mixture of isoforms (heterotypic). *D*isruption of gap junction number or distribution, or gap junction dysfunction, impairs cardiac conduction and predisposes to arrhythmia.

Connexins interact with other molecules within the intercalated disc, especially with desmosomal proteins, regulatory proteins and ion channels, forming macromolecular complexes that coordinate electrical propagation within the syncytium [32]. For example, Cx43 and the principal Na^+ channel isoform $Na_v1.5$ colocalise in the intercalated disc [33]. Desmosomal proteins also have important regulatory roles. For example, a reduction in the desmosomal protein plakophilin-2 significantly reduces Na^+ current at the intercalated disc [34]. It is therefore not only connexins that allow electrical propagation within the syncytium, but the coordinated interaction of several proteins within the intercalated disc.

Arrhythmogenesis

Arrhythmogenesis can be broadly divided into two categories: (1) reentry, in which a propagating impulse persists by continuous re-excitation in a re-entrant pathway, and (2) abnormal impulse formation, which can be subdivided into abnormal automaticity and triggered activity (Fig. 1.10).

Abnormal Automaticity

Abnormal automaticity encompasses enhanced automaticity in pacemaker tissue, or the generation of spontaneous activity in atrial or ventricular myocytes that do not normally spontaneously depolarize. Examples of arrhythmias caused by abnormal automaticity are focal atrial tachycardia, nonparoxysmal junctional tachycardia and accelerated idioventricular rhythm [35]. Abnormal automaticity is generally observed in situations creating a more positive resting membrane potential, which allows phase 4 diastolic depolarization to reach threshold faster.

Afterdepolarizations and Triggered Activity

Afterdepolarizations can be early (EADs) or delayed (DADs). They are transient depolarizations occurring during phases 2 or 3 of the AP (EADs) or following full repolarization in phase 4 (DADs). When the amplitude of afterdepolarizations is sufficient to bring the membrane potential to threshold, spontaneous APs known as triggered beats or triggered activity can occur.

Early Afterdepolarizations (EADs)

EADs occur when the AP is prolonged by a decrease in outward currents or an increase in inward currents. This can result in the reactivation of the L-type Ca^{2+} channel current ($I_{Ca,L}$), since L-type Ca^{2+} channels have a significant overlap between the activation and inactivation vs. voltage curves between potentials of about −30 mV and 0 mV, providing a voltage-range in which there is steady-state depolarizing inward Ca^{2+}-current (the so-called "window current", Fig. 1.11) [36]. The window-current voltage range corresponds to the AP plateau, therefore if the AP plateau is sufficiently prolonged, L-type Ca^{2+} channels can recover from inactivation and subsequently re-activate [37], causing an EAD.

Prolonged repolarization can be achieved by: [1]

1. Inhibiting I_{Ks} and I_{Kr} (e.g. Long QT syndrome Type 1 and 2 respectively, ion-current remodelling in heart failure, and with class Ia and III antiarrhythmic drugs).
2. Increasing the availability/amplitude of $I_{Ca,L}$ (e.g. sympathetic nervous system activation).
3. Increased NCX (e.g. with increased intracellular Ca^{2+} or NCX upregulation as in heart failure).
4. Increased late Na^{+} current (e.g. Long QT syndrome Type 3).

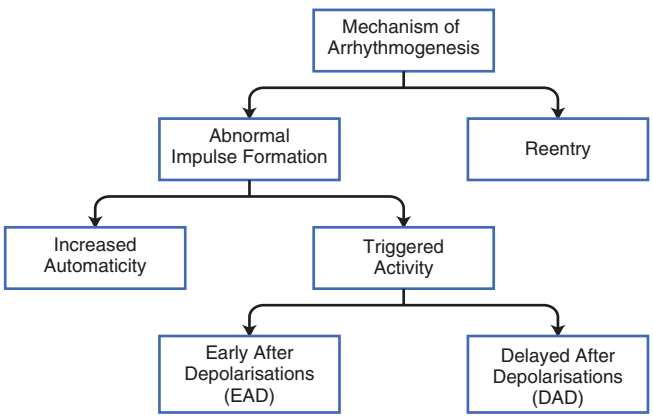


Fig. 1.10 Classification of arrhythmogenic mechanisms

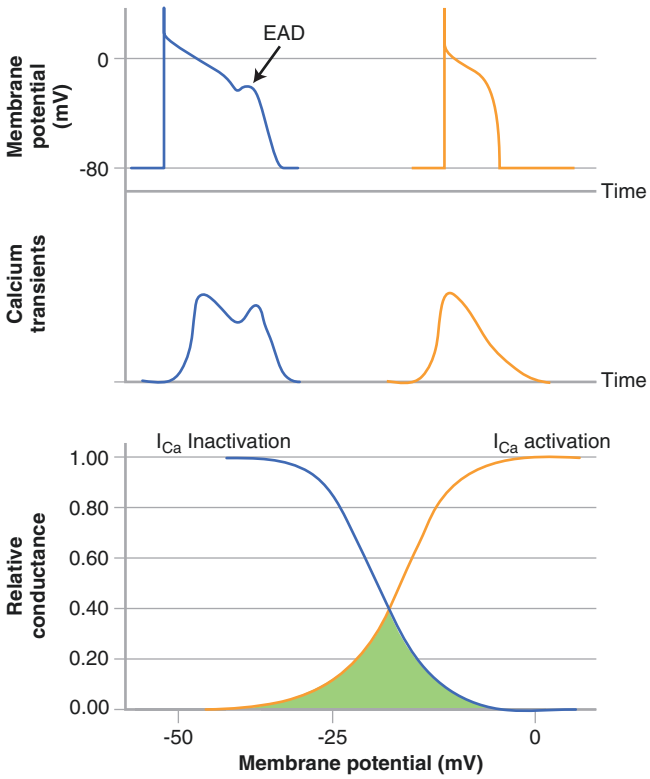


Fig. 1.11 *Top panel*: Diagram of an early afterdepolarization formed during a prolonged AP and the corresponding reactivation of Ca^{2+} depicted below it. To the right is a normal AP, with a single Ca^{2+} transient i.e. no reactivation of the Ca^{2+} current is present. *Bottom panel*: Superimposed activation and inactivation curves for the Ca^{2+} current. The overlapping area shows the window current. Adapted from [2]

EADs preferentially occur in the His-Purkinje system, depolarizing adjacent atrial or ventricular muscle to the threshold for Na^+ channel activation, which in turn can cause triggered beats and tachyarrhythmias.

Delayed Afterdepolarizations (DADs)

DADs are caused by abnormal diastolic release of Ca^{2+} from the SR via RyRs [38, 39]. The released Ca^{2+} is extruded from the cell by NCX, with each Ca^{2+} ion exchanged for 3 extracellular Na^+ ions, producing a net inward current that depolarizes the membrane and causes the DAD [38, 39]. DADs that reach threshold cause premature beats, which can occur singly, can trigger reentry in a vulnerable substrate, and can occur in repetition causing a focal tachyarrhythmia. Arrhythmias induced by DADs include catacholaminergic polymorphic ventricular tachycardia (CPVT), paroxysmal atrial tachycardia, fascicular tachycardia and the bidirectional VT that can be seen in digoxin toxicity [35].

Reentry

Anatomical Reentry

The simplest form of reentry is *circus movement reentry*, in which a cardiac impulse travels in a circuit around a fixed anatomical barrier (Fig. 1.12). In the left panel of the figure, the excitatory wave front travels anterogradely (the usual direction of conduction) down both pathways B and C, and clashing wave fronts cancel each other out. In the right panel, a premature impulse arrives at pathway C when it is refractory from the prior sinus beat, whereas pathway B (which has a shorter refractory period) has recovered excitability and can conduct the impulse. After reaching the distal end of pathway B, the impulse can travel retrogradely up pathway C. If this wavefront is timed in such a manner that when it reaches the beginning of the circuit again and pathway B is no longer refractory, the same wavefront can travel anterogradely down pathway B again, and continue travelling repetitively in a circuitous manner, as long as the tissue ahead of the advancing wavefront has recovered its refractoriness at all points in the circuit.

Examples of this type of reentry around an anatomical obstacle include the supraventricular tachycardias: atrioventricular reentry tachycardia (AVRT), involving a congenital accessory pathway and atrioventricular nodal reentry tachycardia (AVNRT), in which separate pathways exist within the AVN node and form a potential reentry circuit analogous to the circus movement (ring) model of reentry. Experimental atrial flutter is also an example of anatomical reentry, in which the tricuspid annulus forms the anatomical obstacle. Clinical atrial flutter does not appear to involve an anatomical obstacle.

Certain conditions are needed for this form of reentry to occur. For the propagation to continue, there must always be a portion of the circuit ahead of the moving wavefront that

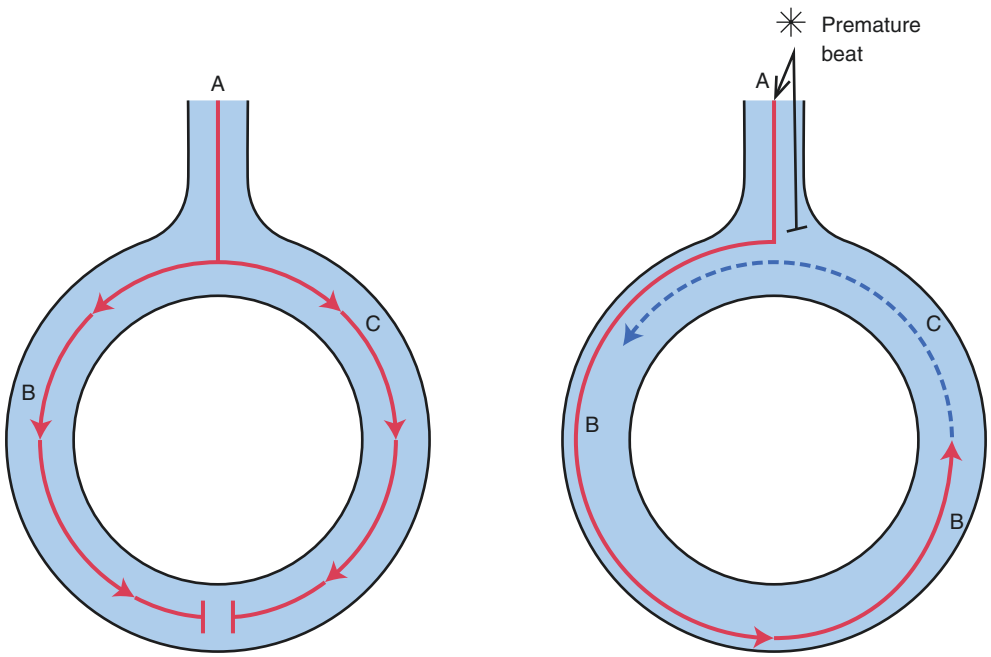


Fig. 1.12 *Left*: diagram showing a cardiac impulse anterogradely propagating down two converging pathways and colliding. *Right*: Reentrant activity as a result of a premature impulse encountering a recovered pathway (*B*) and a pathway (*C*) that is still refractory from the previous sinus beat. The premature impulse conducts anterogradely down pathway *B* and retrogradely up pathway *C* when it has recovered excitability and can continue to propagate around both pathways provided the tissue ahead of the advancing wavefront has recovered its refractoriness

has recovered its excitability, allowing the wavefront to advance. This segment of the circuit is called the *excitable gap* (Fig. 1.13 *left*). The entire length of the circuit (path-length) must equal or exceed the *wavelength*, which is the refractory section of the circuit occupied by the wavefront. Because the wavelength is the distance travelled by a cardiac impulse in one refractory period, it is the shortest distance that can maintain reentry. In mathematical terms, the wavelength is calculated as:

Wavelength = Conduction Velocity × Refractory Period.

Functional Reentry

Reentry can occur in the absence of an anatomical obstacle, on a strictly functional basis. In the 1970s, Allessie *et al.* [41] developed a theory called "the leading circle" (Fig. 1.13, *right*) to account for functional reentry. The authors showed that premature stimuli preferentially travelled in the direction of shorter refractory periods, which led to an arc of refractory tissue, around which a propagating wave front could circulate in the form of reentry. The tissue in the centre of the circle is kept functionally refractory by continuously invading centripetal waves and keeps them from propagating through and interrupting the circulating wavefront. The size of the reentry circuit is determined by the wavelength, because functional reentry naturally establishes itself in the fastest/smallest circuit possible, which has a dimension equal to the wavelength [41]. An advantage of this model is the ability to relate its determinants to familiar and clinically quantifiable concepts also used to describe circus movement reentry such as conduction velocity, refractory period, wavelength and excitable gap. According to the leading circle theory, the persistence of AF depends on the wavelength being reduced so that it is short enough to allow multiple simultaneous reentry circuits to coexist and make AF very stable [42]. Antiarrhythmic drugs stop AF by increasing the wavelength [42].

A problem with the leading circle model is that it fails to account for some important clinical phenomena. For example, in many AF patients and experimental AF models, the wavelength is not reduced and yet AF occurs [43]. In addition, according to the leading circle model, Na^+ channel blocking antiarrhythmic drugs should promote AF by slowing conduction and reducing the wavelength; yet clinically

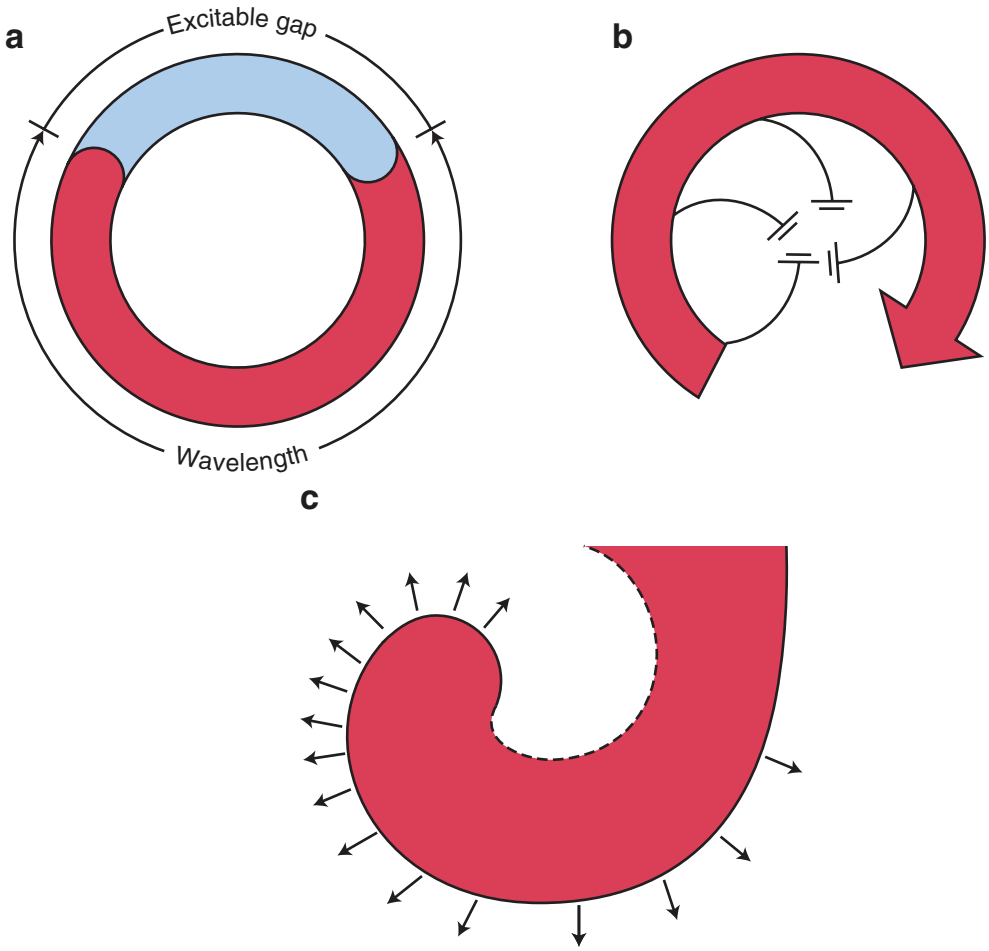


Fig. 1.13 *Left*: Circus movement re-entry (ring model), showing the presence of an excitable gap which is necessary for wave propagation. *Right*: The leading circle model of re-entry. An arc of refractory tissue occurs due to interacting wavefronts. *Bottom*: Spiral wave or rota. The *solid line* represents the depolarizing wave front and the *dashed line* the repolarizing front. Adapted from [40]

they clearly suppress AF [44]. An alternative model of functional reentry is based on the notion of the spiral wave (Fig. 1.13, *bottom*) [40].

The spiral-wave (or "rotor") concept governs reentry-type activity in many systems; a naturally occurring example being a tropical storm (hurricane, typhoon, cyclone) or a spinning top. The persistence of rotational activity depends on the stability of the reentry source, which is governed by the ability of the re-entrant wavefront to constantly propagate through the medium. The ability to propagate depends on the energy of the propagating force, roughly reflected by the speed and tightness of its angular rotation, and the resistance of the medium in front of it to activation, reflected by the amount of energy needed for activation. In cardiac tissue, the rotational "force" is related to the balance between the driving current (generally Na^+ current, the current source), and the resistance to activation, also called the current sink. The current sink is primarily determined by tissue excitability, of which refractoriness is a major determinant.

The analogy of a spinning top can be used to conceptualise rotors. If a spinning top spins quickly, it remains stable. As it begins to slow, its oscillations become larger and it begins to meander and eventually topples over and stops. This helps to understand how reducing the energy and speed of propagation (e.g. by Na^+ channel blockers) can stop reentry maintained by rotors. On the other hand, if the position of a top is stabilized (e.g. by putting a hole in the table which anchors it) it can maintain itself at slower speeds. This may be analogous to the anchoring effect of structural complexities, like tissue fibrosis, that may help to anchor and stabilize AF-maintaining rotors.

The spiral-wave rotor concept is much more successful in accounting for the effects of antiarrhythmic drugs in AF than the leading circle model [40, 44, 45]. In addition, when functional reentry is observed with very high-resolution optical mapping, it takes the form of a spiral wave. Finally, recent technological developments have allowed for the high-resolution mapping of AF in conscious patients, and have provided strong evidence for the existence and presence of rotor activity during AF maintenance in patients [46–49].

Conclusion

This chapter has covered the basics of action potential formation, excitation-contraction coupling of cardiac myocytes, automaticity, cardiac conduction and arrhythmogenesis. The intention is for readers to use this information as a basic reference, upon which to build the more detailed knowledge contained in subsequent chapters.

Acknowledgments The authors would like to thank Dr. Charles Pearman from The University of Manchester for kindly providing the material used to make Fig. 1.4.

References

1. Grant A, Carboni M, Antzelevitch C, Burashnikov A. Cardiac arrhythmia: mechanisms, diagnosis, and management. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2001.
2. MacLeod K. An essential introduction to cardiac electrophysiology. 1st ed. London: Imperial College Press; 2014.
3. Grant AO. Cardiac ion channels. Circ Arrhythm Electrophysiol. 2009;2(2):185–94.
4. Zipes D, Jalife J. Cardiac electrophysiology: from cell to bedside. 6th ed. Philadelphia: Elsevier; 2014.
5. Papadatos GA, Wallerstein PM, Head CE, et al. Slowed conduction and ventricular tachycardia after targeted disruption of the cardiac sodium channel gene Scn5a. Proc Natl Acad Sci U S A. 2002;99(9):6210–5.
6. Antzelevitch C, Yan GX. J-wave syndromes: Brugada and early repolarization syndromes. Heart Rhythm. 2015;12(8):1852–66.
7. Whalley DW, Wendt DJ, Grant AO. Basic concepts in cellular cardiac electrophysiology: part I: ion channels, membrane currents, and the action potential. Pacing Clin Electrophysiol. 1995;18(8):1556–74.
8. Huang FD, Chen J, Lin M, Keating MT, Sanguinetti MC. Long-QT syndrome-associated missense mutations in the pore helix of the HERG potassium channel. Circulation. 2001;104(9):1071–5.
9. Lupoglazoff JM, Denjoy I, Berthet M, et al. Notched T waves on holter recordings enhance detection of patients with LQt2 (HERG) mutations. Circulation. 2001;103(8):1095–101.
10. Brugada R, Hong K, Dumaine R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation. 2004;109(1):30–5.
11. Gaita F, Giustetto C, Bianchi F, et al. Short QT syndrome: a familial cause of sudden death. Circulation. 2003;108(8):965–70.
12. Pfeiffer ER, Tangney JR, Omens JH, McCulloch AD. Biomechanics of cardiac electromechanical coupling and mechanoelectric feedback. J Biomech Eng. 2014;136(2):021007.
13. Bers DM. Cardiac excitation-contraction coupling. Nature. 2002;415(6868):198–205.
14. Kobayashi T, Solaro RJ. Calcium, thin filaments, and the integrative biology of cardiac contractility. Annu Rev Physiol. 2005;67:39–67.
15. Gordon AM, Homsher E, Regnier M. Regulation of contraction in striated muscle. Physiol Rev. 2000;80(2):853–924.
16. Garcia-Frigola C, Shi Y, Evans SM. Expression of the hyperpolarization-activated cyclic nucleotide-gated cation channel HCN4 during mouse heart development. Gene Expr Patterns. 2003;3(6):777–83.
17. Weisbrod D, Khun SH, Bueno H, Peretz A, Attali B. Mechanisms underlying the cardiac pacemaker: the role of SK4 calcium-activated potassium channels. Acta Pharmacol Sin. 2016;37(1):82–97.
18. DiFrancesco D. Funny channels in the control of cardiac rhythm and mode of action of selective blockers. Pharmacol Res. 2006;53(5):399–406.
19. Hagiwara N, Irisawa H, Kasanuki H, Hosoda S. Background current in sino-atrial node cells of the rabbit heart. J Physiol. 1992;448:53–72.
20. Krapivinsky G, Gordon EA, Wickman K, Velimirovic B, Krapivinsky L, Clapham DE. The G-protein-gated atrial K+ channel IKACh is a heteromultimer of two inwardly rectifying K(+)-channel proteins. Nature. 1995;374(6518):135–41.
21. Wickman K, Krapivinsky G, Corey S, et al. Structure, G protein activation, and functional relevance of the cardiac G protein-gated K+ channel, IKACh. Ann N Y Acad Sci. 1999;868:386–98.
22. DiFrancesco D, Ducouret P, Robinson RB. Muscarinic modulation of cardiac rate at low acetylcholine concentrations. Science. 1989;243(4891):669–71.

23. Tamargo J, Caballero R, Gomez R, Valenzuela C, Delpon E. Pharmacology of cardiac potassium channels. Cardiovasc Res. 2004;62(1):9–33.
24. Stern MD, Capogrossi MC, Lakatta EG. Spontaneous calcium release from the sarcoplasmic reticulum in myocardial cells: mechanisms and consequences. Cell Calcium. 1988;9(5–6):247–56.
25. Bogdanov KY, Vinogradova TM, Lakatta EG. Sinoatrial nodal cell ryanodine receptor and na(+)-ca(2+) exchanger: Molecular partners in pacemaker regulation. Circ Res. 2001;88(12):1254–8.
26. van Campenhout MJ, Yaksh A, Kik C, et al. Bachmann's bundle: a key player in the development of atrial fibrillation? Circ Arrhythm Electrophysiol. 2013;6(5):1041–6.
27. Dobrzynski H, Anderson RH, Atkinson A, et al. Structure, function and clinical relevance of the cardiac conduction system, including the atrioventricular ring and outflow tract tissues. Pharmacol Ther. 2013;139(2):260–88.
28. Hancox J, Yuill K, Mitcheson J, Convery M. Progress and gaps in un- derstanding the electrophysiological properties of morphologically normal cells from the cardiac atrioventricular node. Int J Bifurcat Chaos. 2003;13:3675–91.
29. Greener ID, Tellez JO, Dobrzynski H, et al. Ion channel transcript expression at the rabbit atrioventricular conduction axis. Circ Arrhythm Electrophysiol. 2009;2(3):305–15.
30. Greener ID, Monfredi O, Inada S, et al. Molecular architecture of the human specialised atrioventricular conduction axis. J Mol Cell Cardiol. 2011;50(4):642–51.
31. Li J. Alterations in cell adhesion proteins and cardiomyopathy. World J Cardiol. 2014;6(5):304–13.
32. Meens MJ, Kwak BR, Duffy HS. Role of connexins and pannexins in cardiovascular physiology. Cell Mol Life Sci. 2015;72(15):2779–92.
33. Desplantez T, McCain ML, Beauchamp P, et al. Connexin43 ablation in foetal atrial myocytes decreases electrical coupling, partner connexins, and sodium current. Cardiovasc Res. 2012;94(1):58–65.
34. Sato PY, Musa H, Coombs W, et al. Loss of plakophilin-2 expression leads to decreased sodium current and slower conduction velocity in cultured cardiac myocytes. Circ Res. 2009;105(6):523–6.
35. Shu J, Zhou J, Patel C, Yan GX. Pharmacotherapy of cardiac arrhythmias—basic science for clinicians. Pacing Clin Electrophysiol. 2009;32(11):1454–65.
36. Hirano Y, Moscucci A, January CT. Direct measurement of L-type Ca2+ window current in heart cells. Circ Res. 1992;70(3):445–55.
37. January CT, Riddle JM. Early afterdepolarizations: mechanism of induction and block. A role for L-type Ca2+ current. Circ Res. 1989;64(5):977–90.
38. Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev. 2007;87(2):425–56.
39. Bers DM. Cardiac sarcoplasmic reticulum calcium leak: basis and roles in cardiac dysfunction. Annu Rev Physiol. 2014;76:107–27.
40. Comtois P, Kneller J, Nattel S. Of circles and spirals: bridging the gap between the leading circle and spiral wave concepts of cardiac reentry. Europace. 2005;7(Suppl 2):10–20.
41. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. the "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res. 1977;41(1):9–18.
42. Rensma PL, Allessie MA, Lammers WJ, Bonke FI, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res. 1988;62(2):395–410.
43. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation. 1999;100(1):87–95.
44. Aguilar M, Nattel S. The past, present, and potential future of sodium channel block as an atrial fibrillation suppressing strategy. J Cardiovasc Pharmacol. 2015;66(5):432–40.
45. Kneller J, Kalifa J, Zou R, et al. Mechanisms of atrial fibrillation termination by pure sodium channel blockade in an ionically-realistic mathematical model. Circ Res. 2005;96(5):e35–47.
46. Kalifa J, Jalife J, Zaitsev AV, et al. Intra-atrial pressure increases rate and organization of waves emanating from the superior pulmonary veins during atrial fibrillation. Circulation. 2003;108(6):668–71.
47. Cuculich PS, Wang Y, Lindsay BD, et al. Noninvasive characterization of epicardial activation in humans with diverse atrial fibrillation patterns. Circulation. 2010;122(14):1364–72.
48. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial. J Am Coll Cardiol. 2012;60(7):628–36.
49. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation. 2014;130(7):530–8.

Pathophysiology of Atrial Fibrillation

2

Alexander Burashnikov and Charles Antzelevitch

Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in the clinic. It is often associated with hemodynamic and neurohormonal cardiovascular abnormalities, including heart failure (HF), hypertension, valvular and ischemic heart disease. These derangements cause or promote the development of AF triggers and atrial remodeling giving rise to the arrhythmogenic substrate. Rapid activation of the atria during AF leads to further electrical and structural remodeling, thus facilitating the maintenance of AF. For his reason, AF is said to beget-AF. Pulmonary veins are the prime source for AF trigger(s) and may also be the source for AF drivers. Pulmonary vein sleeves are thin muscular structures and as such are sensitive to pressure and volume overload-induced stretch, which may account for their exceptional arrhythmogenic proclivity. Long-term maintenance of AF is believed to be due largely to a reentrant mechanism(s), but direct evidence is often lacking and the controversy continues. The development and maintenance of AF are multifactorial and involve dynamic pathophysiologic processes which are in many cases not well defined or understood. This chapter reviews our current understanding of pathophysiology of AF.

Keywords

Atrial remodeling • Pathophysiology • Electrophysiology • Pharmacology

Introduction

Atrial fibrillation (AF) is the most commonly encountered clinical arrhythmia. Its prevalence increases with age and cardiovascular diseases, including heart failure (HF), hypertension, valvular and ischemic heart disease [1, 2]. These disorders as well as AF itself promote atrial remodeling which facilitates the perpetuation of the arrhythmia. AF may cause and be caused by atrial remodeling. Pathophysiological mechanisms responsible for the initiation and maintenance of AF are multifactorial and dynamic. This chapter reviews our current understanding of the complexities attending the pathophysiology of AF.

Disclosures: Dr. Antzelevitch was a consultant for Gilead Sciences and received funding from Gilead Sciences and Buchang Pharmaceuticals.

A. Burashnikov, Ph.D., F.H.R.S.
Research Associate Professor, Lankeneau Institute for Medical Research, 100 East Lancaster Avenue, Wynnewood, PA 19096, USA
e-mail: burashnikov63@gmail.com

C. Antzelevitch, PhD, FACC, FHRS, FAHA (✉)
Cardiovascular Research, Lankenau Institute for Medical Research, Lankenau Heart Institute, Wynnewood, PA 19096, USA
e-mail: cantzelevitch@gmail.com

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_2

Conditions and Diseases That Affect AF Generation

The occurrence of AF is commonly associated with other diseases and conditions. The risk factors for AF include aging, hypertension, HF, ischemic heart disease, valvular heart disease, cardiomyopathies, obesity, diabetes mellitus, chronic obstructive pulmonary disease, sleep apnea, renal disease, hyperthyroidism and inflammation. These risk factors for development of AF are often found in combinations and the specific causal relation of AF with each remains poorly defined [1, 2].

Age is one of the strongest predictors of AF. The prevalence of AF, 1–2% in the general population, increases with age, from <0.5% at ≤50 years to up to 12% at >80 years of age [1, 2]. This trend is associated with an increase in the prevalence of diseases known to promote AF, particularly hypertension, HF, and ischemic heart disease. Age-related increase in the number and/or severity of these diseases accounts for much of the age-related increase in the prevalence of AF. Aging may promote AF via age-related structural remodeling of the atria, largely due to progressive increases in the degree of fibrosis. However, significant age-mediated atrial remodeling appears to take place only in the eighth decade of life, but not before [3], and may be associated with subclinical cardiovascular disease.

Hypertension is the most prevalent disease associated with the development AF. Fifty-seven percent of patients with AF have a history of hypertension [4, 5]. History of valvular and ischemic heart diseases are present in about 30 and 20% of patients with AF, respectively [1].

Genetics can predispose to development of AF, but the incidence of AF caused purely by genetic defects is relatively small. The majority of people with AF are older than 60 years of age; those who have AF at a younger age commonly have disease conditions that promote AF, largely hypertension but including short QT, Brugada and Early repolarization syndromes [6, 7].

HF can cause AF and AF can aggravate HF, creating a vicious cycle. About 30–40% of patients with HF have AF. The prevalence of AF depends on the underlying etiology of heart failure. Patients with valvular heart disease and hypertension as the primary etiologies of HF have a high prevalence of AF (30–50%) and patients with ischemic heart disease as the primary HF etiology display a lower AF prevalence (15–25%) [8, 9]. About 20–25% of patients with idiopathic dilated cardiomyopathy have AF [5]. AF may cause HF via sustained rapid and irregular ventricular rate. AF is thought to be a principal cause of HF in about 3% of patients with reduced left ventricular ejection fraction (LVEF) and in up to 17% of patients with preserved LVEF [10]. Counter-intuitively, the prevalence of AF decreases in patients with lower LVEF [8, 11–15].

Sustained AF may occur without detectable cardiovascular abnormalities, in which case it is referred to as idiopathic or lone AF. In the past, the prevalence of "lone AF" was estimated to account for 30% of AF cases [5]. It is becoming increasingly clear, however, that most "lone AF" patients have some cardiovascular abnormality, including LV diastolic dysfunction and/or concealed coronary artery disease, so that the prevalence of truly "lone AF" is currently estimated to be about 3% [16].

A robust unifying feature of the diseases that are most often associated with AF is concomitant hemodynamic and neurohormonal derangements.

Pathophysiology of AF Initiation: Triggers and Substrate

Initiation of AF generally requires both a trigger and substrate. AF is commonly initiated by an atrial premature excitation (i.e., AF trigger). Substrate of AF consists largely of electrical heterogeneity, mainly spatial ERP difference. Pressure and volume overload produces stretch of the atrium, which is known to generate arrhythmic activity [17]. Abnormalities in autonomic nervous system function can also induce premature atrial activation [18]. A combination of hemodynamic and neurohormonal derangements strongly enhances the manifestation of atrial premature activations. Abnormalities in intracellular calcium (Ca_i) appear to be principally involved in the triggering of AF in the setting of hemodynamic and neurohormonal derangements [18–20].

The most common source of AF triggers is the pulmonary veins (PV) [21]. The thin structure of the PVs is thought to predispose them to pressure and volume overload-induced stretch, accounting for their exceptional arrhythmogenicity. The level of involvement of PV in AF can change during progression of atrial remodeling. The rate of electrical activation of PV during AF is reported to be reduced with left atrial dilatation and reduced LVEF [22]. Such slowing of activation rate in PV is likely to be explained by an accentuation of atrial structural remodeling. It is generally believed that PV is less likely to be involved in the generation of AF in the setting of more advanced structural remodeling. In a canine model of systolic HF, the development of advanced HF is associated with severe fibrosis giving rise to major depression of PV areas, preventing the occurrence of rapid activity [23]. Involvement of PV in the generation of AF in patients with mild vs. advanced HF is poorly defined.

Pathophysiology of AF Maintenance: Atrial Electrical and Structural Remodeling

The maintenance of AF is associated with both electrical and structural atrial remodeling.

Atrial Electrical Remodeling

Electrical remodeling of the atria may be the result of AF and/or the result of hemodynamic derangements. The most significant proarrhythmic consequence of atrial electrical remodeling due to AF is the abbreviation of atrial effective refractory period (ERP). The AF-induced reduction in ERP is the result of abbreviation of the action potential duration (APD), which is secondary to a decrease in calcium channel current (I_{Ca}), and an increase in I_{K1} and constitutively active acetylcholine sensitive potassium current (CA $I_{K\ ACh}$) [24, 25]. Another manifestation of atrial electrical remodeling is an abnormality of calcium handling which may result from pressure and volume overload as well as of AF [18, 20, 25]. Atrial cells isolated from patients with AF and from experimental models with HF, but without AF, are characterized by enhanced generation of intracellular calcium-mediated triggered activity, which may contribute to both the initiation and maintenance AF [19, 20, 26, 27].

In experimental AF models, without cardiovascular disease, abbreviation of atrial ERP, secondary to pharmacological interventions or sustained rapid atrial activation, is associated with a significant increase in AF vulnerability [28–31]. Patients with AF generally display a briefer atrial ERP than patients without AF but this is likely due to AF itself [32]. In patients with hypertension without history of AF, atrial ERP did not differ between patients who developed AF and those who did not in follow-up [33]. In the diseases that are most often associated with AF (i.e., hypertension, HF, and valvular heart diseases) atrial ERP is commonly prolonged [19, 23, 34–38]. Moreover, aging, a major risk factor for AF, is also associated with prolongation of the atrial ERP [39]. It appears that at the moment of AF initiation in the clinic, atrial ERP is likely to be normal or prolonged. The extent to which dispersion of refractoriness may have played a role in these studies is not known.

AF patients with structural heart disease also have a significantly longer atrial ERP when compared to AF patients without structural heart disease [40]. Development of AF in structurally remodeled atria is associated with less abbreviation of atrial ERP [41]. Simultaneous development of systolic HF with concomitant AF may prolong atrial ERP or may shorten it to a lesser extent compared to AF alone [42–44]. Increased levels of atrial fibrosis have also been reported to be associated with a prolongation of AF cycle length [40, 45–47], so that prolongation of AF cycle length has been suggested as a marker of aggravated structural remodeling [46].

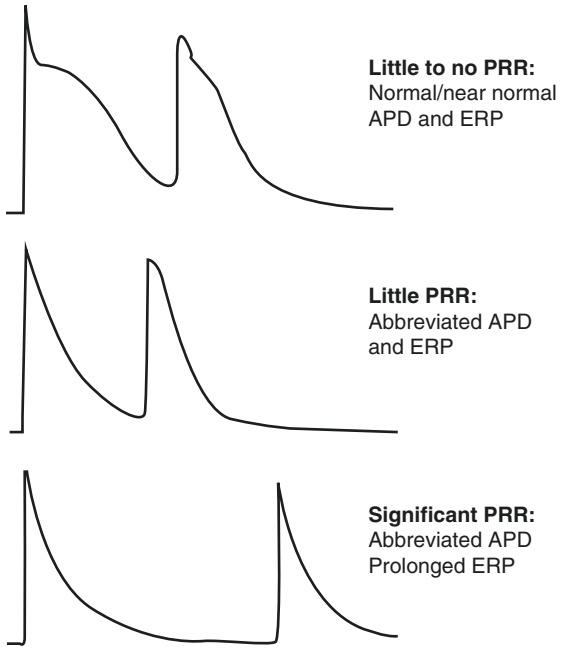


Fig. 2.1 Examples of the heterogeneity of action potential duration (APD) and effective refractory period (ERP) in aright atrium isolated from a dog with tachy-pacing induced HF. The presence of prominent post-repolarization refractoriness (PRR) contributes to the large dispersion of refractoriness. PRR in atria is recognized when ERP exceeds action potential duration measured at 70% (APD_{70}). Each action potential tracing shows a basic beat following by the earliest premature activation (i.e., ERP). In the atrial areas displaying normal activity, the duration of ERP is approximated by $APD_{70–75}$, displaying little to no PRR, similar to "healthy" controls. In atrial regions where APD was abbreviated, the duration of ERP was variable and largely determined by degree of PRR secondary to depression of the sodium channel-dependent parameters. Reproduced with permission from Burashnikov et al. [23]

In "healthy" hearts, atrial ERP approximates action potential duration at 70–90% repolarization ($APD_{70–90}$) [48, 49]. In significantly structurally remodeled atria, ERP can outlast $APD_{70–90}$ due to development of post-repolarization refractoriness (Fig. 2.1). This is often associated with heterogeneity of ERP, which can create a window of vulnerability.

Atrial ERP heterogeneity may [50] or may not [30, 51] be associated with the vulnerability and persistence of AF. In experimental systolic HF, increased AF vulnerability is associated with an augmentation of spatial dispersion of ERP in the atria, but only when the shortest ERP is briefer or equal to control values [23]. When the briefest atrial ERP is longer than control, AF vulnerability is reduced, despite the

presence of a dramatic ERP heterogeneity [23]. AF-mediated electrical remodeling is associated with an abbreviation of ERP and reduction of temporal and spatial heterogeneity of atrial ERP [30]. The abbreviation of ERP is thought to promote AF persistence. The stabilization of AF is associated with a prolongation of the temporal excitable gap, the period of fully recovered excitability between consecutive AF activations [52, 53].

It is generally believed that atrial electrical remodeling resulting in ERP abbreviation is sufficient for the maintenance of paroxysmal AF, but not persistent AF and that the presence of some atrial structural alterations is necessary for the development of persistent AF [30, 54, 55]. In the "AF-begets-AF" models, electrical remodeling occurs relatively fast and is essentially complete within several days of rapid atrial activation. AF becomes persistent only after the development of structural remodeling, which can take several weeks of rapid atrial activation [54]. Sustained AF has been also been shown to develop during reversal of electrical remodeling and in the continued presence of structural remodeling (which is more resistant to recovery) [41, 55, 56].

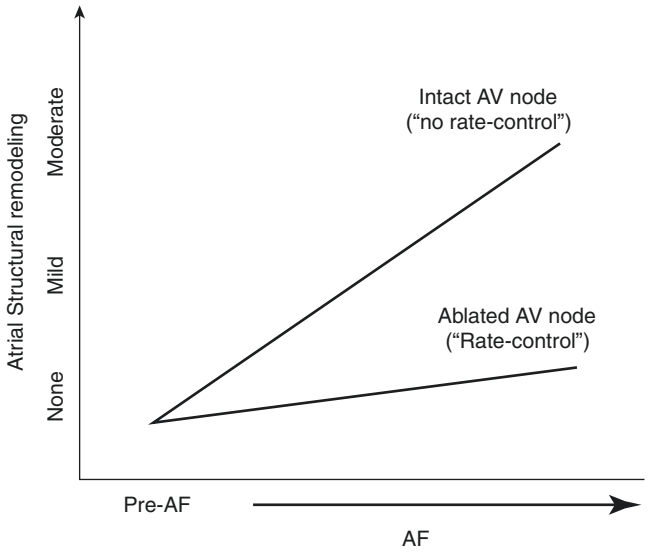


Fig. 2.2 AF-mediated atrial structural remodeling is significantly greater in the setting of intact vs. ablated AV node (i.e., absence and presence of "rate control"). AF-induced hemodynamic overload (via rapid and irregular ventricular activity) contributes more significantly to atrial structural remodeling than rapid atrial activation alone

Atrial Structural Remodeling

Atrial structural alterations are commonly found in patients with AF. Numerous factors are involved in the development of atrial structural remodeling, with fibrosis being a prime hallmark of the remodeling [25]. These factors include transforming growth factor-β1, angiotensin II, Rac1, platelet–derived growth factor, and microRNAs, small non-coding sequences of RNA [25]. Interestingly, atrium develops fibrosis more readily than the ventricle and is more responsive to structural remodeling stimuli including transforming growth factor-β1, angiotensin II, Rac1, and platelet–derived growth factor [57–61].

The most common causes contributing to atrial structural remodeling are pressure and volume overload and AF [32, 54]. In combination these factors can additively or synergistically produce atrial structural remodeling [62–64]. When separated, pressure and volume load are likely to be capable of causing much greater atrial structural remodeling than AF. In experimental studies, atrial dilation is greater in the setting of HF vs. AF [30, 65, 66]. Left atrial diastolic area was reported to increase by 80 and 24% in HF and AF models, respectively [65]. Without AF, the size of the left atrium or left atrial maximum volume could increase by 50–100% in the setting of HF [36, 65–67]. In the absence of significant cardiovascular abnormalities and with intact AV node conduction, persistent AF may enlarge left atrium by 20–45% [29, 65, 68, 69]. With a combination of HF and AF, left atrial maximum volume can reach 100–120% that of healthy controls [13, 63].

A number of experimental studies have shown that when the AV node is ablated, prolonged rapid atrial activation causes a considerably smaller, practically undetectable, atrial structural remodeling than when AV node is intact (Fig. 2.2) [32, 42, 68, 70]. These finding suggest that AF-induced rapid and irregular ventricular activity (causing fluctuations in hemodynamic load) may contribute much more than rapid atrial activation to atrial structural remodeling. It suggests also that rate-controlled AF may cause only minor atrial structural remodeling. It is noteworthy that in the original experimental study of Wijffels and co-workers demonstrating that prolonged AF causes significant structural remodeling and promotes persistent AF ("AF-begets-AF"), the AV node was intact [30]. Rapid atrial activation alone is capable of induction of persistent AF [70] but the AF-induced atrial remodeling mediated by hemodynamic load can further promote the persistent AF. In sheep and dog atrial-tachypaced models, sustained AF is more readily established when AV node conduction is intact [68, 70].

In the clinic, persistent AF is often, if not always, preceded by multiple episodes of paroxysmal AF [1, 54], consistent with the doctrine that "AF-begets-AF". In experimental studies, AF duration was much longer in AF models induced by "AF-begets-AF" vs. "HF", despite the fact that the former causes much smaller atrial enlargement (Fig. 2.3) [30, 34, 65]. Models of AF caused by chronic hypertension and mitral regurgitation are also characterized by relatively short AF (from seconds to hours), despite the development of significant left atrial enlargement [35, 38].

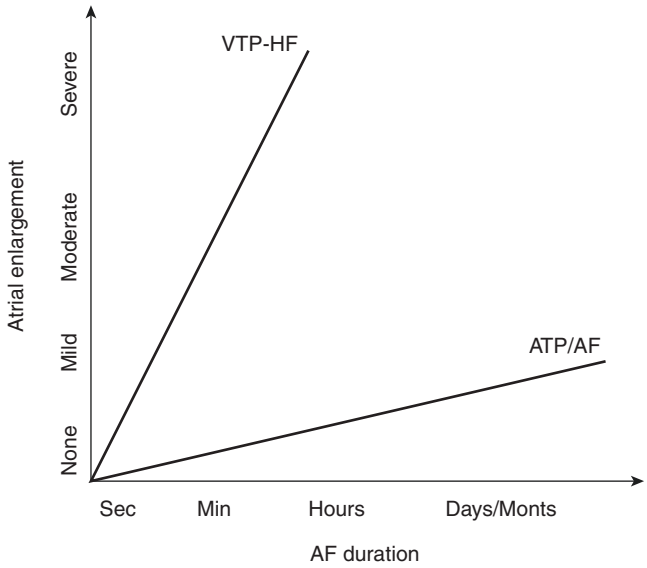


Fig. 2.3 Atrial enlargement and AF persistence. Atrial enlargement is far greater in "heart-failure" vs. "AF-begets-AF" experimental models, but the duration of AF is far longer in the latter [30, 34, 65]. "AF-begets-AF" appears to be a must for AF to become persistent. The degree of atrial enlargement may not be a good index for persistence of AF in the setting of significant structural heart diseases. AF-induced structural remodeling of the atria is facilitated more by fluctuations in hemodynamic load caused by rapid and irregular ventricular activation than by rapid atrial activation (Fig. 2.2). *VTP-HF* ventricular tachy-pacing-induced heart failure, *ATP* atrial tachy-pacing-induced AF

Thus, atrial remodeling caused by hemodynamic derangement does not appear to suit (and is not indispensible requirement) for the maintenance of long-lasting AF (Fig. 2.3). Such remodeling, however, is likely to promote the initiation and maintenance of brief episodes of AF, which, in turn, may remodel the atrium predisposing to development of persistent AF (via "AF-begets-AF"). A high prevalence of AF in patients with HF points to an additive or synergistic effect of AF and HF to promote persistent AF. However, the probability of persistent AF may be a bell-shaped, depending on the degree of atrial structural remodeling. The prevalence of persistent AF is lower in patients with systolic vs. "diastolic" HF [11], with the former exhibiting generally larger left atrial size [13, 67, 71, 72].

While the occurrence of long-lasting AF is commonly associated with atrial structural remodeling, the causal relation of these two is complex. AF may cause and be caused by atrial structural remodeling. There is significant variability in the degree of atrial structural remodeling among patients with cardiovascular disease with and without AF [32, 73]. Patients with persistent AF may have mild atrial structural remodeling and patients without history of AF may have advanced atrial structural remodeling [32, 73].

The relation of AF with atrial structural remodeling can be confounded by numerous factors. Non-AF-mediated hemodynamic derangement appears to cause a significantly greater atrial structural remodeling than AF itself. A rate-controlled AF may cause only minor atrial structural remodeling (Fig. 2.2). Therapeutic interventions may suppress and promote AF as well as delay or reverse cardiac remodeling and outcomes of the treatment may not be "logical". For instance, ivabradine has been consistently shown to reverse cardiac remodeling [74, 75] but to promote AF [76, 77]. Another potential confounding factor of the relation of AF with remodeling is that severe atrial structural remodeling may act to suppress AF [23], as discussed below.

Is There a "Vulnerable Window" for Development of AF in the Spectrum of Atrial Structural Remodeling?

Severely compromised atria have a reduced capability of maintaining rapid activation and it has recently been suggested that advanced atrial structural remodeling may act to suppress AF in the setting of HF [23]. The presence of a temporal "vulnerable window" for the development of AF in the course of development of VTP-induced HF in canines has recently been reported (Fig. 2.4) [23]. This HF model is characterized by the progressive development of HF recapitulating many features of clinical HF, including systolic and diastolic dysfunction [34, 36, 66, 78]. AF vulnerability (i.e., inducibility by a single premature beat) was shown to be higher with moderate vs. advanced atrial remodeling, associated with "early" and "late" stages of HF, respectively (Fig. 2.4) [23]. The increase of AF vulnerability at mild/moderate stages of HF is associated with relatively moderate electro-structural abnormalities in the atrium. The reduction of AF vulnerability in severe atrial remodeling is associated with a rate-dependent depression excitability decreasing the ability of the atrium to sustain rapid activation (Fig. 2.4). In two additional experimental studies of VTP-induced HF in sheep and goat, a greater inducibility of AF was also observed in the median vs. severe stages of HF [36, 42].

Experimental models of VTP-induced HF have advanced the hypothesis that AF more readily occurs in median vs. severe stages of atrial remodeling. A number of studies provide clinical evidence in support of this hypothesis. AF prevalence is reported to be significantly higher in HF patients with preserved vs. reduced LVEF (HF-PEF vs. HF-REF, respectively) and AF prevalence is found to progressively diminish as LVEF is reduced [8, 11–15]. Reduction of LVEF is generally associated with an increase in left atrial size [13, 67, 71, 72]. These data are consistent with notion that AF occurs more readily in median vs. severe atrial remodeling.

There are also clinical data suggesting that in patients with systolic HF cardiac remodeling is less severe in AF vs.

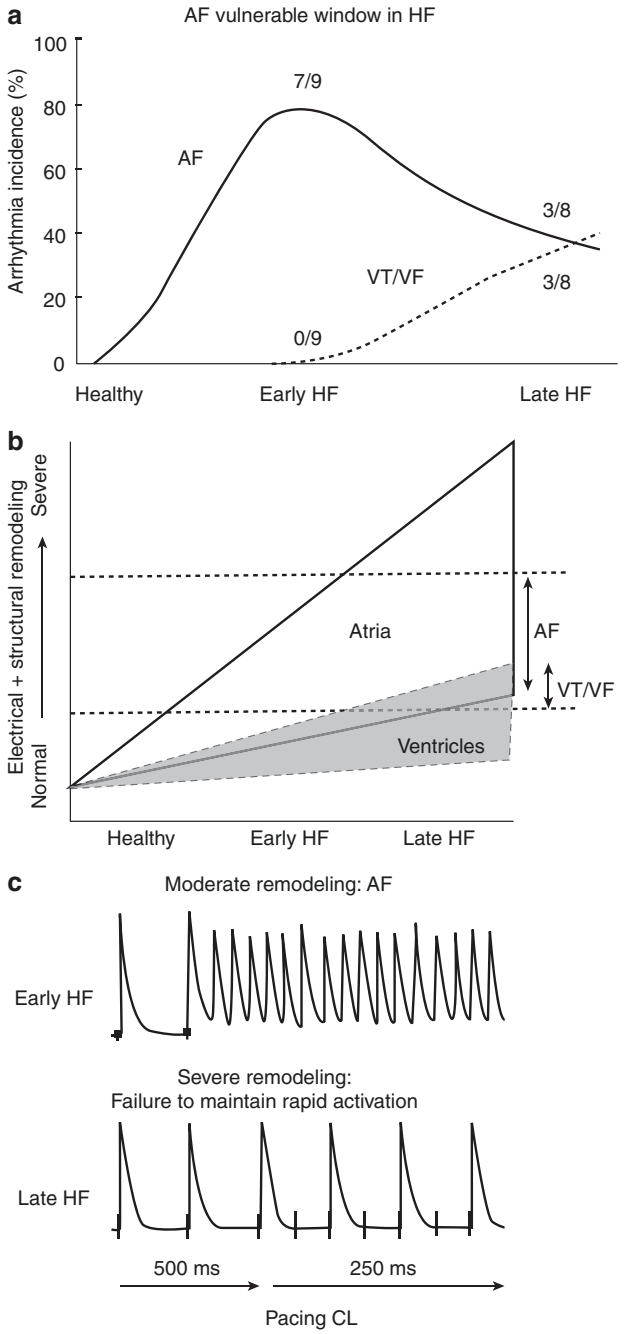


Fig. 2.4 A temporal window of vulnerability for development of atrial fibrillation (AF) with advancing HF (HF): AF more readily occurs at moderate vs. severe electrical +structural atrial remodeling. (**a**) Incidence of AF and ventricular tachycardia and fibrillation (VT/VF) as a function of duration of ventricular tachypacing (i.e., 2–3 weeks of pacing = "Early HF" and 5–6 weeks of pacing = "Late HF"). The highest AF vulnerability occurs relatively early in the course of development of VTP-induced HF, whereas VT/VF develops later. (**b, c**) Schematic depiction of potential mechanisms underlying the "window of vulnerability" for development of AF. Distinctions in atrial electrophysiology between early and late HF. Moderate electrical and structural remodeling in the early stages of HF predispose to the development of AF. In the late stages of HF, electrical and structural remodeling of the atria progress to cause rate-dependent severe depression of excitability and conduction, thus significantly reducing the ability of atria to maintain rapid activation. In the ventricles, electrical and structural remodeling reach the threshold for arrhythmic vulnerability only at the late stage of HF. Reproduced with permission from Burashnikov et al [23]

SR patients and that AF more readily occurs in cases of less advanced cardiac remodeling. Patients with HF and AF commonly have a higher LVEF than patients with SR [79–82], despite the fact that AF acts to reduce LVEF. In HF-PEF patients LVEF has been reported to be higher in SR vs. AF patients [83]. In systolic HF patients who have an advanced functional class (NYHA III-IV; the EVEREST study), those with AF had shorter QRS complex than those with SR [81] and the prevalence of AF history was significantly greater in patients with <120 vs. ≥120 ms QRS duration [84]. Prolongation of QRS is a marker of aggravating cardiac structural remodeling. Interestingly, in HF patients hospitalized for acute systolic HF, those who had AF, particularly new-onset AF, had fewer co-morbidities and less prevalence of predictors of morbidity and mortality than those with SR in the large EVEREST and GWTG-HF studies [80, 81].

The atrium is much thinner than the ventricle, as a consequence hemodynamic derangement more readily remodels the atrium vs. ventricle. Numerous experimental studies have shown that the degree of fibrosis is several fold greater in atria vs. ventricles in experimental models of systolic HF [59]. In VTP-induced canine HF model, LA and LV weight is increased by 80 and 13%, respectively after 3 weeks of VTP [66]. Persistent hypertension causes an atrial predominant remodeling, i.e., LA and LV weight increased by 40–63 and 15–20% in an ovine model [38].

In diseases associated with severe sustained pressure and volume overload, ventricular function is likely to be less affected than atrial function. Consequently the ability of atria to sustain rapid activation (i.e. AF) may be reduced long before that of the ventricle.

Electrophysiological Mechanisms of AF: Focal and Reentry

AF is thought to be initiated by a focal trigger, which can arise as a consequence of enhanced automaticity, delayed or early afterdepolarizations. Autonomic influences, stretch, or abnormal calcium handling may be involved in the triggering [18]. Focal sources may also maintain or contribute to the maintenance of AF [78, 85–90], but the extent of their involvement is not well defined and may depend on the underlying pathology and/or stages of AF persistence.

A reentrant mechanism was long thought to be the predominant mechanism responsible for the maintenance of AF. More recent mapping studies have raised doubt about the predominant role of reentry. In many mapping studies, a full reentrant circuit is rarely if ever observed [86, 87, 89, 91–97]. A new hypothesis of AF maintenance has recently appeared i.e., the "double layer hypothesis", which is claimed by the authors to be neither reentry nor focal [93–96, 98]. This theory stipulates that persistent AF is mediated by endo-epicardial dissociation and that the arrhythmia is maintained by intramural meandering wavelets causing multiple

endo-epicardial breakthroughs. This hypothesis appears to be similar to the original Moe multiple wavelet theory [99].

The multiple wavelet mechanism of AF (i.e., multiple simultaneous meandering reentrant wavelets) first proposed by Moe and co-workers [99] was considered to be the principal mechanism from the 1960s to the early 1990s. Evidence in support of this hypothesis was provided by Allessie and co-workers in 1985 [100]. More recent mapping studies have failed to record multiple reentrant circuits on the epicardial and/or endocardial surfaces of the fibrillating atrium [86, 87, 89–97, 101]. In the 1990s to early 2000s, several groups, led by Jalife and co-workers, reported that AF could be maintained by a single stable reentrant circuit (mother rotor) resulting in fibrillatory conduction as the wavefront encounters regions of refractoriness or anatomical obstacles [101–103]. The "single reentry" theory was considered to be the dominant mechanism for the maintenance of AF in 2000s [103].

Results of mapping studies of AF reported over the past 6 years have provided conflicting data. Using a 64-pole basket catheter, Narayan and co-workers, regularly observed a stable rotor on the endocardial surface during AF [104–106]. Using 128–512 electrodes or optical mapping, other groups either failed to record any reentrant circuits or rarely recorded short-lived episodes of reentry from the epicardial and/or endocardial surfaces [89, 90, 93–97, 107].

A possibility exists that AF could be maintained by a transmural reentrant circuit(s), which cannot be seen on the epicardial or endocardial surfaces. Transmural anatomic reentry has been reported to consistently occur during AF in the study utilizing a simultaneous epicardial and endocardial surface mapping of the atrium [107]. Other studies employing simultaneous epicardial and endocardial mapping, however, have failed to observe transmural reentry [95, 96].

It is difficult to understand why some groups consistently observe stable reentry [102–106] while other groups either do not see reentrant activity at all or see it only rarely as short-lived episodes [89, 90, 93–97]. One possible explanation is that a half loop of activation (i.e., "incomplete reentry") is sometimes taken as evidence for reentry. In the presence of rapid and heterogeneous propagation of conduction, which commonly occurs during AF, "wannabe reentry" is often encountered [90].

The dominant type of reentrant mechanism responsible for AF maintenance has changed over the years. "Leading circle" reentry was the dominant type of AF driver in 1970s to early 1990s [28, 100]. The "leading circle" reentry has no or little temporal excitable gap between succeeding AF activations. Concurrently, the concept of wavelength (the product of ERP and conduction velocity) was considered to be a robust predictor of AF occurrence [108–110]. In the 1990s and beyond, a temporal excitable gap was consistently recorded during AF [52, 111–114] and stabilization of AF was shown to be associated with prolongation of the temporal excitable gap [52]. These data questioned the importance of "leading circle" and "wavelength" theories. Between 1990 and 2010, "spiral wave" theory took over the lead as the dominant reentrant mechanism for AF [103]. The spiral wave theory explains the existence of the "excitable gap" [114], but the presence of spiral waves during AF itself (or at least a high probability of its occurrence) has been questioned as well [89, 90, 93–96].

Conduction disturbance is thought to be important for the development of reentry. The principal role of conduction disturbance in AF can be questioned by the fact that I_{Na} blockers, producing a wide range of conduction alterations, do not or very rarely induce AF *de novo*. Interestingly, conduction velocity has been reported to be increased when compared in 6 vs. 24 h after pacing/AF, when AF is more persistent [30, 50]. This appears to be due to abbreviation of ERP and prolongation of the excitable gap [52].

In summary, at the present time the evidence for reentry as the principal mechanism of AF maintenance, which was thought to be well established in 1980–1990s, remains controversial.

References

1. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;12:1360–420.
2. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;123:e269–367.
3. Boyd AC, Schiller NB, Leung D, Ross DL, Thomas L. Atrial dilation and altered function are mediated by age and diastolic function but not before the eighth decade. JACC Cardiovasc Imaging. 2011;4:234–42.
4. Go O, Rosendorff C. Hypertension and atrial fibrillation. Curr Cardiol Rep. 2009;11:430–5.
5. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J. 2005;26:2422–34.
6. Antzelevitch C, Yan GX. J wave syndromes. Heart Rhythm. 2010;7:549–58.
7. Mandyam MC, Soliman EZ, Alonso A, Dewland TA, Heckbert SR, Vittinghoff E, et al. The QT interval and risk of incident atrial fibrillation. Heart Rhythm. 2013;10:1562–8.
8. De Ferrari GM, Klersy C, Ferrero P, Fantoni C, Salerno-Uriarte D, Manca L, et al. Atrial fibrillation in heart failure patients: prevalence in daily practice and effect on the severity of symptoms. Data from the ALPHA study registry. Eur J Heart Fail. 2007;9:502–9.
9. Pecini R, Moller DV, Torp-Pedersen C, Hassager C, Kober L. Heart failure etiology impacts survival of patients with heart failure. Int J Cardiol. 2011;149:211–5.
10. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol. 2006;47:1997–2004.
11. Lenzen MJ, Scholte op Reimer WJ, Boersma E, Vantrimpont PJ, Follath F, Swedberg K, et al. Differences between patients with a

preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J. 2004;25:1214–20.
12. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251–9.
13. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. 2015;8:295–303.
14. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50:768–77.
15. Gurwitz JH, Magid DJ, Smith DH, Goldberg RJ, McManus DD, Allen LA, et al. Contemporary prevalence and correlates of incident heart failure with preserved ejection fraction. Am J Med. 2013;126:393–400.
16. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, et al. Lone atrial fibrillation: does it exist? J Am Coll Cardiol. 2014;63:1715–23.
17. Nazir SA, Lab MJ. Mechanoelectric feedback and atrial arrhythmias. Cardiovasc Res. 1996;32:52–61.
18. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ Res. 2014;114:1500–15.
19. Stambler BS, Fenelon G, Shepard RK, Clemo HF, Guiraudon CM. Characterization of sustained atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure. J Cardiovasc Electrophysiol. 2003;14:499–507.
20. Yeh YH, Wakili R, Qi XY, Chartier D, Boknik P, Kaab S, et al. Calcium-handling abnormalities underlying atrial arrhythmogenesis and contractile dysfunction in dogs with congestive heart failure. Circ Arrhythm Electrophysiol. 2008;1:93–102.
21. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339:659–66.
22. Seitz J, Horvilleur J, Curel L, Lacotte J, Maluski A, Ferracci A, et al. Active or passive pulmonary vein in atrial fibrillation: is pulmonary vein isolation always essential? Heart Rhythm. 2014;11:579–86.
23. Burashnikov A, Di Diego JM, Sicouri S, Doss MX, Sachinidis A, Barajas-Martinez H, et al. A temporal window of vulnerability for development of atrial fibrillation with advancing heart failure. Eur J Heart Fail. 2014;16:271–80.
24. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol. 2014;63:2335–45.
25. Heijman J, Voigt N, Nattel S, Dobrev D. Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. Circ Res. 2014;114:1483–99.
26. Hove-Madsen L, Llach A, Bayes-Genis A, Roura S, Rodriguez FE, Aris A, et al. Atrial fibrillation is associated with increased spontaneous calcium release from the sarcoplasmic reticulum in human atrial myocytes. Circulation. 2004;110:1358–63.
27. Voigt N, Li N, Wang Q, Wang W, Trafford AW, Abu-Taha I, et al. Enhanced sarcoplasmic reticulum Ca2+ leak and increased Na+−Ca2+ exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. Circulation. 2012;125:2059–70.
28. Allessie MA, Bonke FIM, Schopman JG. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. Circ Res. 1973;33:54–62.
29. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation. 1995;91:1588–95.
30. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92:1954–68.
31. Burashnikov A, Antzelevitch C. Reinduction of atrial fibrillation immediately after termination of the arrhythmia is mediated by late phase 3 early afterdepolarization-induced triggered activity. Circulation. 2003;107:2355–60.
32. Schoonderwoerd BA, Van GI, Van Veldhuisen DJ, van Den Berg MP, Crijns HJ. Electrical and structural remodeling: role in the genesis and maintenance of atrial fibrillation. Prog Cardiovasc Dis. 2005;48:153–68.
33. Healey JS, Israel CW, Connolly SJ, Hohnloser SH, Nair GM, Divakaramenon S, et al. Relevance of electrical remodeling in human atrial fibrillation: results of the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial mechanisms of atrial fibrillation study. Circ Arrhythm Electrophysiol. 2012;5:626–31.
34. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation. 1999;100:87–95.
35. Verheule S, Wilson E, Everett T, Shanbhag S, Golden C, Olgin J. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. Circulation. 2003;107:2615–22.
36. Power JM, Beacom GA, Alferness CA, Raman J, Wijffels M, Farish SJ, et al. Susceptibility to atrial fibrillation: a study in an ovine model of pacing-induced early heart failure. J Cardiovasc Electrophysiol. 1998;9:423–35.
37. Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB, et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. Circulation. 2003;108:1461–8.
38. Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Brooks AG, Worthington M, et al. Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model. Heart Rhythm. 2010;7:1282–90.
39. Kistler PM, Sanders P, Fynn SP, Stevenson IH, Spence SJ, Vohra JK, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. J Am Coll Cardiol. 2004;44:109–16.
40. Uhm JS, Mun HS, Wi J, Shim J, Joung B, Lee MH, et al. Prolonged atrial effective refractory periods in atrial fibrillation patients associated with structural heart disease or sinus node dysfunction compared with lone atrial fibrillation. Pacing Clin Electrophysiol. 2013;36:163–71.
41. Shinagawa K, Li D, Leung TK, Nattel S. Consequences of atrial tachycardia-induced remodeling depend on the preexisting atrial substrate. Circulation. 2002;105:251–7.
42. Schoonderwoerd BA, Van GI, Van Veldhuisen DJ, Tieleman RG, Grandjean JG, Bel KJ, et al. Electrical remodeling and atrial dilation during atrial tachycardia are influenced by ventricular rate: role of developing tachycardiomyopathy. J Cardiovasc Electrophysiol. 2001;12:1404–10.
43. Laurent G, Moe GW, Hu X, Pui-Sze SP, Ramadeen A, Leong-Poi H, et al. Simultaneous right atrioventricular pacing: a novel model to study atrial remodeling and fibrillation in the setting of heart failure. J Card Fail. 2008;14:254–62.
44. Lugenbiel P, Wenz F, Govorov K, Schweizer PA, Katus HA, Thomas D. Atrial fibrillation complicated by heart failure induces

distinct remodeling of calcium cycling proteins. PLoS One. 2015;10:e0116395.
45. Swartz MF, Fink GW, Lutz CJ, Taffet SM, Berenfeld O, Vikstrom KL, et al. Left versus right atrial difference in dominant frequency, K^+ channel transcripts, and fibrosis in patients developing atrial fibrillation after cardiac surgery. Heart Rhythm. 2009;6:1415–22.
46. Platonov PG, Corino VD, Seifert M, Holmqvist F, Sornmo L. Atrial fibrillatory rate in the clinical context: natural course and prediction of intervention outcome. Europace. 2014;16(Suppl 4):iv110-iv9.
47. Walters TE, Teh AW, Spence S, Kistler PM, Morton JB, Kalman JM. Relationship between the electrocardiographic atrial fibrillation cycle length and left atrial remodeling: a detailed electroanatomic mapping study. Heart Rhythm. 2014;11:670–6.
48. Bode F, Kilborn M, Karasik P, Franz MR. The repolarization-excitability relationship in the human right atrium is unaffected by cycle length, recording site and prior arrhythmias. J Am Coll Cardiol. 2001;37:920–5.
49. Burashnikov A, Di Diego JM, Zygmunt AC, Belardinelli L, Antzelevitch C. Atrium-selective sodium channel block as a strategy for suppression of atrial fibrillation: differences in sodium channel inactivation between atria and ventricles and the role of ranolazine. Circulation. 2007;116:1449–57.
50. Fareh S, Villemaire C, Nattel S. Importance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia- induced atrial electrical remodeling. Circulation. 1998;98:2202–9.
51. Hirose M, Carlson MD, Laurita KR. Cellular mechanisms of vagally mediated atrial tachyarrhythmia in isolated arterially perfused canine right atria. J Cardiovasc Electrophysiol. 2002;13:918–26.
52. Shan Z, Yan J, Zhou J, Shi X, Guo J, Yuan H, et al. Role of progressive widening of the temporal excitable gap for perpetuation of atrial fibrillation in the goat. Circ J. 2010;74:655–63.
53. Neuberger HR, Schotten U, Blaauw Y, Vollmann D, Eijsbouts S, van Hunnik A, et al. Chronic atrial dilation, electrical remodeling, and atrial fibrillation in the goat. J Am Coll Cardiol. 2006;47:644–53.
54. Allessie MA, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res. 2002;54:230–46.
55. Cha TJ, Ehrlich JR, Zhang L, Shi YF, Tardif JC, Leung TK, et al. Dissociation between ionic remodeling and ability to sustain atrial fibrillation during recovery from experimental congestive heart failure. Circulation. 2004;109:412–8.
56. Everett TH, Li H, Mangrum JM, McRury ID, Mitchell MA, Redick JA, et al. Electrical, morphological, and ultrastructural remodeling and reverse remodeling in a canine model of chronic atrial fibrillation. Circulation. 2000;102:1454–60.
57. Verheule S, Sato T, Everett T, Engle SK, Otten D, Rubart-von d LM, et al. Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TGF-beta1. Circ Res. 2004;94:1458–65.
58. Burstein B, Libby E, Calderone A, Nattel S. Differential behaviors of atrial versus ventricular fibroblasts: a potential role for platelet-derived growth factor in atrial-ventricular remodeling differences. Circulation. 2008;117:1630–41.
59. Hanna N, Cardin S, Leung TK, Nattel S. Differences in atrial versus ventricular remodeling in dogs with ventricular tachypacing-induced congestive heart failure. Cardiovasc Res. 2004;63:236–44.
60. Xiao HD, Fuchs S, Campbell DJ, Lewis W, Dudley SC Jr, Kasi VS, et al. Mice with cardiac-restricted angiotensin-converting enzyme (ACE) have atrial enlargement, cardiac arrhythmia, and sudden death. Am J Pathol. 2004;165:1019–32.
61. Burashnikov A. Are there atrial selective/predominant targets for "upstream" atrial fibrillation therapy? Heart Rhythm. 2008;5:1294–5.
62. Byrne M, Kaye DM, Power J. The synergism between atrial fibrillation and heart failure. J Card Fail. 2008;14:320–6.
63. Knackstedt C, Gramley F, Schimpf T, Mischke K, Zarse M, Plisiene J, et al. Association of echocardiographic atrial size and atrial fibrosis in a sequential model of congestive heart failure and atrial fibrillation. Cardiovasc Pathol. 2008;17:318–24.
64. Corradi D, Callegari S, Maestri R, Ferrara D, Mangieri D, Alinovi R, et al. Differential structural remodeling of the left-atrial posterior wall in patients affected by mitral regurgitation with or without persistent atrial fibrillation: a morphological and molecular study. J Cardiovasc Electrophysiol. 2012;23:271–9.
65. Shi Y, Ducharme A, Li D, Gaspo R, Nattel S, Tardif JC. Remodeling of atrial dimensions and emptying function in canine models of atrial fibrillation. Cardiovasc Res. 2001;52:217–25.
66. Moe GW, Grima EA, Howard RJ, Armstrong PW. Biatrial appendage hypertrophy but not ventricular hypertrophy: a unique feature of canine pacing-induced heart failure. J Card Fail. 1996;2:127–32.
67. Triposkiadis F, Harbas C, Kelepeshis G, Sitafidis G, Skoularigis J, Demopoulos V, et al. Left atrial remodeling in patients younger than 70 years with diastolic and systolic heart failure. J Am Soc Echocardiogr. 2007;20:177–85.
68. Anne W, Willems R, Holemans P, Beckers F, Roskams T, Lenaerts I, et al. Self-terminating AF depends on electrical remodeling while persistent AF depends on additional structural changes in a rapid atrially paced sheep model. J Mol Cell Cardiol. 2007;43:148–58.
69. Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation. 1990;82:792–7.
70. Avitall B, Bi J, Mykytsey A, Chicos A. Atrial and ventricular fibrosis induced by atrial fibrillation: evidence to support early rhythm control. Heart Rhythm. 2008;5:839–45.
71. Nieuwlaat R, Eurlings LW, Cleland JG, Cobbe SM, Vardas PE, Capucci A, et al. Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of atrial fibrillation: results of the Euro Heart Survey on atrial fibrillation. J Am Coll Cardiol. 2009;53:1690–8.
72. Linssen GC, Rienstra M, Jaarsma T, Voors AA, Van GI, Hillege HL, et al. Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction. Eur J Heart Fail. 2011;13:1111–20.
73. Kottkamp H. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy. Eur Heart J. 2013;34:2731–8.
74. Tardif JC, O'Meara E, Komajda M, Bohm M, Borer JS, Ford I, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. Eur Heart J. 2011;32:2507–15.
75. Ceconi C, Freedman SB, Tardif JC, Hildebrandt P, McDonagh T, Gueret P, et al. Effect of heart rate reduction by ivabradine on left ventricular remodeling in the echocardiographic substudy of BEAUTIFUL. Int J Cardiol. 2011;146:408–14.
76. Fox K, Komajda M, Ford I, Robertson M, Bohm M, Borer JS, et al. Effect of ivabradine in patients with left-ventricular systolic dysfunction: a pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. Eur Heart J. 2013;34:2263–70.
77. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med. 2014;371:1091–9.
78. Okuyama Y, Miyauchi Y, Park AM, Hamabe A, Zhou S, Hayashi H, et al. High resolution mapping of the pulmonary vein and the vein of Marshall during induced atrial fibrillation and atrial tachy-

cardia in a canine model of pacing-induced congestive heart failure. J Am Coll Cardiol. 2003;42:348–60.
79. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. Circulation. 1991;84:40–8.
80. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of get with the guidelines-heart failure. Circ Heart Fail. 2012;5:191–201.
81. Mentz RJ, Chung MJ, Gheorghiade M, Pang PS, Kwasny MJ, Ambrosy AP, et al. Atrial fibrillation or flutter on initial electrocardiogram is associated with worse outcomes in patients admitted for worsening heart failure with reduced ejection fraction: findings from the EVEREST Trial. Am Heart J. 2012;164:884–92.
82. Tveit A, Flonaes B, Aaser E, Korneliussen K, Froland G, Gullestad L, et al. No impact of atrial fibrillation on mortality risk in optimally treated heart failure patients. Clin Cardiol. 2011;34:537–42.
83. Zakeri R, Borlaug BA, McNulty SE, Mohammed SF, Lewis GD, Semigran MJ, et al. Impact of atrial fibrillation on exercise capacity in heart failure with preserved ejection fraction: a RELAX trial ancillary study. Circ Heart Fail. 2014;7:123–30.
84. Wang NC, Maggioni AP, Konstam MA, Zannad F, Krasa HB, Burnett JC Jr, et al. Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction. JAMA. 2008;299:2656–66.
85. Scherf D, Romano FJ, Terranova R. Experimental studies on auricular flutter and auricular fibrillation. Am Heart J. 1948;36:241–51.
86. Zhou S, Chang CM, Wu TJ, Miyauchi Y, Okuyama Y, Park AM, et al. Nonreentrant focal activations in pulmonary veins in canine model of sustained atrial fibrillation. Am J Physiol Heart Circ Physiol. 2002;283:H1244–H52.
87. Fenelon G, Shepard RK, Stambler BS. Focal origin of atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure. J Cardiovasc Electrophysiol. 2003;14:1093–102.
88. Kurotobi T, Iwakura K, Inoue K, Kimura R, Okamura A, Koyama Y, et al. Multiple arrhythmogenic foci associated with the development of perpetuation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3:39–45.
89. Lee S, Sahadevan J, Khrestian CM, Durand DM, Waldo AL. High density mapping of atrial fibrillation during vagal nerve stimulation in the canine heart: restudying the moe hypothesis. J Cardiovasc Electrophysiol. 2013;24:328–35.
90. Lee S, Sahadevan J, Khrestian CM, Cakulev I, Markowitz A, Waldo AL. Simultaneous biatrial high-density (510-512 electrodes) epicardial mapping of persistent and long-standing persistent atrial fibrillation in patients: new insights into the mechanism of its maintenance. Circulation. 2015;132:2108–17.
91. Gray RA, Pertsov AM, Jalife J. Incomplete reentry and epicardial breakthrough patterns during atrial fibrillation in the sheep heart. Circulation. 1996;94:2649–61.
92. Nitta T, Ishii Y, Miyagi Y, Ohmori H, Sakamoto S, Tanaka S. Concurrent multiple left atrial focal activations with fibrillatory conduction and right atrial focal or reentrant activation as the mechanism in atrial fibrillation. J Thorac Cardiovasc Surg. 2004;127:770–8.
93. de Groot NM, Houben RP, Smeets JL, Boersma E, Schotten U, Schalij MJ, et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. Circulation. 2010;122:1674–82.
94. Allessie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL, et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. Circ Arrhythm Electrophysiol. 2010;3:606–15.
95. Eckstein J, Maesen B, Linz D, Zeemering S, van HA, Verheule S, et al. Time course and mechanisms of endo-epicardial electrical dissociation during atrial fibrillation in the goat. Cardiovasc Res. 2011;89:816–24.
96. Eckstein J, Zeemering S, Linz D, Maesen B, Verheule S, van Hunnik A, et al. Transmural conduction is the predominant mechanism of breakthrough during atrial fibrillation: evidence from simultaneous endo-epicardial high-density activation mapping. Circ Arrhythm Electrophysiol. 2013;6:334–41.
97. Lee G, Kumar S, Teh A, Madry A, Spence S, Larobina M, et al. Epicardial wave mapping in human long-lasting persistent atrial fibrillation: transient rotational circuits, complex wavefronts, and disorganized activity. Eur Heart J. 2014;35:86–97.
98. Allessie M, de Groot N. Rotors during AF: drivers or bystanders? Eur Heart J. 2014;35:63–5.
99. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. Am Heart J. 1964;67:200–20.
100. Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, editors. Cardiac electrophysiology and arrhythmias. Orlando: Grune and Stratton; 1985. p. 265–76.
101. Schuessler RB, Grayson TM, Bromberg BI, Cox JL, Boineau JP. Cholinergically mediated tachyarrhythmias induced by a single extrastimulus in the isolated canine right atrium. Circ Res. 1992;71:1254–67.
102. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. Circulation. 2000;101:194–9.
103. Jalife J. Rotors and spiral waves in atrial fibrillation. J Cardiovasc Electrophysiol. 2003;14:776–80.
104. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol. 2012;60:628–36.
105. Narayan SM, Shivkumar K, Krummen DE, Miller JM, Rappel WJ. Panoramic electrophysiological mapping but not electrogram morphology identifies stable sources for human atrial fibrillation: stable atrial fibrillation rotors and focal sources relate poorly to fractionated electrograms. Circ Arrhythm Electrophysiol. 2013;6:58–67.
106. Miller JM, Kowal RC, Swarup V, Daubert JP, Daoud EG, Day JD, et al. Initial independent outcomes from focal impulse and rotor modulation ablation for atrial fibrillation: multicenter FIRM registry. J Cardiovasc Electrophysiol. 2014;25:921–9.
107. Hansen BJ, Zhao J, Csepe TA, Moore BT, Li N, Jayne LA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. Eur Heart J. 2015;36:2390–401.
108. Smeets JL, Allessie MA, Lammers WJ, Bonke FI, Hollen J. The wavelength of the cardiac impulse and reentrant arrhythmias in isolated rabbit atrium. The role of heart rate, autonomic transmitters, temperature, and potassium. Circ Res. 1986;58:96–108.
109. Rensma PL, Allessie MA, Lammers WJEP, Bonke FIM, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res. 1988;62:395–410.
110. Wang J, Feng J, Nattel S. Class III antiarrhythmic drug action in experimental atrial fibrillation. Differences in reverse use dependence and effectiveness between d-sotalol and the new antiarrhythmic drug ambasilide. Circulation. 1994;90:2032–40.
111. Kirchhof C, Chorro F, Scheffer GJ, Brugada J, Konings K, Zetelaki Z, et al. Regional entrainment of atrial fibrillation stud-

ied by high-resolution mapping in open-chest dogs. Circulation. 1993;88:736–49.
112. Kim K-B, Rodefeld MD, Schuessler RB, Cox JL, Boineau JP. Relationship between local atrial fibrillation interval and refractory period in the isolated canine atrium. Circulation. 1996;94:2961–7.
113. Wijffels MC, Dorland R, Mast F, Allessie MA. Widening of the excitable gap during pharmacological cardioversion of atrial fibrillation in the goat: effects of cibenzoline, hydroquinidine, flecainide, and d-sotalol. Circulation. 2000;102:260–7.
114. Kawase A, Ikeda T, Nakazawa K, Ashihara T, Namba T, Kubota T, et al. Widening of the excitable gap and enlargement of the core of reentry during atrial fibrillation with a pure sodium channel blocker in canine atria. Circulation. 2003;107:905–10.

Genomics of Cardiac Arrhythmias

3

Dan M. Roden and M. Benjamin Shoemaker

Abstract

It has long been recognized that certain traits "run in families", and arrhythmias are no exception. The most poignant examples are channelopathies and cardiomyopathies which can take the life of an otherwise healthy child. The current state of knowledge in channelopathies and cardiomyopathies is outlined in other chapters in this volume and the details of the specific genes in these diseases will not be discussed further here. Increasingly robust datasets also support the idea that genetic factors play a role in variable drug responses and in susceptibility to common arrhythmias notably atrial fibrillation (AF) and sudden cardiac death (SCD). Further, inexpensive and accurate genotyping and sequencing technologies introduced in the last decade are revolutionizing not only diagnostics and patient care, but are also introducing new complexities in interpretation of genetic test data with which physicians are only now becoming aware.

Keywords

Genome-wide association study • DNA sequencing • DNA polymorphism • Single nucleotide polymorphism • Long QT syndrome • Atrial fibrillation • Sudden cardiac death • Variant of unknown significance

A human genome includes about three billion base pairs. Genetic variation is common and increasingly well-recognized not only as a cause of familiar genetic diseases but also as a modulator of the severity of common and rare disease and as a determinant of variable drug responses. The challenge and opportunity for genomic medicine is to apply this emerging knowledge to improve patient care: examples include improved diagnostics, new drug development, avoiding drugs likely to be ineffective or dangerous, and improved risk stratification in common and rare disease [1].

Grant Support: Supported by grants from the US National Institutes of Health (P50 GM115305, U01 HG006378, R01 HL049989, and R01 HL118952).

D.M. Roden, M.D. (✉)
Oates Institute for Experimental Therapeutics, Vanderbilt University School of Medicine, 1285 Medical Research Building IV, Nashville, TN 37232, USA
e-mail: dan.roden@vanderbilt.edu

M.B. Shoemaker, M.D.
Department of Internal Medicine, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 300-A, Nashville, TN 37203, USA
e-mail: moore.b.shoemaker@vanderbilt.edu

DNA Variants

The most frequent type of genetic variant is a SNP, or a single nucleotide polymorphism (a glossary of common terms used here is provided as Table 3.1). Any individual harbors approximately 10–20 million SNPs when their whole genome sequence is compared to that of a reference sequence. The vast majority of SNPs are rare: probably only 1% have a minor allele frequency > 1%, and allele frequencies of common and rare variants often differ across ancestries. Exons, the protein-coding regions, represent 1–2% of the genome

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_3

Table 3.1 A glossary

Term	Comment
Allele	A variant form of a gene. The less common variant is termed the "minor" allele. Allele frequency is the relative frequency of a variant in a population. Allele frequencies often vary by ancestry. Variants are often termed common if the minor allele frequency is >1–5% and rare if <1%
Autosomal dominant	A pattern of genetic disease transmission in which a single copy of a variant allele on a non-sex chromosome (an autosome), from either parent, is sufficient to cause a disease. Typical features include both male to female and female to male transmission, and transmission to 50% of children of a carrier
Autosomal recessive	A pattern of genetic disease transmission in which a disease is manifest when both alleles carry disease-causing variants. The child can be homozygous (the same variant; often as a result of consanguineous matings) or compound heterozygous (different variants). Occasionally one variant is inherited and the other arises *de novo*
Copy number variation (CNV)	A polymorphism consisting of changes in the number of copies of a gene or genes. The changes can be large deletions or insertions of one or more copies
De novo mutation	A mutation absent in either parent
Exome	The protein-coding region of the genome, made up of individual exons
Genetic heterogeneity	The same or similar phenotype conferred by mutations in different genes
Genome Wide Association Study (GWAS)	A method that examines associations between phenotypes and hundreds of thousands or millions of common SNPs. GWAS is an unbiased method because it searches all possible genomic regions, and not just those previously implicated by known biology
Indel	A polymorphism consisting of insertion or deletion of nucleotides
Linkage analysis	A method that seeks to identify associations between phenotypes and genomic markers such as STRs or SNPs
Mutation	A rare variant causing a genetic disease
Next generation sequencing	New technologies introduced ~2005 that have dramatically decreased the cost and accelerated the speed of DNA sequencing. Sequencing a while genome in 2002 was estimated to cost $10,000,000 and take weeks-months, while in 2016 a whole genome sequence can be completed in <2 days for <$2000
Penetrance	The extent to which a genetic variant produces a phenotype. Incomplete or variable penetrance indicates that not all variant carriers will display the phenotype
Phenotypic heterogeneity	Mutations in the same gene give rise to multiple distinct phenotypes
Odds ratio (OR)	In genomic medicine, often used to describe the ratio between the odds that a genetic variant will produce a phenotype compared to the odds that the phenotype will arise in the absence of the genetic variant
Single nucleotide polymorphism (SNP)	A DNA polymorphism in which a single nucleotide is substituted in the reference sequence. Exonic SNPs (those in the exome) may or may not change the encoded amino acid (non-synonymous and synonymous respectively). SNPs in non-coding regions may alter protein function by changing messenger RNA splicing or by altering the rate of protein synthesis
Short tandem repeat (STR)	A DNA polymorphism consisting of a sequence of 2–10 nucleotides repeated often dozens or hundreds of times across the genome. STRs were used in initial linkage studies before widespread dense SNP genotyping became available

(the "exome"), so a typical exome contains 50,000,000 base pairs and 10,000–20,000 SNPs. Exonic SNPs may alter the primary amino acid sequence of the encoded protein and are termed "non-synonymous" (nsSNPs). Because the genetic code is redundant (i.e. each amino acid may be encoded by multiple triplet codons), some coding region SNPs do not change the encoded amino acid and are termed "synonymous".

SNPs in non-coding regions can also alter protein function by altering the rate at which messenger RNA and thus protein is generated, or by altering exonic splicing to result in altered protein products. Another type of polymorphism is a short tandem repeat, a sequence of a few (usually <10) nucleotides that is repeated, up to dozens of times; short tandem repeat genotyping allowed the first type of linkage analysis described below. Other genetic variants include small insertion or deletion events ("indels") which again may or may not alter protein expression or function. Larger insertion or deletion events (up to thousands of base pairs), termed copy number variation, may disrupt entire genes up to deletion or duplication of entire chromosomes as in Turner or Down's syndrome; deletion of whole exons has been described as an usual cause of long QT syndrome [2–4]. The term "mutation" is applied to a genetic polymorphism that is clearly associated with a severe disease phenotype. Since severe phenotypes are rare, mutations are rare. Determining whether a rare polymorphism is pathogenic represents a major emerging challenge in genome science.

There is a spectrum of frequencies of genetic variants that can cause, or increase susceptibility to, a common human

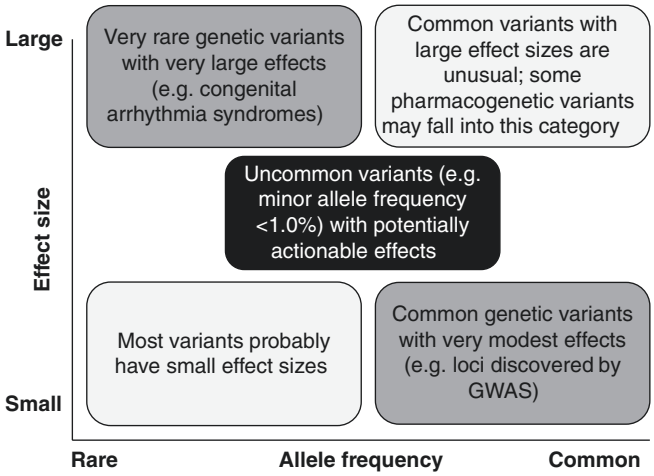


Fig. 3.1 Relationship between allele frequency and clinical effects. Rare variants that produce familial channelopathies or cardiomyopathies fall to the *upper left*, while common variants associated by GWAS with human traits fall to the *lower right*. The vast majority of variants in any individual are rare and produce no effect, small (and generally difficult to detect) effects, or unknown effects (*lower left*). Variants that are common and produce large effects are unusual (*upper right*); some pharmacogenetic variants are common and produce clinically important effects on drug exposure. Other genetically-determined responses to environmental stressors may also fall into this region. The effects of uncommon variants (the *black box* of minor allele frequencies <1.0%) are largely unexplored since those experiments require sequencing or genotyping in large numbers of subjects and these technologies are only now being deployed

trait such as arrhythmias and a rough relationship between the frequency of disease-associated alleles and their effect sizes (Fig. 3.1). At one end of the spectrum are very rare variants with very large effect sizes, such as those seen in channelopathies or cardiomyopathies. Even here, it is not unusual to see a kindred with multiple members carrying the same DNA variant with one carrier having a severe phenotype (such as markedly prolonged QT intervals and multiple episodes of torsades de pointes), and another carrier in the same family having normal QT intervals and no arrhythmias [5]. The reasons for such "incomplete penetrance" remain ill-defined, but a leading hypothesis suggests that "genetic background", the effect of other genetic variants, may promote or inhibit development of the phenotype in the specific individual, even within the same kindred [6–8]. Thus, the phenotype in even monogenic diseases likely has important contributions from other genetic variants.

At the other end of the spectrum are common variants (often defined as a minor allele frequency > 1–5%) in a population. Because such variants are so common, they cannot, by definition, be severely detrimental since otherwise they would not persist in a population. However, as discussed further below, even common variants can contribute modestly to susceptibility to a human trait (including AF and SCD). In addition, common variants can modulate the severity of a rare variant (i.e. they may modulate penetrance). They may also produce large effect sizes on exposure to environmental stressors; a notable example is highly variable drug responses, determined by common genetic variants.

Conventional Approaches to Finding Genes in Familial Traits

The conventional approach (until recently) to finding a disease-associated gene in a family was to identify a multigenerational kindred in which multiple members are affected by a readily ascertained phenotype such as QT interval prolongation, marked septal hypertrophy, or early onset atrial fibrillation. Each member of the family was assigned a phenotype (affected or not), assumptions were made about penetrance, and each family member was genotyped at known common polymorphic sites (often short tandem repeats) across the genome. A formal statistical approach termed "linkage" was then used to identify regions of the genome at which the genotype at the polymorphic sites associated with the phenotype. The linked region would then be searched for specific variants in biologically plausible genes to identify causative mutations in the kindred. The larger the family, the denser the genomic markers, and the more robust the phenotype assignment, the more likely it was that a locus associated with the disease could be identified. Linkage analysis was the technology used to identify the first disease genes in conditions such as hypertrophic cardiomyopathy and the long QT syndromes.

In the long QT syndrome, early studies using linkage analysis identified the three major disease genes *KCNQ1*, *KCNH2*, and *SCN5A*; this is an example of "genetic heterogeneity" the phenomenon that mutations in different genes can confer the same or similar phenotypes. Functional assays were then developed and showed the potassium channel mutations decreased the outward repolarizing potassium currents I_{Kr} and I_{Ks}, while the sodium channel mutation increased late sodium current [9]. These pathophysiologic insights then suggested that rare variants in the same genes might also be causes of the long QT syndrome. However, most families are small, and often include few affected members. In these cases, linkage is not possible and so a common approach is to sequence known disease genes, searching for rare variants previously associated with the disease or for previously-unreported rare variants; the evidence is bolstered if the rare variants are known to alter function in *in vitro* assays. An extension of this logic has been to sequence not only known disease genes, but also genes encoding other ion channels or their interacting proteins known to decrease repolarizing currents or increase late depolarizing sodium

(or calcium) currents. This approach has been used to identify rare variants that then become plausible causes of long QT syndrome in patients in whom mutations in the commoner, more well-established, disease genes are absent [10]. Similarly, initial linkage-based discovery was followed by candidate gene identification in hypertrophic and dilated cardiomyopathies, including arrhythmogenic right ventricular dysplasia. The drawback of this approach is that the statistical argument is weaker than with formal linkage, and the possibility exists that a rare variant, even in a biologically plausible candidate gene, may in fact not be causative.

Contemporary Approaches to Finding Trait Associated Genetic Variation

The initial draft of the first human genome has enabled new tools for analysis of genetic contribution to both rare and common diseases. One such tool is the ability to genotype large numbers of known common polymorphic sites across the genome, and associate variability at those sites with common human diseases, the "genome wide association study" (GWAS) paradigm discussed further below. In addition, in the last 10 years, newer "next generation" sequencing approaches have become increasingly inexpensive and robust and are rapidly finding a place in discovery of new disease genes and variants.

A wonderful example of the power of new sequencing approaches to find disease genes is illustrated by a study that examined two neonates with a particularly severe form of the long QT syndrome [11]. In both cases, the parents were phenotypically normal and there were no other affected family members. In such cases, the causative variant likely represents a "*de novo* mutation" (i.e. one arising in the absence of that mutation in either parent) or a case of autosomal recessive disease (i.e. both parents carry an abnormal allele, but are phenotypically normal and the phenotype only arises in the child who inherits the abnormal allele from both parents). Prior to the availability of next generation sequencing, analysis of such cases as this would be confined to sequencing only of known candidate genes, such as the already described long QT syndrome disease genes. In these two cases, sequencing the known genes found no likely causative variant. However, sequencing whole exomes identified ~20,000 coding region variants in each child. Of these, a very small minority (~30) were *de novo* (determined by exome sequencing in the parents), and an even smaller subset were non-synonymous, never observed previously, and validated by conventional sequencing. After this filtering exercise, both children were found to harbor mutations in the calcium sensing protein calmodulin. Interestingly, three separate genes encode the identical calmodulin protein, presumably some with preferential expression in heart, and one proband had a mutation in *CALM1* and the other in *CALM2*. Both variants alter calmodulin affinity for calcium and while the underlying details of the mechanisms whereby these mutations prolong QT interval remain to be fully elucidated, the genetic approaches demonstrate the power of next generation sequencing to identify new disease genes even in small kindreds, and demonstrate rare variants in calmodulin can confer arrhythmia phenotypes. Interestingly, other mutations in calmodulin have now been associated with catecholaminergic polymorphic VT and other phenotypes, an example of the phenomenon of "phenotypic heterogeneity" in which different mutations in the same gene can cause a range of different phenotypes.

The Genome-Wide Association Study

The GWAS paradigm studies large numbers of subjects drawn from a general population and assigned a phenotype. Phenotypes analyzed by GWAS can be categorical (e.g. atrial fibrillation by age 60: yes/no) or continuous (QRS or QT interval duration). Individuals across the population are genotyped at approximately a million known common SNP sites and sites associated with the trait are then identified. In general, since GWAS focuses on common SNP sites, the effect size of each SNP is very modest, although the associated P-values can be amazingly small. For example, in a GWAS analyzing variability in the QTc across ~100,000 subjects, the most statistically significant associations were with SNPs near the *NOS1AP* gene, encoding an accessory protein for neuronal nitric oxide synthase: the P-values were as low as 10^{-213}, but the effect size per variant SNP was approximately 3.5 ms per allele [12]. GWAS has now been used to study over 2000 traits [13]; there are several important points a reader should bear in mind when presented with GWAS data:

1. GWAS is a starting point for further studies to elucidate function at the linked locus and thus mechanisms underlying the association. A number of studies have implicated *NOS1AP* as a modulator of calcium, potassium, or sodium channel function in heart [14, 15], its exact role remains incompletely determined.
2. The "best" SNP association merely identifies a region of the genome associated with the trait and does not imply that the specific SNP analyzed has any function. Rather, it serves as a "signpost" in the genome to indicate the region probably contains functional variants.
3. The P-value does not imply a large effect size, as described above. It is, in fact, unusual for GWAS to yield odds ratios (OR) >2, with a couple of exceptions noted below. While an exact cut-off for an OR to become "actionable" is not defined, a value >10 has been proposed [16]. Thus

genotyping patients for risk SNPs discovered by GWAS is unlikely to be clinically useful. At this point, GWAS associations are best interpreted as new biology, waiting for underlying mechanisms. Many of these associations will be false positives; however, some may lead to new biomarkers or new drugs.

4. Most SNP associations are not in coding regions but are intronic or intergenic. Indeed, the gene closest to a highly statistically significant SNP may not be the gene that harbors causative variants accounting for the trait. One nice example came from a GWAS examining variability in QRS duration [17]: the top SNP was in *SCN10A*, a gene encoding a sodium channel known to be important in dorsal root ganglion function but previously not thought to have a role in the heart. Subsequent studies have implicated the *SCN10A* gene product as potentially playing a role in modulating late sodium current in cardiomyocytes [18]. However, it is also clear that the variant in *SCN10A* is within a regulatory region important for modulating expression of *SCN5A*, the gene that encodes the cardiac sodium channel that is directly adjacent to *SCN10A* in the genome [19, 20]. Thus, the top SNPs in the QRS GWAS are within *SCN10A* but modulate cardiac conduction by regulating expression not of *SCN10A* but of *SCN5A*, the adjacent cardiac sodium gene.
5. GWAS provides an unbiased look across the whole genome and thus identifies new biological pathways that other approaches will miss. The idea that variants near *NOS1AP* modulate QTc would not have been discovered without an unbiased look across the whole genome. The post-GWAS challenge is to identify the functional variants conferring the signal, and the underlying biology.
6. The GWAS paradigm generates P values associated with a million or more independent tests of association and so has a very high false positive rate. A generally accepted P-value threshold for significance is therefore not 0.05 but rather $0.05/10^6$, $P < 10^{-8}$. Moreover, a GWAS signal at "genome-wide" significance generally represents an initial hypothesis requiring further validation. This can come in the form of data from different methods such as functional studies or more commonly replication of the signal in other large datasets. Thus, reports of GWAS often include thousands or tens of thousands of cases and controls.
7. There are exceptions to the rule of very large numbers. One is in pharmacogenetics, possibly because there is no evolutionary or survival disadvantage to a common pharmacogenetic variant since drug exposure is a new environmental stressor. For example, a GWAS examining a very small number (51) of cases of hepatitis after exposure to a new antibiotic and 282 controls exposed to the antibiotic but not developing hepatitis identified a single GWAS association in the major histocompatibility complex region with a P-value of 8.7×10^{-33}. Follow up studies have identified a specific HLA allele, HLA-B*57:01 as conferring risk with an OR = 81. Another example is a study that compared a relatively small number of cases (312) of Brugada syndrome and 1115 population controls and identified two very strong signals [21], one at the *SCN10A* locus controlling conduction and the other near *HEY2*, a gene previously not implicated in cardiac electrophysiology and now thought to regulate ion channel expression. Despite the relatively small numbers (for a GWAS), the OR for individuals carrying multiple risk alleles was as high as 21.5.
8. GWAS associations can point to modulators of penetrance in rare disease. For example, a number of studies have identified common variants at *NOS1AP* as modulators of penetrance in the long QT syndromes. Each variant *NOS1AP* allele appears to confer a 1.4-fold increase in risk of arrhythmias, even among individuals with similar QT intervals [6, 7]. A second example is in kindreds of multiple affected members with atrial fibrillation, where common AF-associated variants at the 4q25 locus discussed further below have been found to modulate penetrance [22].

Specific Arrhythmias: Atrial Fibrillation

The Framingham Heart Study has reported that a parental history of AF confers an OR > 3 for AF risk [23]. Up to 20% of subjects with AF and no other risk factors (sometimes termed "lone" AF) have a family member with AF [24, 25], further supporting a genetic contribution to susceptibility. Linkage in large kindreds has identified variants in *KCNQ1* and in *NPPA* (encoding atrial natriuretic peptide [ANP]) [26, 27]; interestingly, in both cases the causative mutation is a "gain of function" (increased K^+ current, increased ANP concentration). However, most kindreds with AF are too small for linkage or even exome sequencing. In some cases, rare variants in logical candidate genes, such as ion channel genes [22, 28], have been identified, although the strength of the evidence in these cases is less strong than with conventional linkage.

One of the most dramatic examples of the success of GWAS to identify new biological pathways has been its application in AF. In an initial study, 550 Icelandic AF cases and 4476 controls were used to identify a risk locus at chromosome 4q25 [29]. Interestingly, the closest gene, *PITX2,* encodes a transcription factor with a cardiac specific splice variant thought to regulate left-right asymmetry during development. Within several weeks of publication of the initial GWAS result came a report that *PITX2* is critical for the development of the "pulmonary myocardium", the sleeve of left atrial myocardium that invaginates, to a variable degree,

into the pulmonary veins [30] and represents a common source for AF [31].

Sequencing the *PITX2* coding region has not identified non-synonymous SNPs associated with AF. In mice in which the cardiac specific isoform has been deleted, AF is readily induced, and transcripts encoding for known pro-AF genes, such as *KCNQ1* and *NPPA*, are increased [32]. The most recent large AF meta-analysis involved 6707 cases and 52,426 controls (with replication in a further 5381 cases and 10,030 controls) [33]; the 4q25 variants near *PITX2* were replicated with P-values as low as 10^{-74} and each allele conferring a risk of ~1.6. Taken together, therefore, the statistical and functional data suggest that variants in *PITX2* drive AF susceptibility, although that formally remains a hypothesis.

Other studies, notably in lone AF, have identified variants near the potassium channel *KCNN3* [34] and the transcription factor *ZFHX3* [35], and the large meta-analysis confirmed these and identified six further linked loci. AF-associated variants near 4q25 have been studied in multiple clinical scenarios related to AF, and have been associated with successful rhythm control by antiarrhythmic drugs [36], recurrent AF after cardioversion [37], risk for post-cardiac surgery AF [38], success of catheter ablation for AF [39], risk of cardioembolic stroke [40, 41], and penetrance of rare AF-associated variants in families with multiple affected members [22]. Another study has reported that a common nsSNP in the beta1 adrenergic receptor gene increases the likelihood of successful rate control in AF [42].

Specific Arrhythmias: Sudden Cardiac Death

SCD most commonly occurs as a complication of an acute coronary syndrome. Thus, a major genetic contributor to SCD risk are those genes involved in lipid metabolism and susceptibility to myocardial infarction, not further discussed here. There are data, described further below, that a family history of SCD increases the risk in an individual patient. One possibility is that coronary occlusion increases the likelihood of a fatal arrhythmia in a patient with a subclinical channelopathy such as long QT syndrome or Brugada syndrome [43]. Another possibility is that variants in other genes, as yet undetected, contribute to risk.

The Paris Prospective Study I followed 7079 men recruited in 1967–1972 and followed over time. There were 118 sudden deaths in individuals age < 65, and having a parent with SCD at age < 65 conferred a statistically significant OR = 2.0 [44]. The Arrhythmia Genetics in the NEtherlands Study (AGNES) compared 330 individuals with ventricular fibrillation (VF) within the first 90 min of a first ST segment elevation myocardial infarction (STEMI) with 372 controls with a first STEMI but no VF. There were only two multivariate predictors of VF, the extent of ST segment elevation (OR 1.3–2) and a family history of sudden death (OR 1.8–4.0). The AGNES study has been analyzed by GWAS and a single statistically significant associated locus was identified at chromosome 21p21 [45]; the nearest gene is *CXADR*, which encodes a receptor for Coxsackie virus that has been implicated in myocarditis susceptibility and as a modulator of cardiac conduction. The GWAS is small, and further functional and/or genetic studies will be required to validate this signal.

Specific Arrhythmias: Drug-Induced Torsades de Pointes

Torsades de pointes, polymorphic ventricular tachycardia occurring at a "relatively" slow rate (e.g. 160–300 beats per minute) in setting of QT prolongation is the rhythm typically seen in congenital long QT syndromes as well as in a drug-induced form. There is some evidence that risk for drug-induced torsades de pointes (diTdP) includes an individual susceptibility or genetic component. In one study, first degree relatives of subjects with diTdP displayed greater QT interval prolongation on challenge with quinidine than did subjects without a family history of diTdP [46]. In another study, challenge with intravenous sotalol in subjects with a history of diTdP produced much greater QT prolongation than did the same challenge in age- and sex-matched controls [47].

The clinical similarities between the congenital and drug-induced forms of the arrhythmia also suggest a genetic basis for the disease. Early after identification of the first congenital long QT syndrome disease genes, a number of groups tested the hypothesis that diTdP actually represents subclinical cases of the congenital syndrome, revealed by drug challenge. Anecdotes and small series [48–51] support the idea that 5–20% (as high as 40% in one series [52]) of cases of diTdP do arise through this mechanism.

In a candidate gene study, genotypes at 1424 SNPs in 18 candidate genes were assessed in 176 cases of diTdP and two sets of controls, 207 patients receiving QT prolonging antiarrhythmics and tolerating them without marked QT prolongation, and 837 population controls. In that study, a single nsSNP, resulting in D85N in *KCNE1* (a protein modulating the "slow" cardiac repolarizing potassium current I_{Ks}) was present in 1.8–2.9% of controls and 8.6% of cases with an OR = 9–12. A GWAS compared 216 cases of diTdP to 771 drug-exposed or population ancestry-matched controls and found no signal even approaching genome-wide significance [53]. Exome sequencing in 65 cases of diTdP and 148 controls previously tolerating QT prolonging antiarrhythmics revealed a slightly higher frequency of rare nsSNPs in cardiac potassium channel genes in cases (37%) compared to controls (21%). Taken together, these genomic data suggest that subclinical congenital long QT syndrome is a mecha-

nism for diTdP in a minority of cases, that *KCNE1* D85N represents a common risk allele, and that as yet undescribed factors contribute to risk. One recently-described potential contributor is drug-induced enhancement of late sodium current [54].

Antiarrhythmic Drug Pharmacogenetics

Genetic factors may modulate plasma concentrations and effects of many widely-used drugs including antiarrhythmics and anticoagulants [55]. When a drug is eliminated by a single cytochrome P450 (CYP) or requires bioactivation by a single CYP, genetic variants that cause loss of function may produce especially prominent clinical effects, a situation termed "high risk pharmacokinetics" [56].

The sodium channel blocking antiarrhythmic propafenone, which also has beta blocking activity, is metabolized by CYP2D6 to 5-hydroxypropafenone, a metabolite with some sodium channel-blocking activity but devoid of beta blockade. Poor metabolizer (PM) subjects, those in whom CYP2D6 activity is absent (5–10% of the Caucasian and African ancestry populations), are homozygotes or compound heterozygotes for loss-of-function variants in the gene. In PM subjects, propafenone plasma concentrations accumulate to a greater degree than in extensive metabolizers and beta blockade is more readily demonstrated [57, 58]; some cases of propafenone related bradycardia or bronchospasm likely arise through this mechanism. Flecainide is also a CYP2D6 substrate, but is also eliminated by renal excretion of unchanged drug. Therefore, under ordinary conditions, even a PM subject receiving flecainide does not demonstrate unusual drug accumulation or toxicity. However, if such a subject develops renal failure, flecainide accumulation and toxicity can ensue [59]. A number of beta blockers such as metoprolol and timolol are also metabolized by CYP2D6 and PM subjects may therefore demonstrate greater beta blocking activity [60, 61].

Procainamide is metabolized by N-acetylation and other drug metabolizing pathways, notably oxidation, have also been described. Subjects with loss-of-function variants in *NAT2* ("slow acetylators") are known to have a higher incidence of procainamide-induced lupus [62]. One theory suggests that in these subjects, more drug is subject to oxidative metabolism, with generation of reactive metabolites that then elicit the lupus syndrome.

Other antiarrhythmic drugs are metabolized by multiple pathways and pharmacogenetic variants do not generally affect their plasma concentrations or efficacy. However, both quinidine and amiodarone are potent inhibitors of a number of CYPs, notably CYP2D6 and, in the case of amiodarone, other CYPs such as CYP3A4 and CYP2C9. Therefore, patients receiving drugs metabolized through these pathways may demonstrate changing efficacy or toxicity when quinidine or amiodarone is added to their regimens. One notable example is warfarin, whose active enantiomer is metabolized by CYP2C9. Amiodarone, by inhibiting CYP2C9, predisposes to elevated drug concentration and bleeding risk unless dosages are adjusted downward.

Common variants in *CYP2C9* which reduce or eliminate CYP2C9 function have been described. In Caucasians, these include CYP2C9*2 (reduction of function) and CYP2C9*3 (loss of function) [63, 64] while other variants (*6, *8, and *11) predominate in subjects of African origin [65]. Warfarin exerts its anticoagulant effects by inhibiting vitamin K metabolism by binding to VKORC1, a component of the vitamin K complex. Rare variants in *VKORC1* have been described in subjects with relative or absolute warfarin resistance (requiring >10–20 mg/day for anticoagulation) [66, 67]. In addition, very common variants in the VKORC1 promotor modulate the amount of messenger RNA detected in the liver, and this, in turn, correlates well with warfarin dose requirement [68]; variants other genes involved in vitamin K metabolism (notably *CYP4F2*) have also been implicated in variable warfarin dose requirements [69, 70]. Large randomized clinical trials have compared genetically-guided warfarin dosing algorithms to clinical warfarin dosing and have detected either no difference in or a small difference in time in therapeutic range during the first 30–90 days of therapy [71, 72]. However, these trials did not examine influence of genetics on bleeding since they followed subjects for only 3 months and bleeding events were rare. Other studies have accrued larger numbers of subjects with warfarin related bleeding (and controls), and have reported that variants in *CYP2C9* and in *CYP4F2* increase bleeding risk [73, 74].

Summary and Cautionary Notes

The application of modern genetic techniques to families with rare but highly lethal conditions has represented a triumph in modern diagnostics and has led to important understanding of underlying physiologic processes: for example, elucidating the role of individual ion currents in the congenital long QT syndrome has provided a framework for hundreds of studies examining normal and abnormal repolarization. The application of genotyping and sequencing technologies to common and rare arrhythmia syndromes has led to identification of new genetic markers of arrhythmia susceptibility whose biology is only now being explored and may, therefore, similarly alter our view of normal physiology and how it is perturbed in arrhythmias.

As sequencing becomes more and more widespread, patients with rare variants in key arrhythmia genes, such as the congenital long QT syndrome disease genes, are increasingly identified. In one study in over 2022 normal subjects,

11% harbored rare non-synonymous variants in *SCN5A* and *KCNH2*, and while 34% of these variants were judged by experienced laboratories to be potentially pathogenic, very few subjects had any associated arrhythmia phenotype [75]. Thus, the difficulty facing the practicing physician will be how to interpret genetic data while robust tools to assess likely pathogenicity of those variants are still in development. Further, as sequence data become increasingly available to physicians and patients, the question of when an odds ratio or some other metric of genetic effect size becomes "actionable" is likely to loom large. Actions might include changing a drug, diagnostic evaluations for arrhythmia risk, or initiating device ablation or drug therapy. Each of these may impose risks as well as benefits and understanding that balance will be an emerging challenge in arrhythmia genomics.

References

1. Manolio TA, Chisholm RL, Ozenberger B, Roden DM, Williams MS, Wilson R, et al. Implementing genomic medicine in the clinic: the future is here. Genet Med. 2013;15(4):258–67.
2. Koopmann TT, Alders M, Jongbloed RJ, Guerrero S, Mannens MM, Wilde AA, et al. Long QT syndrome caused by a large duplication in the KCNH2 (HERG) gene undetectable by current polymerase chain reaction-based exon-scanning methodologies. Heart Rhythm. 2006;3(1):52–5.
3. Barc J, Briec F, Schmitt S, Kyndt F, Le Cunff M, Baron E, et al. Screening for copy number variation in genes associated with the long QT syndrome: clinical relevance. J Am Coll Cardiol. 2011;57(1):40–7. Epub 2010/12/28.
4. Williams VS, Cresswell CJ, Ruspi G, Yang T, Atak TC, McLoughlin M, et al. Multiplex ligation-dependent probe amplification copy number variant analysis in patients with acquired long QT syndrome. Europace. 2015;17(4):635–41. Epub 2015/01/08.
5. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. Circulation. 1999;99(4):529–33.
6. Crotti L, Monti MC, Insolia R, Peljto A, Goosen A, Brink PA, et al. NOS1AP Is a Genetic Modifier of the Long-QT Syndrome. Circulation. 2009;120(17):1657–63.
7. Tomas M, Napolitano C, De GL, Bloise R, Subirana I, Malovini A, et al. Polymorphisms in the NOS1AP gene modulate QT interval duration and risk of arrhythmias in the long QT syndrome. J Am Coll Cardiol. 2010;55(24):2745–52.
8. Duchatelet S, Crotti L, Peat RA, Denjoy I, Itoh H, Berthet M, et al. Identification of a KCNQ1 polymorphism acting as a protective modifier against arrhythmic risk in long-QT syndrome. Circ Cardiovasc Genet. 2013;6(4):354–61.
9. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell. 2001;104(4):569–80.
10. Schwartz PJ, Ackerman MJ, George Jr AL, Wilde AAM. Impact of genetics on the clinical management of channelopathies. J Am Coll Cardiol. 2013;62(3):169–80.
11. Crotti L, Johnson CN, Graf E, De Ferrari GM, Cuneo BF, Ovadia M, et al. Calmodulin mutations associated with recurrent cardiac arrest in infants. Circulation. 2013;127(9):1009–17.
12. Arking DE, Pulit SL, Crotti L, van der Harst P, Munroe PB, Koopmann TT, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. Nat Genet. 2014;46(8):826–36. Epub 2014/06/24.
13. Hindorff LA, MacArthur J, Morales J, Junkins HA, Hall PN, Klemm AK, et al. A catalog of published genome-wide association studies. 2015. www.genome.gov/gwastudies. Accessed 30 Dec 2015.
14. Chang KC, Barth AS, Sasano T, Kizana E, Kashiwakura Y, Zhang Y, et al. CAPON modulates cardiac repolarization via neuronal nitric oxide synthase signaling in the heart. Proc Natl Acad Sci USA. 2008;105(11):4477–82.
15. Kapoor A, Sekar Rajesh B, Hansen Nancy F, Fox-Talbot K, Morley M, Pihur V, et al. An enhancer polymorphism at the cardiomyocyte intercalated disc protein NOS1AP locus is a major regulator of the QT interval. Am J Hum Genet. 2014;94(6):854–69.
16. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am J Epidemiol. 2004;159(9):882–90.
17. Sotoodehnia N, Isaacs A, de Bakker PI, Dorr M, Newton-Cheh C, Nolte IM, et al. Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction. Nat Genet. 2010;42(12):1068–76.
18. Yang T, Atack TC, Stroud DM, Zhang W, Hall L, Roden DM. Blocking Scn10a channels in heart reduces late sodium current and is antiarrhythmic. Circ Res. 2012;111(3):322–32.
19. van den Boogaard M, Wong LYE, Tessadori F, Bakker ML, Dreizehnter LK, Wakker V, et al. Genetic variation in T-box binding element functionally affects SCN5A/SCN10A enhancer. J Clin Invest. 2012;122(7):2519–30.
20. van den Boogaard M, Smemo S, Burnicka-Turek O, Arnolds DE, van de Werken HJ, Klous P, et al. A common genetic variant within SCN10A modulates cardiac SCN5A expression. J Clin Invest. 2014;124(4):1844–52. Epub 2014/03/20.
21. Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud J-B, Simonet F, et al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet. 2013;45(9):1044–9.
22. Ritchie MD, Rowan S, Kucera G, Stubblefield T, Blair M, Carter S, et al. Chromosome 4q25 variants are genetic modifiers of rare ion channel mutations associated with familial atrial fibrillation. J Am Coll Cardiol. 2012;60(13):1173–81.
23. Fox CS, Parise H, D'Agostino Sr RB, Lloyd-Jones DM, Vasan RS, Wang TJ, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA. 2004;291(23):2851–5.
24. Darbar D, Herron KJ, Ballew JD, Jahangir A, Gersh BJ, Shen WK, et al. Familial atrial fibrillation is a genetically heterogeneous disorder. J Am Coll Cardiol. 2003;41(12):2185–92.
25. Ellinor PT, Yoerger DM, Ruskin JN, Macrae CA. Familial aggregation in lone atrial fibrillation. Hum Genet. 2005;118(2):179–84.
26. Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY, et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. Science. 2003;299(5604):251–4.
27. Hodgson-Zingman DM, Karst ML, Zingman LV, Heublein DM, Darbar D, Herron KJ, et al. Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation. N Engl J Med. 2008;359(2):158–65.
28. Weeke P, Muhammad R, Delaney JT, Shaffer C, Mosley JD, Blair M, et al. Whole-exome sequencing in familial atrial fibrillation. Eur Heart J. 2014;35(36):2477–83. Epub 2014/04/15.
29. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. Nature. 2007;448(7151):353–7.
30. Mommersteeg MTM, Brown NA, Prall OWJ, de Gier-de Vries C, Harvey RP, Moorman AFM, et al. Pitx2c and Nkx2-5 are required for the formation and identity of the pulmonary myocardium. Circ Res. 2007;101(9):902–9.
31. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by

ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659–66.
32. Wang J, Klysik E, Sood S, Johnson RL, Wehrens XH, Martin JF. Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification. Proc Natl Acad Sci U S A. 2010;107(21):9753–8. Epub 2010/05/12.
33. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, et al. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. Nat Genet. 2012;44(6):670–5. Epub 2012/05/01.
34. Ellinor PT, Lunetta KL, Glazer NL, Pfeufer A, Alonso A, Chung MK, et al. Common variants in KCNN3 are associated with lone atrial fibrillation. Nat Genet. 2010;42(3):240–4.
35. Gudbjartsson DF, Holm H, Gretarsdottir S, Thorleifsson G, Walters GB, Thorgeirsson G, et al. A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. Nat Genet. 2009;41(8):876–8.
36. Parvez B, Vaglio J, Rowan S, Muhammad R, Kucera G, Stubblefield T, et al. Symptomatic response to antiarrhythmic drug therapy is modulated by a common single nucleotide polymorphism in atrial fibrillation. J Am Coll Cardiol. 2012;60(6):539–45. Epub 2012/06/26
37. Parvez B, Shoemaker MB, Muhammad R, Richardson R, Jiang L, Blair MA, et al. Common genetic polymorphism at 4q25 locus predicts atrial fibrillation recurrence after successful cardioversion. Heart Rhythm. 2013;10(6):849–55.
38. Body SC, Collard CD, Shernan SK, Fox AA, Liu KY, Ritchie MD, et al. Variation in the 4q25 chromosomal locus predicts atrial fibrillation after coronary artery bypass graft surgery. Circ Cardiovasc Genet. 2009;2(5):499–506.
39. Shoemaker MB, Bollmann A, Lubitz SA, Ueberham L, Saini H, Montgomery J, et al. Common genetic variants and response to atrial fibrillation ablation. Circ Arrhythm Electrophysiol. 2015;8(2):296–302. Epub 2015/02/17.
40. Gretarsdottir S, Thorleifsson G, Manolescu A, Styrkarsdottir U, Helgadottir A, Gschwendtner A, et al. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. Ann Neurol. 2008;64(4):402–9.
41. Lemmens R, Buysschaert I, Geelen V, Fernandez-Cadenas I, Montaner J, Schmidt H, et al. The association of the 4q25 susceptibility variant for atrial fibrillation with stroke is limited to stroke of cardioembolic etiology. Stroke. 2010;41(9):1850–7. Epub 2010/07/31.
42. Parvez B, Chopra N, Rowan S, Vaglio JC, Muhammad R, Roden DM, et al. A common beta1-adrenergic receptor polymorphism predicts favorable response to rate-control therapy in atrial fibrillation. J Am Coll Cardiol. 2012;59(1):49–56. Epub 2011/12/24.
43. Albert CM, MacRae CA, Chasman DI, VanDenburgh M, Buring JE, Manson JE, et al. Common variants in cardiac ion channel genes are associated with sudden cardiac death. Circ Arrhythm Electrophysiol. 2010;3(3):222–9.
44. Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population: the Paris Prospective Study I. Circulation. 1999;99(15):1978–83.
45. Bezzina CR, Pazoki R, Bardai A, Marsman RF, de Jong JS, Blom MT, et al. Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction. Nat Genet. 2010;42(8):688–91.
46. Kannankeril PJ, Roden DM, Norris KJ, Whalen SP, George Jr AL, Murray KT. Genetic susceptibility to acquired long QT syndrome: pharmacologic challenge in first-degree relatives. Heart Rhythm. 2005;2(2):134–40.
47. Kaab S, Hinterseer M, Nabauer M, Steinbeck G. Sotalol testing unmasks altered repolarization in patients with suspected acquired long-QT-syndrome--a case-control pilot study using i.v. sotalol. Eur Heart J. 2003;24(7):649–57.
48. Donger C, Denjoy I, Berthet M, Neyroud N, Cruaud C, Bennaceur M, et al. KVLQT1 C-terminal missense mutation causes a forme fruste long-QT syndrome. Circulation. 1997;96(9):2778–81.
49. Napolitano C, Priori SG, Schwartz PJ, Cantu F, Paganini V, Matteo PS, et al. Identification of a long QT syndrome molecular defect in drug-induced torsades de pointes. Circulation. 1997;96:I–211.
50. Paulussen AD, Gilissen RA, Armstrong M, Doevendans PA, Verhasselt P, Smeets HJ, et al. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. J Mol Med. 2004;82(3):182–8.
51. Yang P, Kanki H, Drolet B, Yang T, Wei J, Viswanathan PC, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation. 2002;105(16):1943–8. Epub 2002/05/09.
52. Itoh H, Sakaguchi T, Ding WG, Watanabe E, Watanabe I, Nishio Y, et al. Latent genetic backgrounds and molecular pathogenesis in drug-induced long QT syndrome. Circ Arrhythm Electrophysiol. 2009;2:511–23.
53. Behr ER, Ritchie MD, Tanaka T, Kaab S, Crawford DC, Nicoletti P, et al. Genome wide analysis of drug-induced torsades de pointes: lack of common variants with large effect sizes. PLoS One. 2013;8(11):e78511. Epub 2013/11/14.
54. Yang T, Chun YW, Stroud DM, Mosley JD, Knollmann BC, Hong C, et al. Screening for acute IKr block is insufficient to detect torsades de pointes liability: role of late sodium current. Circulation. 2014;130(3):224–34. Epub 2014/06/05.
55. Roden DM, Johnson JA, Kimmel SE, Krauss RM, Medina MW, Shuldiner A, et al. Cardiovascular pharmacogenomics. Circ Res. 2011;109(7):807–20. Epub 2011/09/17.
56. Roden DM, Stein CM. Clopidogrel and the concept of high-risk pharmacokinetics. Circulation. 2009;119(16):2127–30.
57. Siddoway LA, Thompson KA, McAllister CB, Wang T, Wilkinson GR, Roden DM, et al. Polymorphism of propafenone metabolism and disposition in man: clinical and pharmacokinetic consequences. Circulation. 1987;75:785–91.
58. Lee JT, Kroemer HK, Silberstein DJ, Funck-Brentano C, Lineberry MD, Wood AJ, et al. The role of genetically determined polymorphic drug metabolism in the beta-blockade produced by propafenone. N Engl J Med. 1990;322:1764–8.
59. Evers J, Eichelbaum M, Kroemer HK. Unpredictability of flecainide plasma concentrations in patients with renal failure: relation to side effects and sudden death? Ther Drug Monit. 1994;16:349–51.
60. Edeki TI, He H, Wood AJ. Pharmacogenetic explanation for excessive beta-blockade following timolol eye drops. Potential for oral-ophthalmic drug interaction. J Am Med Assoc. 1995;274(20):1611–3.
61. Lennard MS, Silas JH, Freestone S, Trevethick J. Defective metabolism of metoprolol in poor hydroxylators of debrisoquine. Br J Clin Pharmacol. 1982;14:301–3.
62. Woosley RL, Drayer DE, Reidenberg MM, Nies AS, Carr K, Oates JA. Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. N Engl J Med. 1978;298:1157–9.
63. Rettie AE, Wienkers LC, Gonzalez FJ, Trager WF, Korzekwa KR. Impaired (S)-warfarin metabolism catalysed by the R144C allelic variant of CYP2C9. Pharmacogenetics. 1994;4(1):39–42.
64. Steward DJ, Haining RL, Henne KR, Davis G, Rushmore TH, Trager WF, et al. Genetic association between sensitivity to warfarin and expression of CYP2C9*3. Pharmacogenetics. 1997;7(5):361–7.
65. Ramirez AH, Shi Y, Schildcrout J, Delaney JT, Xu H, Oetjens M, et al. Predicting warfarin dosages in European-American and African-American subjects using DNA samples linked to an electronic health record. Pharmagenomics. 2012;13(4):407–18.

66. Rost S, Fregin A, Ivaskevicius V, Conzelmann E, Hortnagel K, Pelz HJ, et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature. 2004;427(6974):537–41.
67. Harrington DJ, Gorska R, Wheeler R, Davidson S, Murden S, Morse C, et al. Pharmacodynamic resistance to warfarin is associated with nucleotide substitutions in VKORC1. J Thromb Haemost. 2008;6(10):1663–70.
68. Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. 2005;352(22):2285–93.
69. Takeuchi F, McGinnis R, Bourgeois S, Barnes C, Eriksson N, Soranzo N, et al. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. PLoS Genet. 2009;5(3):e1000433.
70. Caldwell MD, Awad T, Johnson JA, Gage BF, Falkowski M, Gardina P, et al. CYP4F2 genetic variant alters required warfarin dose. Blood. 2008;111(8):4106–12.
71. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med. 2013;369(24):2283–93.
72. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med. 2013;369(24):2294–303.
73. Roth JA, Boudreau D, Fujii MM, Farin FM, Rettie AE, Thummel KE, et al. Genetic risk factors for major bleeding in warfarin patients in a community setting. Clin Pharmacol Ther. 2014;95(6):636–43. Epub 2014 Feb 6.
74. Kawai VK, Cunningham A, Vear SI, Van Driest SL, Oginni A, Xu H, et al. Genotype and risk of major bleeding during warfarin treatment. Pharmacogenomics. 2014;15(16):1973–83. Epub 2014/12/19.
75. Van Driest S, Wells Q, Stallings S, Bush W, Gordon A, Nickerson D, et al. Association Of arrhythmia related genetic variants with phenotypes documented in electronic health records. JAMA. 2016;315(1):47–57.

Channelopathies: Clinical Presentation and Genetics

4

J. Martijn Bos and Michael J. Ackerman

Abstract

Over the last three decades, the field of genetic cardiac arrhythmia diseases has transformed to where genetic testing has become an integral part of diagnosis, treatment and follow- up, including family evaluation. In fact, in some cases these genetic discoveries have enabled pre-clinical diagnosis thereby possibly preventing one of its most devastating, and sometimes sentinel, event of sudden cardiac death (SCD). This is certainly true for the cardiac channelopathies, heritable cardiac arrhythmia syndromes caused by abnormal ion channel function clinically leading to syncope, seizures, and SCD, often in the setting of a structurally normal heart. These inherited and potentially lethal arrhythmia disorders include a variety of diseases, of which the most common ones—long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT)—will be discussed in this chapter. As will be outlined, not only can genetics help (or complicate) diagnosis of these channelopathies, important genotype-phenotype correlations have emerged that might aid in risk stratification for these conditions, and genotype specific therapies are available in certain situations.

Keywords

Arrhythmias • Brugada syndrome (BrS) • Catecholaminergic polymorphic ventricular tachycardia (CPVT) • Channelopathies • Genes • Genetics • Implantable cardioverter defibrillator (ICD) • Long QT syndrome (LQTS) • Sudden cardiac death • Syncope • Beta-blockers

J.M. Bos, M.D., Ph.D. (✉)
Division of Pediatric Cardiology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA

Department of Molecular Pharmacology and Experimental, Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA
e-mail: Bos.Martijn@mayo.edu

M.J. Ackerman, M.D., Ph.D.
Division of Heart Rhythm Services, Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Division of Pediatric Cardiology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA

Department of Molecular Pharmacology and Experimental Therapeutics, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA
e-mail: Ackerman.Michael@mayo.edu

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_4

Abbreviations

ATS	Andersen-Tawil syndrome
BrS	Brugada syndrome
CPVT	Catecholaminergic polymorphic ventricular tachycardia
JLNS	Jervell and Lange-Nielsen syndrome
LQTS	Long QT syndrome
SCD	Sudden cardiac death

Long QT Syndrome (LQTS)

Clinical Presentation of LQTS

Congenital long QT syndrome (LQTS) comprises a distinct group of cardiac channelopathies characterized by delayed repolarization of the myocardium, electrocardiographic QT prolongation, and increased risk for syncope, seizures, and SCD. Often defined as a QTc over 470 ms for men or 480 ms for women, a QTc of 480 ms represents the 50th percentile among patients with genetically proven LQTS, which in contrast represents the 99th percentile among otherwise healthy women. The incidence of LQTS is approximately 1 in 2000 to 2500 individuals [1, 2]. However, diagnosis and recognition of LQTS is often complicated by the fact that patients might not demonstrate QT prolongation on a resting 12-lead surface electrocardiogram (ECG). In fact, about 30–40% of patients with genetically proven LQTS have a QTc < 460 ms at rest [3]. In LQTS, the resulting abnormal repolarization is generally without consequence and therefore, an affected patient can be asymptomatic throughout their whole life. However, in some cases, the repolarization abnormality can degenerate into a potentially life threatening, ventricular arrhythmia known as Torsades des Pointes (TdP). Typically, the arrhythmia spontaneously returns to sinus rhythm resulting in "just" arrhythmic syncope, but, in some cases, the arrhythmia persists thereby precipitating SCD. It is estimated that approximately 5% of patients with undiagnosed and therefore untreated LQTS succumb to SCD as their sentinel event. In such cases, a complete medico-legal autopsy, careful review of the deceased medical history and evaluation of possibly dismissed prior syncopal episodes is needed to elucidate the cause of death and might reveal an underlying cardiac arrhythmia syndrome [4, 5]. In fact, it is estimated that nearly half of individuals experiencing autopsy negative SCD may have exhibited prior warning signs (i.e. exertional syncope, family history of premature sudden death) that went unrecognized. Especially in the setting of a normal autopsy, genetic testing might aid in diagnosis, and subsequent evaluation and treatment for potential family members at risk.

While the arrhythmias can occur at any time, certain (genotype-specific) triggers, such as exertion and swimming in LQT1, emotion, auditory triggers (startles, alarm clocks), and the post-partum period in LQT2, are well established [6–9]. Importantly, it is critical for physicians to carefully distinguish benign syncope from a faint caused by a potentially lethal cardiac disease (see Chap. 19). Additionally, when evaluating someone suspected to have LQTS, one must distinguish congenital LQTS from the patient who exhibits QT prolongation caused by other conditions associated with QT prolongation as the abnormal cardiac repolarization, QT prolongation, and even TdP seen in LQTS can also result from numerous comorbidities (e.g., pheochromocytoma, anorexia, diabetes, and hypertrophic cardiomyopathy to name a few), electrolyte derangements particularly hypokalemia, and Food and Drug Administration (FDA)–approved medications (www.crediblemeds.org) [10, 11]. In fact, currently there are over 100 FDA approved drugs known to prolong the QT on the market and QT liability and drug-induced TdP (DI-TdP) followed by DI-SCD have been among the most common reasons for withdrawing drugs.

Treatment recommendations for LQTS are summarized in Table 4.1. In general, management of LQTS consists of (a) basic SCD prevention measures such as QT drug avoidance, electrolyte/hydration replenishment particularly in setting of vomiting and diarrheal illnesses, use of antipyretics to reduce fever, and the acquisition of a personal automatic external defibrillator AED as well as (b) medical treatments, such as prescription drug therapy (mainly beta blockers) or more invasive treatment or prevention methods, such as an implantable cardioverter defibrillator (ICD) or left cardiac sympathetic denervation (LCSD)) [12]. Although prior guidelines were very restrictive, current guidelines state that (competitive) sports participation may be considered following comprehensive evaluation and a clear, patient specific treatment plan [13]. Pharmacologically, beta blockers are the first line of treatment for patients with LQTS, including those with a normal ECG but hosting a known LQTS associated mutation, and preference should go to long lasting agents such as nadolol [12].

An ICD is recommended in patients with a prior cardiac arrest (Class I recommendation) and can be considered in high risk patients who experience events on beta blocker therapy [12]. An LCSD, involving resection of the lower half of the left stellate ganglion along with an extended sympathectomy from T2 to T4, is indicated in high risk patients who experience appropriate VF-terminating ICD therapies, have breakthrough events on beta blockers, patients in who an ICD is contra-indicated or patients who are intolerant to beta blocker therapy [12].

Table 4.1 Treatment options for channelopathies

Disease	Therapy	Expert guideline recommendation	Class
LQTS	Life style changes (Avoidance of QT drugs, identification and correction of electrolyte imbalances	**Recommended** in all patients	**I**
	Beta blockers	**Recommended** in all patients with LQTS who have QTc > 470 ms, are symptomatic or have documented history of VT, VF	**I**
		Useful for patients with QTc < 470 ms	**IIa**
	ICD	**Recommended** for all patients who have survived cardiac arrest	**I**
		Useful for patients who experience recurrent cardiac events while on beta blocker	**IIa**
	LCSD	**Recommended** in all patients contraindicated for ICD, who have refused ICD, or for whom beta blockers are not effective of tolerated	**I**
		Useful in patients with recurrent cardiac events while on beta-blockers or with ICD	**IIa**
	Sodium channel blockers	**Useful** as add-on therapy for patients with LQT3 with QTc > 500 ms whose QTc shortened by >40 ms on oral drug test	**IIa**
BrS	Life style changes (Avoidance of drugs that might aggravate BrS, avoidance of excessive alcohol intake, and immediate treatment of fever)	**Recommended** in all patients	**I**
	ICD	**Recommended** in patients who have survived cardiac arrest or have documented sustained VT	**I**
		Useful in patients with spontaneous diagnostic type I ECG patients with a history of cardiogenic syncope	**IIa**
		May be considered in patients with inducible VF	**IIb**
	Quinidine	**Can be useful** in patients with history or arrhythmic storms or patients with ICD contraindication, and/or history of supraventricular tachycardia requiring treatment.	**IIa**
		May be considered in asymptomatic patients with spontaneous type I ECG	**IIb**
CPVT	Lifestyle changes (Limit to avoidance of competitive sports, strenuous exercise, stressful situations	**Recommended** for all patients	**I**
	Beta-blockers	**Recommended** for all symptomatic patients	**I**
		Can be useful in asymptomatic, mutation-positive patients	**IIa**
	ICD	**Recommended in patients** with a previous cardiac arrest, or recurrent syncope of polymorphic/ bidirectional VT despite optimal medical treatment and/or LCSD	**I**
	Flecainide	**Can be useful** as an addition to beta blockers in patients with recurrent syncope or polymorphic/ bidirectional VT while on beta blockers	**IIa**
	LCSD	**May be considered** in patients with recurrent syncope or polymorphic/bidirectional VT while on beta blockers, or contraindicated for ICD	**IIb**

Genetic Basis and Genotype-Phenotype Correlations

Originally known as Romano-Ward syndrome, LQTS is a genetically heterogeneous disorder largely inherited in an autosomal dominant pattern. Hundreds of mutations have now been identified over 15 LQTS-susceptibility genes. Approximately 75% of patients with a clinically robust diagnosis of LQTS host either loss-of-function (K channels) or gain-of –function (Na channels) mutations in one of the three major LQTS-causative genes that encode for the critical pore-forming alpha subunits of the essential ion channels that govern the cardiac action potential (Table 4.2; Fig. 4.1). Variants in the two most common genes, the *KCNQ1*-encoded I_{Ks} (Kv7.1) potassium channel (LQT1, ~35%) and the *KCNH2*—encoded I_{Kr} (Kv11.1) potassium channel (LQT2, ~30%, loss-of-function)—lead to loss-of-function of the potassium channels during phase 3 of the cardiac action potential (Fig. 4.1) resulting in abnormal repolarization and QT prolongation. Approximately 10% of patients have a mutation in the *SCN5A*-encoded I_{Na} (Nav1.5) sodium channel (LQT3) leading to gain-of-function of this channel during phase 0 of the action potential (Fig. 4.1).

While LQTS is caused by single mutations in the majority of cases, approximately 5–10% of patients have multiple mutations in these three genes and these patients commonly show a more severe disease phenotype with expression at younger age and higher rate of symptoms [14–16]. In fact, this is demonstrated in the rare occasions where LQTS is inherited in autosomal recessive fashion such as Jervell and Lange-Nielsen syndrome (JLNS) characterized by

Table 4.2 Summary of long QT syndrome-susceptibility genes

Gene	Locus	Protein
Long QT syndrome		
Major LQTS Genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (KvLQT1, Kv7.1)
KCNH2 (LQT2)	7q35–36	I_{Kr} potassium channel alpha subunit (HERG, Kv11.1)
SCN5A (LQT3)	3p21-p24	Cardiac sodium channel alpha subunit (NaV1.5)
Minor LQTS Genes (alphabetically)		
AKAP9	7q21-q22	Yotiao
ANKB	4q25-q27	Ankyrin B *(Ankyrin B syndrome)*
CACNA1C	12p13.3	Voltage gated L-type calcium channel (CaV1.2) (*Timothy Syndrome, Cardiac-Only Timothy Syndrome*)
CALM1	14q32.11	Calmodulin 1
CALM2	2p21	Calmodulin 2
CALM3	19q13.32	Calmodulin 3
CAV3	3p25	Caveolin-3
KCNE1	21q22.1	Potassium channel beta subunit (MinK)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNJ2	17q23	I_{K1} potassium channel (Kir2.1; *Andersen Tawil syndrome*)
KCNJ5	11q24	Inwardly rectifying potassium channel (Kir3.4)
SCN4B	11q23.3	Sodium channel beta 4 subunit
SNTA1	20q11.2	Syntrophin-alpha 1
TRDN[a]	6q22.31	Triadin (*Triadin Knock-Out Syndrome*)

[a]Autosomal recessive inheritance

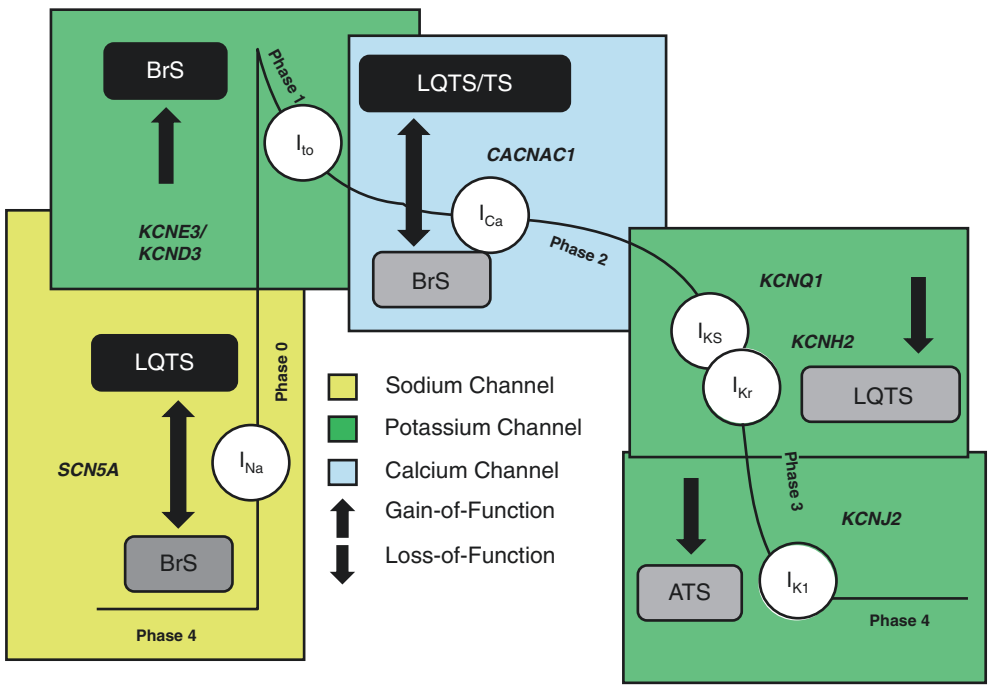


Fig. 4.1 Cardiac channelopathies and the cardiac action potential. Schematic representation of the phases of the cardiac action potential, the ion channels involved and how gain- or loss-of-function mutations in the genes encoding for these channels might lead to the cardiac phenotype of Andersen Tawil syndrome (ATS), Brugada syndrome (BrS), long QT syndrome (LQTS) or Timothy syndrome (TS)

homozygous/heterozygous mutations in *KCNQ1*, a severe cardiac phenotype and sensorineural hearing loss (reviewed in [17]), or in the recently described triadin knock-out (TKO) syndrome characterized by compound heterozygous/homozygous mutations in *TRDN*-encoded triadin, QT prolongation with extensive T-wave inversions, and early, exercise-induced cardiac arrest [18].

The minor LQTS-susceptibility genes (Table 4.2) encode for (a) ion channels responsible for other phases of the cardiac action potential (for example gain-of-function variants in the phase 2 associated, *CACNA1C*-encoded voltage gated L-type calcium channel), (b) key cardiac *ch*annel *i*nteracting *p*roteins ("ChIPs") that generally regulate the native ion channel current, or (c) structural membrane scaffolding proteins that function in proper localization of channels to the plasma membrane. Mutations in these genes are nevertheless relatively rare and collectively explain less than 10% of LQTS.

Lastly, there are several, albeit rare conditions that could be considered syndromic LQTS, which aside from QT prolongation and arrhythmias can present with additional clinical (extra-cardiac) features. In addition to JLNS and TKO syndrome described above, one such syndrome is Andersen-Tawil syndrome (ATS) which is caused by loss-of-function mutations in the *KCNJ2*-encoded I_{K1} (Kir2.1) potassium channel and characterized by triad of clinical features: periodic paralysis, dysmorphic features and ventricular arrhythmias [19]. QT prolongation in these patients is commonly modest and often overestimated by inclusion of prominent U-waves on ECG. Patients can also demonstrate ventricular ectopy, including bigeminy, and bidirectional—or polymorphic ventricular tachycardia (VT). Consequently, *KCNJ2*-mediated catecholaminergic polymorphic ventricular tachycardia (CPVT or CPVT3) is possible [20].

Interestingly, gain-of-function mutations in the *CACNA1C*-encoded voltage gated L-type calcium channel can lead to LQTS alone or syndromic LQTS with divergent phenotypes, including Timothy syndrome (TS), characterized by high risk of SCD, syndactyly, craniofacial and odontic abnormalities, possible congenital heart defects, hypertrophic cardiomyopathy (HCM) and autism spectrum disorders [21], or the recently described cardiac-only Timothy syndrome (COTS), which as its name suggests is similar to TS but is devoid of any extra-cardiac features [22]. Approximately 20–25% of clinical definite cases of LQTS remain genetically elusive.

Importantly, the majority of mutations found in LQTS-associated genes are unique mutations and there are no particular 'hot-spots'. While whole exome- and whole genome sequencing (WES and WGS respectively) techniques have yielded some of the newest LQTS-associated genes, such as *CACNA1C* or *CALM1* [23, 24]), these discoveries have not brought forth a large, new contributor to the 20–25% remnant of genetically elusive LQTS. In fact, the emergence of clinical genetic testing and publication of large population exome collections have more demonstrated that rate of rare variants in the population is approximately 5–10% (depending on the gene panel and ethnicity) making distinguishing the next, novel pathogenic mutation from 'background noise' of utmost importance and rather difficult [25–29].

Specific genotype/phenotype associations in LQTS have emerged, suggesting relatively gene-specific triggers, ECG patterns, and response to pharmacotherapy. For example, LQT1 is strongly associated with exercise-induced events (including swimming) and in fact, the LQTS substrate can be elucidated by either exercise testing or epinephrine QT stress testing on patients with electrocardiographically concealed LQT1 [30–34].

LQT2's cardiac events are associated with auditory triggers (startles, alarm clock) as well and an increased risk of events occurring during the postpartum period, while events occurring during periods of sleep/rest are more common in LQT3. Electrocardiographically, LQT1 can be recognized by broad-based T waves compared to low amplitude notched or biphasic T waves in LQT2, or a long isoelectric segment followed by a narrow-based T wave in LQT3 [35]. However, exclusions to patterns exist and due caution must be exercised in making a pre-genetic test prediction as the underlying genetic basis ultimately heavily influences the response to standard LQTS pharmacotherapy. Recent studies in large population of patients have shown there are differences between the different beta-blockers and that genotype-specific effects can be observed. Overall, all beta-blockers are equally effective in reducing risk of cardiac events in patients with LQTS, although among the specific genotypes beta blockers are extremely protective in patients LQT1, but less so in LQT2 of LQT3. In fact, nadolol is the only one to demonstrate significant risk reduction in patients with LQT type 2 [36]. Additionally, propranolol has shown to have a significantly better QTc shortening effect, possibly because of its effects on of late sodium current and is therefore may be preferred in patients with LQT3. Conversely, cardiac breakthrough events were significantly more common in genotyped patients on metoprolol (29%) compared to propranolol (8%) or nadolol (7%), and should therefore be avoided in these patients [37]. In addition, agents such as mexiletine, flecainide, or ranolazine targeting the pathologic, LQT3-associated late sodium current may be useful adjunctive therapy for some LQT3 patients as long as there is no evidence of a SCN5A overlap syndrome phenotype for these patients [38, 39]. Unlike beta-blockers, attenuation in repolarization with clinically apparent shortening in the QTc has been demonstrated with late sodium current blockers. Although there is no evidence-based demonstration of survival benefit thus far, recent studies show an attenuation in LQT3-associated cardiac events with mexiletine [38].

Akin to pharmaceutical therapy, genotype-dependent efficacy occurs with LCSD as well. While overall a 90%

reduction on arrhythmia burden in seen following LCSD, the attenuation in events and the elimination of post-LCSD breakthroughs is greatest in LQT1 followed by LQT2 and then LQT3 [40, 41]. Larger studies are however still needed to fully determine the true role of LCSD in LQT3.

In addition, intra-genotype risk stratification has been realized for the two most common subtypes of LQTS based upon mutation type, mutation location, and cellular function [42–48]. Patients with LQT1 with Kv7.1 missense mutations localizing to the transmembrane-spanning domains clinically have a twofold greater risk of a LQT1-triggered cardiac event than LQT1 patients with mutations localizing to the C-terminal region [47]. Trumping location, patients with mutations resulting in a greater degree of Kv7.1 loss-of-function at the cellular *in vitro* level (i.e. dominant negative—most commonly missense variants) have a twofold greater clinical risk than those mutations that damage the biology of the Kv7.1 channel less severely (haploinsufficiency—commonly nonsense, frameshift and splice site variants) as in the latter the complete loss of a mutant allele leads to the unaffected allele contributing to normal channel formation. More recently, a detailed study into *KCNQ1* demonstrated that among these previously considered equivalent, haploinsufficiency-associated variants that nonsense mutations are associated with a lower cardiac event rate, while patients with a frameshift mutations are associated with a higher risk, comparable to that seen in patients with missense (dominant negative) variants [49].

Location of variants is equally important in patients with LQT2 [44, 46]. Phenotypically, patients with variants in the pore region of Kv11.1 have a longer QT interval, a more severe clinical manifestation of the disorder, and experience significantly more arrhythmia-related cardiac events occurring at a younger age compared to those with non-pore of the channel. Additionally, studies have shown a possible relationship between location and outcome of the disease suggesting that LQT2 patients with mutations involving the transmembrane pore region had the greatest risk for cardiac events, those with frame-shift/nonsense mutations in any region had an intermediate risk, and those with missense mutations in the C-terminus had the lowest risk for cardiac events. Further, a more recent study showed a striking gender difference for mutation location where, in contrast to men, LQT2 women experience a high rate of life-threatening events independent of mutation location [48].

Risk Stratification in LQTS

Based on these observations, both clinical and genetic findings can guide risk stratification in patients with LQTS. Patients should be considered high risk if they have experienced a prior cardiac arrest, have cardiac events despite optimal treatments, or have a QTc over 500 ms, especially if a LQT2 post-pubertal female [12]. Patients with complex syndromes, such as JLNS or ATS or multiple mutations should be considered high risk as while mutation type- and location discussed above should be taken in account (except for women with LQT2) [12]. Conversely, a low risk (but not zero) can be assigned to asymptomatic patients with concealed LQT1 substrates, especially when residing in post-pubertal males.

Brugada Syndrome (BrS)

Clinical Presentation of BrS

Brugada syndrome (BrS) is a rare heritable arrhythmia syndrome characterized by syncope, nocturnal agonal respiration palpitations and/or chest discomfort, or VF or aborted cardiac arrest. BrS typically manifests during adulthood, and is 8–10 time more prevalent in males than females. Mean age of sudden death of about 40 years. BrS-triggered events often occur during rest or sleep, or when in a febrile state; they are rarely associated with exercise [12, 50]. Additionally, akin to LQTS, certain drugs can increase risk of cardiac events for patients with BrS (www.brugadadrugs.org) [51]. Although the exact prevalence is unknown, the prevalence is much higher in Asian and Southeast Asian men and is estimated to be as high as 1 per 1000 individuals. In fact, sudden unexplained nocturnal death (SUND) in young males is endemic to Southeast Asia and is somewhat allelic with BrS. Electrocardiographically, BrS can be recognized in the presence of coved type ST-segment elevation (≥2 mm) in one or more of the right precordial leads V_1 through V_3 when positioned in the second, third or fourth intercostal space. This is referred to as a type 1 Brugada ECG pattern and, if not present with standard ECG lead placement, it can be captured with cephalad movement of the right precordial leads 1–2 intercostal spaces with respect to their standard positions. These 3 serial ECGs, obtained by consecutively moving the precordial leads of V1-V3, is referred to as the Brugada high lead ECG protocol. There is no prognostic value as to which intercostal space elicits a type 1 Brugada ECG pattern as it is reflecting the anatomic location of the right ventricular outflow tract in the chest[Reviewed in [52]]. Alternatively, drug challenge testing with intravenous administration of a sodium channel blocking drugs such as ajmaline (not available in the United States), procainamide or flecainide, can be used. Ajmaline is a superior provocative drug. It is unknown whether procainamide drug challenge with high right lead placement would achieve similar diagnostic performance characteristics as ajmaline provocation with standard lead placement.

The primary treatment and SCD prevention strategy for symptomatic patients with BrS is an ICD (Table 4.1). Herein, an ICD is recommended for patients who have experienced a prior cardiac arrest or sustained VT [12]. Furthermore, consensus guidelines state an ICD can be useful for patients with spontaneous Type 1 BrS ECG pattern and a history of syncope that is judged to be caused ventricular arrhythmias, and may be considered if the patient with suspected BrS has inducible VF on EP studies. An ICD is not indicated for asymptomatic patients with a drug-induced type 1 Brugada ECG pattern and a family history of SCD [12]. Pharmacological treatment for BrS is aimed at rebalancing the affected ion currents (inhibition of transient outward potassium channel or increase of sodium and calcium channels) using for example isoproterenol and quinidine, however large scale studies have not been performed. Regardless of clinical presentation, all patients with BrS should avoid potentially BrS-associated, pro-arrhythmic drugs (www.brugadadrugs.org), avoid alcohol intoxication, avoid cocaine and marijuana use, and treat fever immediately [53].

Genetic Basis and Genotype-Phenotype Correlations

BrS is inherited generally as an autosomal dominant trait. There are currently up to 20+ BrS-associated genes, however, only SCN5A-mediated BrS (BrS1) shows true case: control over-representation [54, 55] (Table 4.3, Fig. 4.1). BrS1 stems from loss-of-function mutations in the *SCN5A*-encoded cardiac sodium channel. Although the most common BrS substrate, SCN5A accounts for less than 25% of all BrS. Additionally, loss-of-function mutations have been reported in the *CACNA1C*-encoded L-type calcium channel as well as the *KCNE3* and *KCND3*-encoding outward potassium channels (Fig. 4.1). A recent study evaluating 12 BrS-associated genes showed that among unrelated patients a *SCN5A* variant was found in 16% of patients, while the remaining 11 genes accounted for <5% of BrS [56]. In a large multicenter compendium of variants, the yield of mutation detection may be significantly higher among familial forms rather than in sporadic cases. The majority of the mutations are missense (66%), followed by frameshift (13%), nonsense, (11%), splice-site (7%), and in-frame deletions/insertions (3%) [54]. Approximately 3% of the genotype-positive patients host multiple putative pathogenic *SCN5A* mutations, and akin to observations in LQTS, patients hosting multiple *SCN5A* mutations tend to show a more severe clinical phenotype and younger age at diagnosis. Similarly, there is no particular mutational "hot spot" as nearly 80% of the BrS related *SCN5A* mutations occur as "private" single family mutations. Common variants seen in approximately 10% of patients are: E1784K, F861WfsX90, D356N, and G1408R. Interestingly, the most common occurring BrS1 mutation, E1784K, has is also one of the most commonly seen LQT3-associated *SCN5A* mutations,

Table 4.3 Summary of Brugada syndrome- and cathecholeminergic polymorphic ventricular tachycardia-susceptibility genes

Gene	Locus	Protein
Brugada syndrome		
SCN5A (BrS1)	3p21-p24	Cardiac sodium channel alpha subunit (NaV1.5)
ABCC9	12p12.1	ATP-binding cassette, sub-family C
CACNA1C	2p13.3	Voltage gated L-type calcium channel (CaV1.2)
CACNA2D1	7q21.11	Voltage gate L-type calcium channel, alpha 2, delta subunit
CACNB2	10p12	Voltage gated L-type calcium channel beta 2 subunit
FGF12	3q29	Fibroblast growth factor 12
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1-like
HCN4	15q24.1	Hyperpolarization-activated cyclic nucleotide-gated potassium channel
KCND2	7q31.31	Voltage gated potassium channel, shal related subfamily D, member 2
KCND3	1p13.2	Transient Outward Current (Ito) Kv4.3 α-Subunit
KCNE3	11q13.4	Potassium channel beta subunit (MiRP2)
KCNE5	Xq23	Voltage gate potassium channel beta 5 subunit
KCNJ8	12p12.1	Inwardly rectifying potassium channel
PKP2	12p11.21	Plakophilin 2
RANGRF/MOG1	17p13.1	RAN guanine nucleotide release factor
SCN1B	19q13	Sodium channel beta 1
SCN2B	11q23.3	Voltage gated sodium channel, beta 2 subunit
SCN3B	11q24.1	Voltage gated sodium channel, beta 3 subunit
SCN10A	3p22.2	Voltage-gated sodium channel, type x alpha subunit
SLMAP	3p14.3	Sarcolemma associated protein
SEMA3A	7q21.11	Semaphorin 3A
TRPM4	19q13.33	Transient receptor potential cation channel
Catecholaminergic polymorphic ventricular tachycardia		
RYR2 (CPVT1)	1q42.1-q43	Ryanodine Receptor 2
CASQ2 (CPVT2)	1p13.3	Calsequestrin 2
KCNJ2 (CPVT3)	17q23	I_{K1} potassium channel (Kir2.1)

illustrating how the same exact DNA alteration in a given gene can lead to two distinct cardiac arrhythmia syndromes most likely as a result of other environmental or genetic modifying factors [54]. Additionally, aside from the overlap with LQT3, it was shown that the background noise rate of *SCN5A* variants in the population is approximately 2–5% complicating interpretation of clinical genetic tests with novel *SCN5A*-associated variants [27].

Since potentially monogenetic lesions explain less than one-third of all BrS cases, genotype-phenotype correlations in BrS have been less informative and less detailed than for LQTS. On ECG, patients with BrS1 tend to have longer HV intervals than patients with genotype negative BrS. Additionally, within the subset of BrS1, *SCN5A*-genotype positive patients with either nonsense or frameshift, premature truncation-causing mutations exhibit a more severe phenotype than patients with a missense variants [57]. A recent large cohort study involving the spectrum and prevalence of mutations involving all BrS-associated genes demonstrated there was a range in yield of genetic testing between symptomatic patients with family history of BrS and a drug induced BrS pattern (0%), and symptomatic patients without family history and a BrS1 ECG pattern (50%). More strikingly, among clinically diagnosed BrS1 patients only, yield of genetic testing was significantly higher in patients under 20 (75% yield) compared to patients between 20 and 40 (22% yield) and patients >40 (15% yield; $p = 0.0003$). This difference was even more striking for male patients emphasizing the male predominance of this disease [56]. However, unlike LQTS genetic testing where the triad of diagnostic, prognostic, and therapeutic impact has been fulfilled, the impact of BrS genetic testing remains limited by its lower yield (25% for BrS vs. 75% for LQTS) and lack of therapeutic contribution from knowing the genotype.

Risk Stratification in BrS

Due to the limited data on genetics and genotype-phenotype correlations, risk stratification for BrS is mainly predicated on clinical factors. Strong predictors of risk are male gender (males have sevenfold risk of SCD with mean age of event between age 39 and 48) and a history of aborted SCD or cardiogenic syncope [53]. A spontaneous Brugada ECG pattern (in absence of fever or drugs) is a sign of increased risk as well. Conversely, a family history of SCD or the presence of an *SCN5A* mutation are not personal risk factors [53].

Additional proposed risk markers for BrS are the presence of a fragmented QRS, presence of an effective refractory period below 200 ms and spontaneous atrial fibrillation (seen in up to 50% of patients with BrS) are associated with increased risk of cardiac events, While the literature on utility and prognostic value for electrophysiological studies (EPS) is controversial, for asymptomatic patients, a recent study in over 300 patients with BrS identified EPS inducibility (HR 11.4), spontaneous type I ECG pattern (HR 4.0) and previous sinus node dysfunction (HR 8.0) as univariate risk factors for cardiac events [58]; EPS inducibility was the only predictor to remain significant in multivariate analyses. Most recently, the presence of a wide and/or large S-wave in lead I has been suggested as a powerful predictor of cardiac events in previously asymptomatic patients with BrS [59].

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Clinical Presentation of CPVT

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a heritable arrhythmia syndrome that classically manifests with exercise-induced syncope or SCD, is predominately expressed in the young, and closely mimics some of LQT1's clinical features (exertionally triggered events and structurally normal heart) sans the QT prolongation. However, compared to LQT1, CPVT's lethality and cardiac event rate is much higher. Like LQT1, swimming is a potentially lethal arrhythmia precipitating trigger in CPVT as both have been shown to underlie several cases of unexplained drowning or near-drowning in the young healthy swimmer [60]. Importantly, in contrast to LQTS, CPVT is associated with a normal resting ECG devoid of any QT prolongation (although bradycardia and U waves can be observed) and is electrocardiographically suspected following either exercise or catecholamine stress testing that demonstrates significant ventricular ectopy with its hallmark feature of bidirectional and polymorphic VT [61]. It must be recognized that premature ventricular complexes in bigeminy however are far more likely to be observed than the more specific finding of bidirectional VT.

Clinically, a presentation of exercise-induced syncope and a QTc < 460 ms should always prompt first consideration of CPVT rather than electrocardiographically concealed LQTS. Once thought to manifest only during childhood, more recent studies have suggested that the age of first presentation can vary from during infancy to 40 years of age. More than one-third of patients have a positive family history of premature SCD and up to as many as many as 60% of families hosting CPVT1-associated RyR2 mutations. Moreover, approximately 15% of autopsy negative sudden unexplained deaths in the young and some cases of SIDS have been attributed to CPVT [4, 62]. From a diagnosis as well as treatment perspective, it is essential to distinguish LQT1 and CPVT given the superior efficacy of beta blockers in LQT1 compared to CPVT and the greater lethality in CPVT compared to LQT1. In one study, strikingly, nearly a

third of patients diagnosed as "possible/atypical" LQTS (QTc < 480 ms) cases with exertion-induced syncope were instead *RYR2* mutation positive [63]. Similarly, some patients diagnosed with CPVT, based on the presence of bi-directional VT on exercise, have been identified subsequently as *KCNJ2* positive (CPVT3) which is far less severe than *RYR2*-mediated CPVT (CPVT1).

The treatment options and recommendation for CPVT are summarized in Table 4.1. Beta blocker therapy remains the first line of therapy in CPVT (nadolol preferred) [12]. Additionally, flecainide decreases the ectopy burden in patients experiencing breakthrough cardiac events on beta blocker therapy [64, 65]. Following the current guidelines, an ICD is recommended (Class I recommendation) in CPVT patients who have experienced a cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal medical treatment [12]. However, ICD treatment cannot be a standalone treatment and therefore must be in combination with full pharmacologic treatment. Furthermore, due to CPVT's specific arrhythmic fingerprint, ICD treatment can be complicated by a failure to restore the cardiac rhythm and the initiation of ICD storms (VF-shock-VF-shock cycles) in CPVT, which should be considered and discussed with the patients when implanting an ICD. In fact, a recent large, multicenter study has shown that LCSD has a potent, anti-fibrillatory effect in patients with CPVT suggesting a growing and possible alternative role for this procedure over ICD implantation [66]. When an ICD is being considered, perhaps triple protection with nadolol, flecainide, and LCSD should be part of a comprehensive anti-electrical storm strategy.

Genetic Basis and Genotype-Phenotype Correlations of CPVT

Perturbations in key components of intracellular calcium-induced calcium release from the sarcoplasmic reticulum serve as the pathogenic basis for CPVT. The three main genetic causes of CPVT are shown in Table 4.3. Inherited in an autosomal dominant fashion, mutations in the *RYR2*-encoded cardiac ryanodine receptor/calcium release channel represent the most common genetic subtype of CPVT (CPVT1), accounting for 60% of clinically "strong" cases of CPVT. Gain-of-function mutations in RyR2 produce "leaky" calcium release channels that cause increased intracellular calcium levels during diastole, particularly during sympathetic stimulation. This can precipitate calcium overload, delayed afterdepolarizations (DADs), and ventricular arrhythmias. Again, most unrelated CPVT families are identified with their own unique, 'private' *RYR2* mutation and about 5% of unrelated mutation-positive patients host multiple putative pathogenic mutations.

While there are not any specific mutation "hot-spots" in the large gene *RYR2*, there are 3 regional "hot-spots" or "domains" where unique mutations cluster. Before next generation sequencing technologies emerged, this observation lent itself towards targeted genetic testing of *RYR2* (~61 exons, approximately 2/3rds of complete gene) rather than a complete scan of *RYR2,* which is one of the largest genes in the human genomie [63]. In fact, two-thirds of all CPVT1-associated mutations in *RYR2* are confined to <20 of its 105 translated exons. Greater than 90% of RYR2 mutations discovered to date represent missense mutations; however perhaps as much as 5% of unrelated CPVT patients host large gene rearrangements consistent with large whole exon deletions, akin to what has been observed in LQTS. Again, akin to LQTS and BrS, interpretation of the genetic test is complicated by the rate of 'background noise' variants in the normal population of 3% giving it a 'signal-to-noise' ratio of approximately 20:1 when the CPVT case is a robust one. However, more recent data has shown that a strong clinical phenotype, overrepresentation of rare variants in cases versus controls and mutation location are strongest predictors of a pathogenic mutation. In fact, this study has led to a refinement of the exons most likely to host a pathogenic variant, whereby mutations residing outside the 35 case-predictive exons should be approached with caution (Kapplinger 2016, manuscript submitted).

Risk Stratification in CPVT

Risk stratifiers for CPVT include male gender, the occurrence of aborted cardiac arrest prior to diagnosis (not syncope), and early diagnosis [67]. Following diagnosis, the persistence of ectopy on exercise test despite medical treatment has been associated with worse outcome [67]. Additionally, mutations located in the C-terminus of *RYR2* carry a higher risk [68].

References

1. Ackerman MJ. Cardiac channelopathies: it's in the genes. Nat Med. 2004;10(5):463–4.
2. Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, et al. Prevalence of the congenital long-QT syndrome. Circulation. 2009;120(18):1761–7.
3. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med. 2003;348(19):1866–74.
4. Tester DJ, Ackerman MJ. The role of molecular autopsy in unexplained sudden cardiac death. Curr Opin Cardiol. 2006;21(3):166–72.
5. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. J Am Coll Cardiol. 2007;49(2):240–6.

6. Ackerman MJ, Tester DJ, Porter CJ. Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. Mayo Clin Proc. 1999;74(11):1088–94.
7. Khositseth A, Tester DJ, Will ML, Bell CM, Ackerman MJ. Identification of a common genetic substrate underlying postpartum cardiac events in congenital long QT syndrome. Heart Rhythm. 2004;1(1):60–4.
8. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103(1):89–95.
9. Wilde AA, Jongbloed RJ, Doevendans PA, Duren DR, Hauer RN, van Langen IM, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). J Am Coll Cardiol. 1999;33(2):327–32.
10. CredibleMeds—QT drug list. www.crediblemeds.org. Accessed June 30, 2017
11. Ackerman MJ. Molecular basis of congenital and acquired long QT syndromes. J Electrocardiol. 2004;37(Suppl):1–6.
12. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10(12):1932–63.
13. Ackerman MJ, Zipes DP, Kovacs RJ, Maron BJ. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 10: the cardiac channelopathies: a scientific statement from the American Heart Association and American College of Cardiology. Circulation. 2015;132(22):e326–9.
14. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. Heart Rhythm. 2005;2:507–17.
15. Westenskow P, Splawski I, Timothy KW, Keating MT, Sanguinetti MC. Compound mutations: a common cause of severe long-QT syndrome. Circulation. 2004;109(15):1834–41.
16. Mullally J, Goldenberg I, Moss AJ, Lopes CM, Ackerman MJ, Zareba W, et al. Risk of life-threatening cardiac events among patients with long QT syndrome and multiple mutations. Heart Rhythm. 2013;10(3):378–82.
17. Schwartz PJ, Spazzolini C, Crotti L, Bathen J, Amlie JP, Timothy K, et al. The Jervell and Lange-Nielsen syndrome: natural history, molecular basis, and clinical outcome. Circulation. 2006;113(6):783–90.
18. Altmann HM, Tester DJ, Will ML, Middha S, Evans JM, Eckloff BW, et al. Homozygous/compound heterozygous triadin mutations associated with autosomal-recessive long-QT syndrome and pediatric sudden cardiac arrest: elucidation of the triadin knockout syndrome. Circulation. 2015;131(23):2051–60.
19. Yoon G, Oberoi S, Tristani-Firouzi M, Etheridge SP, Quitania L, Kramer JH, et al. Andersen-Tawil syndrome: prospective cohort analysis and expansion of the phenotype. Am J Med Genet A. 2006;140(4):312–21.
20. Eckhardt LL, Farley AL, Rodriguez E, Ruwaldt K, Hammill D, Tester DJ, et al. KCNJ2 mutations in arrhythmia patients referred for LQT testing: a mutation T305A with novel effect on rectification properties. Heart Rhythm. 2007;4(3):323–9.
21. Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell. 2004;119(1):19–31.
22. Boczek NJ, Ye D, Jin F, Tester DJ, Huseby A, Bos JM, et al. Identification and functional characterization of a novel CACNA1C-mediated cardiac disorder characterized by prolonged QT intervals with hypertrophic cardiomyopathy, congenital heart defects, and sudden cardiac death. Circ Arrhythm Electrophysiol. 2015;8(5):1122–32.
23. Boczek NJ, Best JM, Tester DJ, Giudicessi JR, Middha S, Evans JM, et al. Exome sequencing and systems biology converge to identify novel mutations in the L-type calcium channel, CACNA1C, linked to autosomal dominant long QT syndrome. Circ Cardiovasc Genet. 2013;6(3):279–89.
24. Marsman RF, Barc J, Beekman L, Alders M, Dooijes D, van den Wijngaard A, et al. A mutation in CALM1 encoding calmodulin in familial idiopathic ventricular fibrillation in childhood and adolescence. J Am Coll Cardiol. 2014;63(3):259–66.
25. Kapa S, Tester DJ, Salisbury BA, Harris-Kerr C, Pungliya MS, Alders M, et al. Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. Circulation. 2009;120(18):1752–60.
26. Refsgaard L, Holst AG, Sadjadieh G, Haunso S, Nielsen JB, Olesen MS. High prevalence of genetic variants previously associated with LQT syndrome in new exome data. Eur J Hum Genet. 2012;20(8):905–8.
27. Ackerman MJ, Splawski I, Makielski JC, Tester DJ, Will ML, Timothy KW, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. Heart Rhythm. 2004;1(5):600–7.
28. Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. Mayo Clin Proc. 2003;78(12):1479–87.
29. Ackerman MJ. Genetic purgatory and the cardiac channelopathies: exposing the variants of uncertain/unknown significance issue. Heart Rhythm. 2015;12(11):2325–31.
30. Horner JM, Ackerman MJ. Ventricular ectopy during treadmill exercise stress testing in the evaluation of long QT syndrome. Heart Rhythm. 2008;5(12):1690–4.
31. Takenaka K, Ai T, Shimizu W, Kobori A, Ninomiya T, Otani H, et al. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. Circulation. 2003;107(6):838–44.
32. Wong JA, Gula LJ, Klein GJ, Yee R, Skanes AC, Krahn AD. Utility of treadmill testing in identification and genotype prediction in long-QT syndrome. Circ Arrhythm Electrophysiol. 2010;3(2):120–5.
33. Ackerman MJ, Khositseth A, Tester DJ, Hejlik JB, Shen WK, Porter CB. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. Mayo Clin Proc. 2002;77(5):413–21.
34. Shimizu W, Noda T, Takaki H, Kurita T, Nagaya N, Satomi K, et al. Epinephrine unmasks latent mutation carriers with LQT1 form of congenital long-QT syndrome. J Am Coll Cardiol. 2003;41(4):633–42.
35. Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox J, Giuli LC, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. Circulation. 2000;102(23):2849–55.
36. Abu-Zeitone A, Peterson DR, Polonsky B, McNitt S, Moss AJ. Efficacy of different beta-blockers in the treatment of long QT syndrome. J Am Coll Cardiol. 2014;64(13):1352–8.
37. Chockalingam P, Crotti L, Girardengo G, Johnson JN, Harris KM, van der Heijden JF, et al. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. J Am Coll Cardiol. 2012;60(20):2092–9.
38. Mazzanti A, Maragna R, Faragli A, Monteforte N, Bloise R, Memmi M, et al. Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3. J Am Coll Cardiol. 2016;67(9):1053–8.

39. Schwartz PJ, Priori SG, Locati EH, Napolitano C, Cantu F, Towbin JA, et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na+ channel blockade and to increases in heart rate. Implications for gene-specific therapy. Circulation. 1995;92(12):3381–6.
40. Bos JM, Bos KM, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation in long QT syndrome: analysis of therapeutic nonresponders. Circ Arrhythm Electrophysiol. 2013;6(4):705–11.
41. Schwartz PJ, Priori SG, Cerrone M, Spazzolini C, Odero A, Napolitano C, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. Circulation. 2004;109(15):1826–33.
42. Jons C, Moss AJ, Lopes CM, McNitt S, Zareba W, Goldenberg I, et al. Mutations in conserved amino acids in the KCNQ1 channel and risk of cardiac events in type-1 long-QT syndrome. J Cardiovasc Electrophysiol. 2009;20(8):859–65.
43. Moss AJ, Shimizu W, Wilde AA, Towbin JA, Zareba W, Robinson JL, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. Circulation. 2007;115(19):2481–9.
44. Moss AJ, Zareba W, Kaufman ES, Gartman E, Peterson DR, Benhorin J, et al. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. Circulation. 2002;105(7):794–9.
45. Shimizu W, Horie M, Ohno S, Takenaka K, Yamaguchi M, Shimizu M, et al. Mutation site-specific differences in arrhythmic risk and sensitivity to sympathetic stimulation in the LQT1 form of congenital long QT syndrome: multicenter study in Japan. J Am Coll Cardiol. 2004;44(1):117–25.
46. Shimizu W, Moss AJ, Wilde AA, Towbin JA, Ackerman MJ, January CT, et al. Genotype-phenotype aspects of type 2 long QT syndrome. J Am Coll Cardiol. 2009;54(22):2052–62.
47. Barsheshet A, Goldenberg I, OU J, Moss AJ, Jons C, Shimizu W, et al. Mutations in cytoplasmic loops of the KCNQ1 channel and the risk of life-threatening events: implications for mutation-specific response to beta-blocker therapy in type 1 long-QT syndrome. Circulation. 2012;125(16):1988–96.
48. Migdalovich D, Moss AJ, Lopes CM, Costa J, Ouellet G, Barsheshet A, et al. Mutation and gender-specific risk in type 2 long QT syndrome: implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome. Heart Rhythm. 2011;8(10):1537–43.
49. Ruwald MH, Xu Parks X, Moss AJ, Zareba W, Baman J, McNitt S, et al. Stop-codon and C-terminal nonsense mutations are associated with a lower risk of cardiac events in patients with long QT syndrome type 1. Heart Rhythm. 2016;13(1):122–31.
50. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. 2005;111(5):659–70.
51. Brugada Syndrome drug list. www.brugadadrugs.org. Accessed June 30, 2017.
52. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation. 2002;106(19):2514–9.
53. Adler A, Rosso R, Chorin E, Havakuk O, Antzelevitch C, Viskin S. Risk stratification in Brugada syndrome: clinical characteristics, electrocardiographic parameters, and auxiliary testing. Heart Rhythm. 2016;13(1):299–310.
54. Kapplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm. 2010;7(1):33–46.
55. Le Scouarnec S, Karakachoff M, Gourraud JB, Lindenbaum P, Bonnaud S, Portero V, et al. Testing the burden of rare variation in arrhythmia-susceptibility genes provides new insights into molecular diagnosis for Brugada syndrome. Hum Mol Genet. 2015;24(10):2757–63.
56. Crotti L, Marcou CA, Tester DJ, Castelletti S, Giudicessi JR, Torchio M, et al. Spectrum and prevalence of mutations involving BrS1- through BrS12-susceptibility genes in a cohort of unrelated patients referred for Brugada syndrome genetic testing: implications for genetic testing. J Am Coll Cardiol. 2012;60(15):1410–8.
57. Meregalli PG, Tan HL, Probst V, Koopmann TT, Tanck MW, Bhuiyan ZA, et al. Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. Heart Rhythm. 2009;6(3):341–8.
58. Sieira J, Ciconte G, Conte G, Chierchia GB, de Asmundis C, Baltogiannis G, et al. Asymptomatic Brugada syndrome: clinical characterization and long-term prognosis. Circ Arrhythm Electrophysiol. 2015;8(5):1144–50.
59. Calo L, Giustetto C, Martino A, Sciarra L, Cerrato N, Marziali M, et al. A new electrocardiographic marker of sudden death in Brugada syndrome: the S-wave in lead I. J Am Coll Cardiol. 2016;67(12):1427–40.
60. Choi G, Kopplin LJ, Tester DJ, Will ML, Haglund CM, Ackerman MJ. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. Circulation. 2004;110(15):2119–24.
61. Liu N, Ruan Y, Priori SG. Catecholaminergic polymorphic ventricular tachycardia. Prog Cardiovasc Dis. 2008;51(1):23–30.
62. Tester DJ, Dura M, Carturan E, Reiken S, Wronska A, Marks AR, et al. A mechanism for sudden infant death syndrome (SIDS): stress-induced leak via ryanodine receptors. Heart Rhythm. 2007;4(6):733–9.
63. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, Hofman N, Bikker H, van Tintelen JP, et al. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome: a comprehensive open reading frame mutational analysis. J Am Coll Cardiol. 2009;54(22):2065–74.
64. van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol. 2011;57(22):2244–54.
65. Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med. 2009;15(4):380–3.
66. De Ferrari GM, Dusi V, Spazzolini C, Bos JM, Abrams DJ, Berul CI, et al. Clinical management of catecholaminergic polymorphic ventricular tachycardia: the role of left cardiac sympathetic denervation. Circulation. 2015;131(25):2185–93.
67. Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff JM, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Circulation. 2009;119(18):2426–34.
68. van der Werf C, Nederend I, Hofman N, van Geloven N, Ebink C, Frohn-Mulder IM, et al. Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives. Circ Arrhythm Electrophysiol. 2012;5(4):748–56.

Extended ECG Monitoring

5

Christian Steinberg, Matthew T. Bennett,
and Andrew D. Krahn

Abstract

Despite the high prevalence of arrhythmias in the population, their diagnosis may be challenging, as they can be intermittent, short-lasting and/or asymptomatic. Prolonged ambulatory rhythm monitoring is a key element in diagnosing non-permanent arrhythmias and in evaluating potential arrhythmic symptoms and the mechanism of syncope. It is also useful in assessing arrhythmic risk, e.g., atrial fibrillation (AF) burden as it relates to risk for embolism or ventricular ectopy as it may relate to prognosis. Historically, prolonged rhythm monitoring was limited to short-term Holter recordings over 24–72 h. Over the past 20 years, a variety of more advanced non-invasive and invasive devices for prolonged rhythm monitoring have entered clinical practice, and the spectrum of clinical indications for their use has progressively expanded.

Keywords

Syncope • ECG • Cardiac monitoring • Atrial fibrillation • Diagnosis • Implantable device • Sudden death • Holter monitor • Palpitations • Undiagnosed arrhythmia • Loop recorder • Event recorder • Ambulatory rhythm monitoring

Introduction

Despite the high prevalence of arrhythmias in the population, their diagnosis may be challenging, as they can be intermittent, short-lasting and/or asymptomatic. Prolonged ambulatory rhythm monitoring is a key element in diagnosing non-permanent arrhythmias and in evaluating potential arrhythmic symptoms and the mechanism of syncope. It is also useful in assessing arrhythmic risk, e.g., atrial fibrillation (AF) burden as it relates to risk for embolism or ventricular ectopy as it may relate to prognosis. Historically, prolonged rhythm monitoring was limited to short-term Holter recordings over 24–72 h. Over the past 20 years, a variety of more advanced non-invasive and invasive devices for prolonged rhythm monitoring have entered clinical practice, and the spectrum of clinical indications for their use has progressively expanded.

Disclosures: The authors have no conflicts of interest to declare.

C. Steinberg, M.D.
Heart Rhythm Services, University of British Columbia, Vancouver, BC, Canada

M.T. Bennett, M.D. • A.D. Krahn, M.D. (✉)
Heart Rhythm Services, University of British Columbia, Vancouver, BC, Canada

Department of Medicine, Vancouver General Hospital, 9th Floor, Gordon and Leslie Diamond Health Care Centre, 2775 Laurel Street, Vancouver, BC, Canada, V5Z 1M9
e-mail: matthew.bennett@vch.ca; akrahn@mail.ubc.ca

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_5

The aim of this chapter is to provide an overview of the evidence for the use of the currently available tools and devices for prolonged rhythm monitoring in common cardiac scenarios.

Recording Systems for Extended Rhythm Monitoring

Commonly used recording systems for prolonged ambulatory rhythm monitoring are summarized in Table 5.1. Based on the current evidence, the choice of tool for prolonged ambulatory rhythm monitoring should be guided by the frequency of symptoms and by the purpose of the monitoring. For frequent symptoms occurring daily to perhaps at least once weekly, a 24–48 h Holter monitoring may be adequate. Specialists tend to dismiss the merits of short-term recordings, reflecting referral bias because their lens is to see patients with failed short-term recording. Cardiac event recorders are the diagnostic modality of choice for less frequent symptoms (<1 episode per week but ≥1 episode per month). For very infrequent symptoms (<1 episode per month) an implantable cardiac monitor (ICM) should be considered [1, 2].

Holter-ECG

Holter-ECG recording is the most commonly prescribed tool for ambulatory rhythm monitoring and consists of a portable recording device connected to cutaneous electrodes placed on the chest wall (Fig. 5.1). Holter ECGs provide 2, 3 or 12 ECG-channels for 24–48 h. An extended version with real time monitoring can monitor for up to 2 weeks [3]. The advantages of Holter monitoring include its widespread availability, simple application, complete data capture (not just events) and the independence of patient-activated event recording. The major disadvantages are that the short monitoring time frame results in a low diagnostic yield in patients with infrequent symptoms (see clinical application of extended monitoring), the inconvenience of a portable, continuous recording system and the local skin irritation from electrodes [1, 2, 4]. Because of inappropriate patient selection and repeat non-diagnostic testing, short-term Holter monitoring is not cost-effective for the majority of patients as the symptoms of interest only occur during the monitoring period in a minority of patients [2].

Table 5.1 Examples of commonly used device systems for prolonged rhythm monitoring

	Typical duration of monitoring	Beat-to-beat acquisition	Automated data collection	Patient-activated data acquisition	Possibility of remote monitoring
Holter-ECG	24–48 h (up to 7 days possible)	+	+	–	–
Event recorders					
Non-looping (post event)					
Omron HeartScan HCG-801®	Usually 30 days (capacity for 400 ECG recordings)	–	–	Exclusively	–
Braemar *PER900 Post Event*™	Usually 30 days	–	–	Exclusively	–
Looping					
King of Hearts Express®	2–4 weeks	+	+	+	–
CardioCall^{ST80}	2–4 weeks	+	+	+	–
MCOT™	2–4 weeks	+	+	+	–
ZIO® Patch	14 days	+	+	+	–
Medtronic Seek	30 days	+	+	+	+
Implantable cardiac monitors					
CONFIRM	Up to 3 years	+	+	+	+
REVEAL DX® 9528	Up to 3 years	+	+	+	+
REVEAL XT® 9529	Up to 3 years	+	+	+	+
Reveal LINQ™ LNQ11	Up to 3 years	+	+	+	+

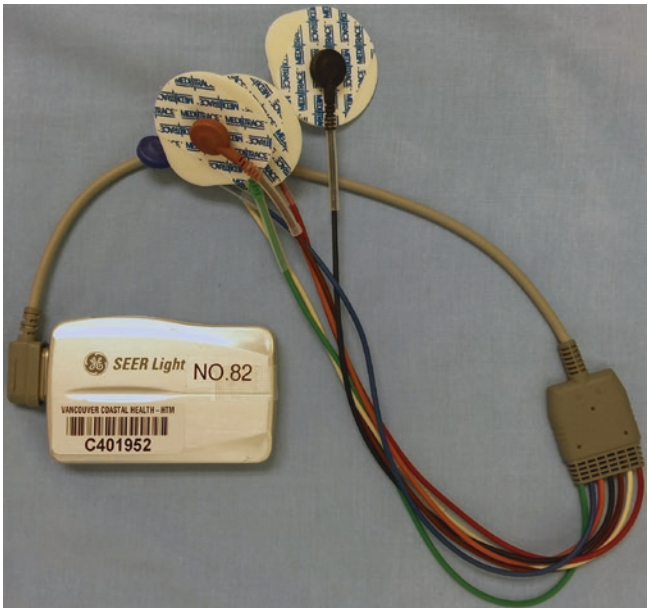


Fig. 5.1 Holter ECG

External Cardiac Event Recorders

Cardiac event recorders are portable monitoring systems that are either continuously worn (looping event recorder) or intermittently applied (non-looping or post-event recorders). External event recorders typically record a single- or dual-channel ECG and allow prolonged monitoring periods of typically 14–30 days. The recorded rhythm ECG strips are stored in the device for analysis and transmission or transmitted in real time via cell phone signal.

Non-looping event recorders are portable, cordless devices that are either handheld devices or worn on the wrist and are patient activated when symptoms occur. For rhythm recording the patient places the device on the chest wall and activates a recording button (Fig. 5.2). Non-looping event recorders may be selected in the investigation of sustained symptoms that are long enough to record the heart rhythm by applying the recorder. Non-looping event recorders avoid skin irritation associated with the electrodes required for the looping event recorders, but by definition cannot capture the

Fig. 5.2 Examples of non-looping (post event) external cardiac event recorders. (**a**) Omron HeartScan HCG-801® (Omron Healthcare, Kyoto, Japan). (**b**) Braemar *PER900 Post Event*™ (Braemar, Eagan, MN, USA)

onset of events because they are only applied after development of symptoms.

Looping event recorders are continuously worn and only removed for bathing and showering. These either use electrodes applied from an external recorder or are all-in-one patches (Fig. 5.3). Rhythm recording is either initiated by patient activation or automatically triggered (according to pre-programmed criteria) and will capture a programmable

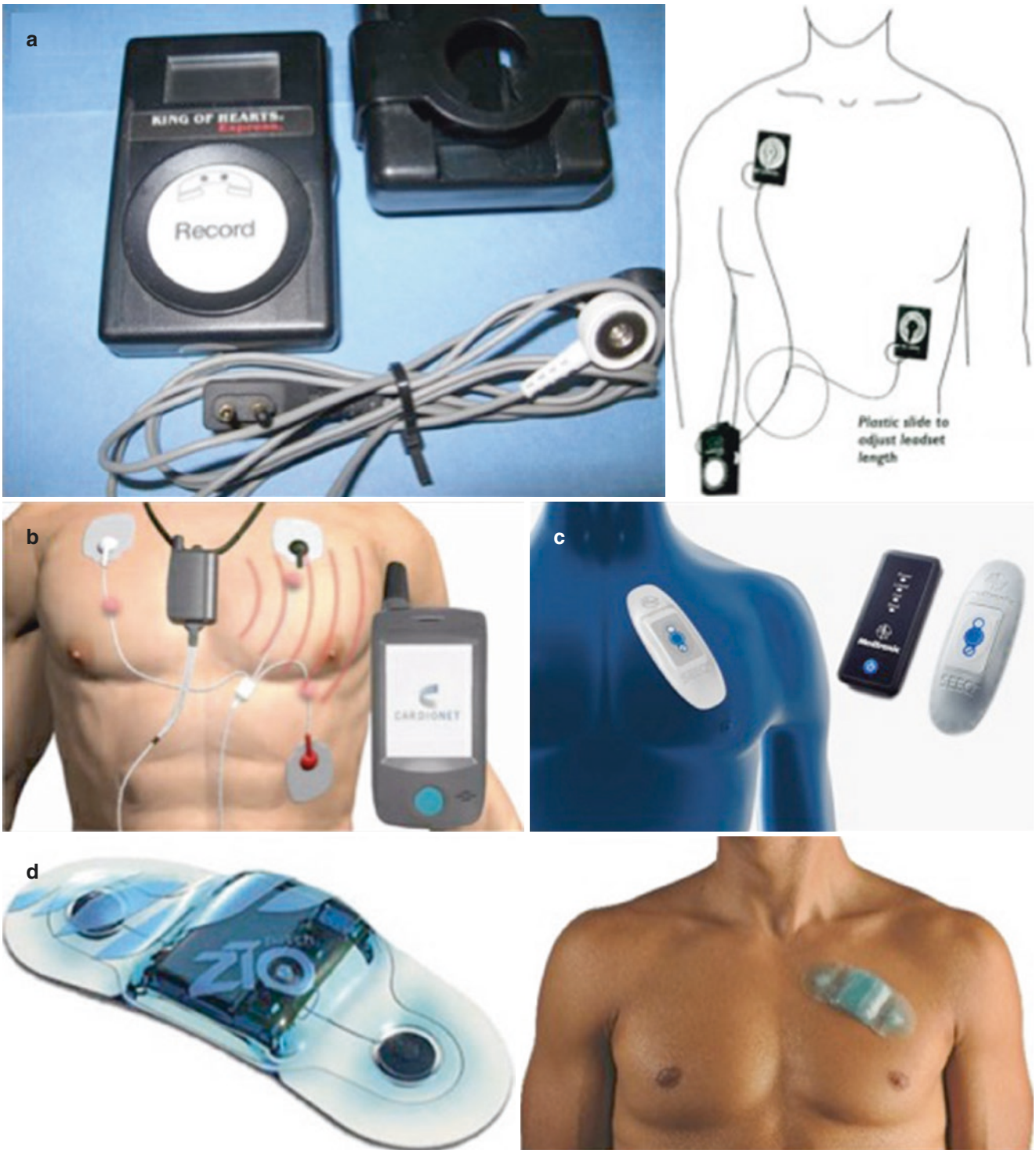


Fig. 5.3 Examples of looping external cardiac event recorders. (**a**) King of Hearts Express® (Instromedix®, San Diego, CA, USA) with instructions for electrode placement. (**b**) Mobile Cardiac Outpatient Telemetry (MCOT™ (CardioNet, Malvern, PA, USA). (**c**) Medtronic SEEQ™ (Medtronic, Minneapolis, MN, USA). (**d**) ZIO® Patch (iRhythm Technologies, Inc., San Francisco, CA, USA)

duration of seconds to minutes before and after the event. Looping event recorders are preferred for short symptom episodes that occur without warning as well as for patients with known or suspected high-risk arrhythmias. The prototype of this technology has been referred to as mobile cardiac outpatient telemetry (MCOT™; CardioNet Inc., SanDiego, California) and is now provided by several companies [5, 6]. The recording function is coupled to cellular phone technology that transmits detected events to a receiving central station that can be analyzed and acted upon based on a prescribed action plan by the ordering physician. Moreover, some of the MCOT devices also retain continuous recording tracings in their memory for up to 3 weeks and can be interrogated as a 3-week Holter type recording.

Non-looping event recorders and looping recorders have their memory downloaded in the office or transtelephonically where the ECG findings can be printed out and evaluated. Overall, the diagnostic yield of looping event recorders is superior to non-looping event recorders (see sections "Palpitations and Unknown Arrhythmia" and "Unexplained Syncope and Vasovagal Syncope" and Tables 5.2 and 5.3).

More recently, a new variant of the non-looping monitors has appeared. It is the use of smartphone technology in which electrodes are attached or coupled to the cellphone and an app in the phone is used to record and then transmit a rhythm strip. This is now being used by patients in growing numbers—both to valid medical diagnostic or follow-up purposes and by worried, anxious individuals without true cardiac pathology.

Implantable Cardiac Monitors (ICMs)

Implantable cardiac monitors are small leadless, long-term rhythm monitoring devices that are implanted under the skin of the left parasternal/left precordial chest wall. They are the preferred diagnostic tools for patients with very infrequent symptoms. They are the only type of monitor that can accurately assess AF burden. The original device, which is the size of a USB drive (volume of 6.5–9 mL), weighs 12–15 g, and has two integrated electrodes that continuously record a single-lead ECG (Fig. 5.3) was/is implanted surgically. Most available ICMs have a battery longevity of 3 years. All current ICMs are hybrid systems where arrhythmia recording is either triggered upon automatic detection or patient activated and, like looping external event recorders, will record and store the ECG strip before and after the arrhythmia onset. For data analysis, the ICM is interrogated with a standard pacemaker programmer or through remote monitoring system transmission—such as a nightly download from home.

Table 5.2 Prolonged rhythm monitoring for unexplained palpitations or undiagnosed arrhythmia

Study name	Year of publication	Sample size	Type of monitoring	Duration of monitoring	Yield of any arrhythmia detection(%)
Non-comparative studies					
Locate et al.	2014	164	Automated looping event recorder	24.1 ± 8.9 days	85.6%
Turakhia et al.	2013	26,751	Automated looping event recorder	7.6 ± 3.6 days	60.3%
Comparative studies					
De Asmundis et al.	2014	625	24-h Holter monitor vs. non-looping event recorder	15 days	1.8% vs. 89% ($p < 0.01$)
Barrett et al.	2014	146	24-h Holter vs. looping event recorder	14 days	61 vs. 96 detected arrhythmia ($p < 0.01$)
Kinlay et al.	1996	43	48-h Holter vs. looping event recorder	3 months	35% vs. 67% ($p < 0.001$)
Rothman et al.	2007	266	Patient-activated non-looping event recorder vs. looping event recorder	30 days	75% vs. 88% ($p = 0.008$)
Balmelli et al.	2003	101	Patient-activated event recorder vs. automated looping event recorder	7 days	16% vs. 84%
Giada et al.	2007	50	ICM vs. conventional[a] monitoring	279 ± 228 days	73% vs. 21% ($p < 0.001$)

[a]Conventional monitoring included 24-h Holter recording, a 4-week period of external event recorder and an electrophysiology study if the first two tests were negative

Table 5.3 Prolonged rhythm monitoring for unexplained syncope or presyncope

Study name	Year of publication	Sample size	Type of monitoring	Duration of monitoring	Diagnostic yield (%) (documentation of first recurrent syncope/ presyncope)
Croci et al.	2002	308	72-h Holter	72 h	16%
Sivakumaran et al. (COLAPS)	2004	100	48-h Holter vs. external looping event recorder	1 month	22% vs. 56% ($p < 0.001$)
Krahn et al. (REVEAL)	1999	85	ICM	10.5 ± 4 months	42%
Seidl et al.	2000	133	ICM	10.8 ± 4.3 months	87%
Krahn et al. (RAST)	2001	60	Conventional investigation[a] vs. ICM	12 months	19% vs. 55% ($p = 0.0014$)
Brignole et al.	2001	198	ICM	15 months	Normal heart tilt-positive: 29%
Moya et al.	2001				Normal heart tilt-negative: 28%
Menozzi et al. (ISSUE-1)	2002				Bundle branch block: 46%
					Structural heart disease: 40%
Brignole et al. (ISSUE-2)	2006	392	ICM	9 months (IQR 3–17)	26% with recurrent syncope
					Based on ICM findings 55% of patients eligible for specific therapy[b]
					Recurrent syncope in 10% of ICM-based therapy vs. 41% in patients without ICM-based therapy ($p = 0.002$)
Brignole et al. (ISSUE-3)[c]	2012	511	ICM	12 ± 10 months	17% with recurrent syncope
					Recurrent syncope at 2 years in pacemaker ON vs. OFF group: 25% vs. 57% ($p = 0.039$); overall risk reduction of 57% (95% CI 4–81)

[a]Conventional investigation included monitoring for 2–4 weeks with an external event recorder, followed by a tilt-test and an electrophysiology study

[b]Specific therapy was applied after the first ICM-documented syncope and included pacemaker implantation in 88%, ICD in 2%, catheter ablation in 8% and antiarrhythmic medication in 2%

[c]Patients with ICM-documented recurrent syncope and reflex bradycardia underwent implantation of a dual-chamber pacemaker and were subsequently randomized to a pacemaker ON or pacemaker OFF group

[d]The ISSUE-1 trial enrolled four different groups of patients: (1) normal heart with or without positive tilt-test, (2) underlying bundle branch block, (3) structural heart disease

Implantable cardiac monitors are minimally invasive and associated with a low rate of complications. In addition, patient acceptance is high because the leadless device does not interfere with individual activities and causes minimal aesthetic inconvenience. Automatic arrhythmia detection will record several types of arrhythmia including bradycardia, asystole, ventricular tachycardia and atrial fibrillation. Most devices have a memory capacity of 40–60 min.

The most recent type of ICM is the Medtronic Reveal LINQ™ LNQ11 (Medtronic, Minneapolis, MN, USA) (Fig. 5.4) [7]. This miniaturized ICM weighs only 2.5 ± 0.5 g, has a volume of 1.2 cm^3 (dimensions 44.8 mm × 7.2 mm × 4.0 mm), and can be inserted without suture closure with the help of device-specific insertion tool. It is about the length of the clip on pens that can be clipped to a pocket, but slightly wider. The recommended sites of insertion are displayed in Fig. 5.4. The projected device longevity is 3 years. Similar to conventional ICMs, arrhythmia recording is in response to automatic detection and patient activation. The ECG storage capacity of the

Fig. 5.4 Examples of commonly used ICMs. (**a**) Medtronic Reveal LINQ™ (Medtronic, Minneapolis, MN, USA). (**b**) Medtronic REVEAL XT® 9529 (Medtronic, Minneapolis, MN, USA). (**c**) St. Jude Medial™ Confirm DM2100 (St. Jude Medical, St. Paul, MN, USA). (**d**) BioMonitor 2 (Biotronik, Berlin, Germany). (**e**) Patient assistant for all Medtronic ICMs. (**f**) Recommended insertion locations for Medtronic Reveal LINQ™. The preferred subcutaneous location is over the fourth intercostal space along the V2-V3 electrode orientation with a 45° angle to the sternum. Alternatively the device can be inserted over the fourth intercostal space, parallel to the sternum with a distance of 2 cm ± 1 cm

Reveal LINQ™ is 57 min (27 min storage for automatically detected arrhythmia, 30 min for patient-triggered event recording). In contrast to conventional ICMs, the insertion of the Reveal LINQ™ does not require a dedicated procedure or operation room, but can be performed as a bedside procedure in a semi-sterile environment. The device insertion takes approximately 5 min (personal experience). Like other current ICMs the Reveal LINQ™ is compatible with remote monitoring. Although the upfront device costs are currently higher compared to conventional ICMs, the ease of insertion is less time-consuming and reduces procedure related costs [8].

Clinical Applications of Non-invasive ECG Monitoring

Atrial Fibrillation and Cryptogenic Stroke

Ischemic cerebrovascular accidents represent a leading cause of cardiovascular mortality and morbidity and a significant socioeconomic burden [9]. One of the major risk factors for stroke or transitory ischemic attack (TIA) is AF accounting for approximately 24% of events in the overall stroke population and for 36% of events in individuals >80 years [9, 10]. Despite extensive cardiovascular evaluation the inciting mechanism remains unexplained in 25–30% of ischemic strokes being termed embolic stroke of unknown source (ESUS) strokes [11]. Prediction models based on gene expression profiles and infarct location on neuroimaging suggest that up to 58% of cryptogenic strokes might be caused by occult intermittent AF [12]. Even short-lasting episodes of 6 min have been associated with an increased the risk of stroke as demonstrated by the ASSERT trial [13]. The same study also showed that only 16% of those episodes are symptomatic. The yield of detection of AF depends on underlying risk factors and the duration of monitoring.

Screening for occult AF during the acute phase of ischemic stroke has traditionally been limited to relatively short periods of continuous in-hospital telemetry monitoring over 24–48 h. This is associated with a low yield for the detection of AF (2.6%) [14]. Prolonged rhythm monitoring during the acute and subacute phase of an ischemic cerebrovascular event will detect subclinical AF in up to 16% of patients not known to have atrial fibrillation (Table 5.4) [14–19]. The strongest evidence comes from the CRYSTAL-AF and EMBRACE trials, two recent large-scale randomized trials [18, 19]. The most recent American Stroke Association guidelines recommend rhythm monitoring up to 30 days for patients with ESUS stroke or TIA, however the results of CRYSTAL-AF and EMBRACE were not available at the time of publication [20–21]. CRYSTAL-AF revealed that approximately 30% of patients with cryptogenic stroke will manifest AF upon up to 3 years of monitoring with an implanted monitor.

AF Burden Directing Medical or Invasive Management

The use of prolonged ambulatory rhythm monitoring for the assessment of AF burden is of growing interest, and there are numerous ongoing clinical trials addressing the role of prolonged rhythm monitoring for various issues of AF management. For example, the role of oral anticoagulation in subclinical AF detected by ICMs is being addressed in the ongoing ARTESiA trial (NCT01938248). Other potential indications for prolonged rhythm monitoring include surveillance and adjustment of antiarrhythmic or rate controlling medication or documentation of changes in AF burden through lifestyle modifications [22, 23]. With regard to pulmonary vein isolation, ICMs are particularly useful for the documentation of procedural success and detection of early AF recurrence [24–26].

Palpitations and Unknown Arrhythmia

Paroxysmal palpitations are a common symptom affecting up to 16% of unselected patients who present to a general medicine facility. However, an underlying primary rhythm disorder is found in only 43%, whereas 57% of palpitations are related to psychiatric or miscellaneous conditions such as medication or metabolic causes [27]. The diagnostic yield of cardiac investigations is related to underlying comorbidities, clinical circumstances/triggers, frequency of palpitations, and duration of monitoring (Table 5.2). Resting 12-lead ECG and 24–48 h Holter-ECG monitoring are the most commonly prescribed tests for unexplained palpitations [28]. However, the diagnostic yield of a single 24-h Holter monitoring is only diagnostic in 12–29% [29]. Cardiac event recorders are superior and more cost-effective compared to conventional Holter monitoring providing a diagnostic yield of 66–84% and 26–52% for loop and non-loop devices respectively [1, 29–33]. The superiority of automatically triggered event recorders is supported by a limited number of prospective comparative studies [34, 35].The diagnostic yield of patient-activated event recorders is variable across different studies and highly dependent on individual motivation, the duration of symptoms, and whether or not the event produces cerebral impairment (dizziness, syncope) that prevents application of the monitor [36, 37].

There is limited data with regard to the optimal duration for rhythm monitoring with external event recorders. Most experts and guidelines recommend an initial duration of 30 days [1]. Two small prospective studies using patient-activated

Table 5.4 Prolonged rhythm monitoring for occult AF in patients with embolic stroke of uncertain source

Study name	Year of publication	Sample size	$CHADS_2$ score	Type of monitoring	Duration of monitoring	Yield of AF detection(%)
Non-comparative studies						
Grond et al.	2013	1135	N/A	72-h Holter	72 h	4.3% (95% CI 3.4–5.2%)
Douen et al.	2008	144	N/A	Serial ECGs[a] + prolonged Holter recording[a]	3–5 days	Overall incidence of 19.4%
						6.3% with history of AF at baseline
						New AF detection
						13.5% (Holter + serial ECGs)
						11.3% (serial ECGs alone)
Jabaudon et al.	2004	149	N/A	Serial ECGs +24-h Holter followed by 7-days external loop recorder	up to 7 days	Standard ECGs 6.7% (95% CI 3.6–12.1)
						24-h Holter 5% (95% CI 2.3–10.2)
						7-days external loop recorder 5.7% (2.1–12.9)
Comparative studies						
Rizos et al.	2012	496	3[b] [3, 4]	CEM vs. aCEM vs. 24-h Holter	64[b] h (43.0–89.8)	24-h Holter: 2.8%
						CEM: 5.4%
						aCEM: 7.7%
Sanna et al. (CRYSTAL-AF)	2014	441	2–34%	ICM vs. conventional follow-up	6 months	8.9% vs. 1.4% (HR 6.4; 95% CI 1.9–21.7; $p < 0.001$)
			3–41%		12 months	12.4% vs. 2.0% (HR 7.3; 95% CI 2.6–20.8; $p < 0.001$)
			4–19%			
			5–6%			
Gladstone et al. (EMBRACE)	2014	527	3[b] [2–6]	30-days non-looping event recorder vs. 24-h Holter	3 months	16.1% vs. 3.2% (95% CI, 8.0–17.6; $p < 0.001$)

CEM continuous bedside ECG monitoring, *aCEM* automated continuous bedside ECG monitoring
[a]Serial ECGs = 3 ECGs within 72 h; average duration of Holter monitoring was 4.75 days
[b]Median (IQR)

continuous loop recorders suggested that a duration of 2 weeks is associated with the highest diagnostic yield and cost-effectiveness [38, 39]. Patients with very rare episodes should be considered for ICM insertion (Table 5.2) [40].

Unexplained Syncope and Vasovagal Syncope

Syncope is a common cause of consultation and the cumulative lifetime prevalence in the general population is about 35% (95% CI 31–39%) with women being affected more often than men (41% vs. 28%; p = 0.003) [41]. The three major etiologies include neurally-mediated (reflex) syncope, orthostatic hypotension, and cardiovascular causes [42]. Syncope with serious or life-threatening features, especially if abrupt in onset and without focal neurological findings upon regaining consciousness, is usually of cardiac origin and represents 10–17% of all cases [43, 44]. The etiology of up to 37% of all syncopal episodes remains unexplained after initial assessment and is associated with a 22% risk of recurrence [43].

Although commonly prescribed, the diagnostic yield of a 24-h Holter is extremely low and symptom-rhythm correlation is only found in 2–6% [45–47]. Even extending Holter

monitoring up to 72 h only modestly increases the diagnostic yield to 16% [48]. Overall, the diagnostic yield for unexplained syncope depends on the frequency of symptoms, duration of monitoring and modality of prolonged rhythm recording (Table 5.3). External cardiac event recorders and ICMs are superior and more cost-effective than conventional Holter monitoring and provide a diagnostic yield of 20–56% and 42–87% respectively [36, 49, 50–53]. To maximize the diagnostic yield the duration of monitoring should be adjusted to the frequency of symptoms. Based on available data a minimal duration of 30 days is recommended for external cardiac event recorders in most patients [50, 51]. With regards to ICMs, data from a pooled population of patients with unexplained syncope showed that 93% of recurrent events occurred within 12 months post implantation. The probability of recurrent syncope after 1 year was low, particularly in younger patients without additional risk factors [54].

It is important to emphasize that frequency and etiology of unexplained syncope strongly depend on underlying risk factors and the type of patient population as demonstrated by the ISSUE-1 study (Table 5.3). Neurally-mediated syncope with reflex-bradycardia is the most common cause in patients without structural heart disease, whereas brady- or tachyarrhythmias dominate in patients with overt heart disease or underlying conduction abnormalities [55–57]. In addition, ISSUE-1 also showed the low sensitivity and poor predictive value of tilt-testing if applied to all syncope patients rather than to those appropriately pre-selected for higher index of suspicion for vagally mediated syncope [56]. The subsequent ISSUE-2 and ISSUE-3 study demonstrated the benefits of ICM-based management in unexplained and vasovagal syncope respectively (Table 5.3) [58, 59]. Based on ICM-recordings during recurrent syncope 51% of patients in the ISSUE-2 study were eligible for a specific therapy including pacemaker implantation in 88%. The result was a 80% relative risk reduction of recurrent syncope [58]. Patients in ISSUE-3 who had ICM-documented cardioinhibitory response (syncope with asystole ≥3 s or non-syncopal asystole ≥6 s) had a reduction in recurrent syncope following dual chamber pacemaker implantation, suggesting selection of patients with a profound cardioinhibitory response represents the subset of neurally mediated patients that should be considered for pacing [59].

Screening for Ventricular Arrhythmia and Risk Assessment of Sudden Cardiac Death

Although risk assessment for sudden cardiac death is a major goal in the management of patients with structural heart disease or primary electrical disorders [60, 61], the role of routine prolonged rhythm monitoring to screen for malignant ventricular arrhythmia remains undefined for most of those conditions. Conventional Holter monitoring alone provides a low yield of actionable findings in patients with ischemic cardiomyopathy and is only routinely recommended for hypertrophic cardiomyopathy [62–65]. Most evidence for ambulatory ECG monitoring in ischemic cardiomyopathy is derived from the MUSTT trial that enrolled patients with mild to moderate reduction of left ventricular systolic function post myocardial infarction (LVEF 36–40%) [66–68]. In MUSTT, patients with ambulatory documentation of asymptomatic non-sustained ventricular tachycardia underwent an electrophysiology study and those with inducible sustained ventricular tachycardia were randomized to antiarrhythmic medication or ICD implantation (after failure of antiarrhythmics) vs. conventional treatment. A mortality benefit was shown for patients with ICD implantation. However, it is important to emphasize that the MUSTT trial was conducted before the era of primary angioplasty, and substantial evolution of medical therapy of the study population has subsequently occurred.

Heart rate turbulence and microvolt T-wave alternans are novel, emerging ECG markers that can be derived from Holter monitoring that have shown promising results in initial studies [69–71]. The utility of these markers for risk prediction and decision-making with regard to ICD implantation in ischemic cardiomyopathy is currently being tested in an ongoing large-scale randomized trial (trial number NCT00673842).

Conclusion

Extended ambulatory rhythm monitoring plays a crucial role for diagnosis and management of various rhythm disorders. Conventional Holter-ECG recording has significant limitations and is not cost-effective for the majority of scenarios where it is prescribed. A large arsenal of newer, more advanced monitoring tools is available allowing longer and more selective monitoring with increased diagnostic yield. To obtain optimal diagnostic information the choice of device has to be individualized according to symptom description and frequency.

References

1. Zimetbaum P, Goldman A. Ambulatory arrhythmia monitoring: choosing the right device. Circulation. 2010;122(16):1629–36.
2. Krahn AD, Andrade JG, Deyell MW. Selecting appropriate diagnostic tools for evaluating the patient with syncope/collapse. Prog Cardiovasc Dis. 2013;55(4):402–9.
3. Kennedy HL. The evolution of ambulatory ECG monitoring. Prog Cardiovasc Dis. 2013;56(2):127–32.
4. Subbiah R, Gula LJ, Klein GJ, Skanes AC, Yee R, Krahn AD. Syncope: review of monitoring modalities. Curr Cardiol Rev. 2008;4(1):41–8.
5. Joshi AK, Kowey PR, Prystowsky EN, et al. First experience with a Mobile Cardiac Outpatient Telemetry (MCOT) system for the diagnosis and management of cardiac arrhythmia. Am J Cardiol. 2005;95(7):878–81.

6. Rothman SA, Laughlin JC, Seltzer J, et al. The diagnosis of cardiac arrhythmias: a prospective multi-center randomized study comparing mobile cardiac outpatient telemetry versus standard loop event monitoring. J Cardiovasc Electrophysiol. 2007;18(3):241–7.
7. Purerfellner H, Sanders P, Pokushalov E, et al. Miniaturized Reveal LINQ insertable cardiac monitoring system: First-in-human experience. Heart Rhythm. 2015;12(6):1113–9.
8. Kanters TA, Wolff C, Boyson D, et al. Cost comparison of two implantable cardiac monitors in two different settings: reveal XT in a catheterization laboratory vs. Reveal LINQ in a procedure room. Europace. 2016;18(6):919-912.
9. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29–322.
10. Reiffel JA. Atrial fibrillation and stroke: epidemiology. Am J Med. 2014;127(4):e15–6.
11. Liberman AL, Prabhakaran S. Cryptogenic stroke: how to define it? How to treat it? Curr Cardiol Rep. 2013;15(12):423.
12. Jickling GC, Stamova B, Ander BP, et al. Prediction of cardioembolic, arterial, and lacunar causes of cryptogenic stroke by gene expression and infarct location. Stroke. 2012;43(8):2036–41.
13. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366(2):120–9.
14. Grond M, Jauss M, Hamann G, et al. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke: a prospective multicenter cohort study. Stroke. 2013;44(12):3357–64.
15. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. Stroke. 2004;35(7):1647–51.
16. Douen AG, Pageau N, Medic S. Serial electrocardiographic assessments significantly improve detection of atrial fibrillation 2.6-fold in patients with acute stroke. Stroke. 2008;39(2):480–2.
17. Rizos T, Guntner J, Jenetzky E, et al. Continuous stroke unit electrocardiographic monitoring versus 24-hour Holter electrocardiography for detection of paroxysmal atrial fibrillation after stroke. Stroke. 2012;43(10):2689–94.
18. Gladstone DJ, Sharma M, Spence JD, EMBRACE Steering Committee and Investigators. Cryptogenic stroke and atrial fibrillation. N Engl J Med. 2014;371(13):1260.
19. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370(26):2478–86.
20. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160–236.
21. Flint AC, Banki NM, Ren X, Rao VA, Go AS. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. Stroke. 2012;43(10):2788–90.
22. Mittal S, Movsowitz C, Steinberg JS. Ambulatory external electrocardiographic monitoring: focus on atrial fibrillation. J Am Coll Cardiol. 2011;58(17):1741–9.
23. Malmo V, Nes BM, Amundsen BH, et al. Aerobic interval training reduces the burden of atrial fibrillation in the short term: a randomized trial. Circulation. 2016;133(5):466–73. doi:10.1161/CIRCULATIONAHA.115.018220.
24. Hindricks G, Pokushalov E, Urban L, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: Results of the XPECT trial. Circ Arrhythm Electrophysiol. 2010;3(2):141–7.
25. Pokushalov E, Romanov A, Corbucci G, et al. Use of an implantable monitor to detect arrhythmia recurrences and select patients for early repeat catheter ablation for atrial fibrillation: a pilot study. Circ Arrhythm Electrophysiol. 2011;4(6):823–31.
26. Kapa S, Epstein AE, Callans DJ, et al. Assessing arrhythmia burden after catheter ablation of atrial fibrillation using an implantable loop recorder: the ABACUS study. J Cardiovasc Electrophysiol. 2013;24(8):875–81.
27. Weber BE, Kapoor WN. Evaluation and outcomes of patients with palpitations. Am J Med. 1996;100(2):138–48.
28. Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA guidelines for ambulatory electrocardiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee to revise the guidelines for ambulatory electrocardiography). Circulation. 1999;100(8):886–93.
29. Hoefman E, Bindels PJ, van Weert HC. Efficacy of diagnostic tools for detecting cardiac arrhythmias: systematic literature search. Neth Hear J. 2010;18(11):543–51.
30. Kinlay S, Leitch JW, Neil A, Chapman BL, Hardy DB, Fletcher PJ. Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations. A controlled clinical trial. Ann Intern Med. 1996;124(1 Pt 1):16–20.
31. Turakhia MP, Hoang DD, Zimetbaum P, et al. Diagnostic utility of a novel leadless arrhythmia monitoring device. Am J Cardiol. 2013;112(4):520–4.
32. Locati ET, Vecchi AM, Vargiu S, Cattafi G, Lunati M. Role of extended external loop recorders for the diagnosis of unexplained syncope, pre-syncope, and sustained palpitations. Europace. 2014;16(6):914–22.
33. Barrett PM, Komatireddy R, Haaser S, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. Am J Med. 2014;127(1):95e11–97.
34. Balmelli N, Naegeli B, Bertel O. Diagnostic yield of automatic and patient-triggered ambulatory cardiac event recording in the evaluation of patients with palpitations, dizziness, or syncope. Clin Cardiol. 2003;26(4):173–6.
35. Reiffel JA, Schwarzberg R, Murry M. Comparison of autotriggered memory loop recorders versus standard loop recorders versus 24-hour Holter monitors for arrhythmia detection. Am J Cardiol. 2005;95(9):1055–9.
36. Gula LJ, Krahn AD, Massel D, Skanes A, Yee R, Klein GJ. External loop recorders: determinants of diagnostic yield in patients with syncope. Am Heart J. 2004;147(4):644–8.
37. de Asmundis C, Conte G, Sieira J, et al. Comparison of the patient-activated event recording system vs. traditional 24 h Holter electrocardiography in individuals with paroxysmal palpitations or dizziness. Europace. 2014;16(8):1231–5.
38. Zimetbaum PJ, Kim KY, Josephson ME, Goldberger AL, Cohen DJ. Diagnostic yield and optimal duration of continuous-loop event monitoring for the diagnosis of palpitations. A cost-effectiveness analysis. Ann Intern Med. 1998;128(11):890–5.
39. Hoefman E, van Weert HC, Boer KR, Reitsma J, Koster RW, Bindels PJ. Optimal duration of event recording for diagnosis of arrhythmias in patients with palpitations and light-headedness in the general practice. Fam Pract. 2007;24(1):11–3.
40. Giada F, Gulizia M, Francese M, et al. Recurrent unexplained palpitations (RUP) study comparison of implantable loop recorder versus conventional diagnostic strategy. J Am Coll Cardiol. 2007;49(19):1951–6.
41. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, van Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. J Cardiovasc Electrophysiol. 2006;17(11):1172–6.
42. Brignole M, Hamdan MH. New concepts in the assessment of syncope. J Am Coll Cardiol. 2012;59(18):1583–91.
43. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. N Engl J Med. 2002;347(12):878–85.

44. Brignole M, Alboni P, Benditt DG, et al. Guidelines on management (diagnosis and treatment) of syncope--update 2004. Europace. 2004;6(6):467–537.
45. Gibson TC, Heitzman MR. Diagnostic efficacy of 24-hour electrocardiographic monitoring for syncope. Am J Cardiol. 1984;53(8):1013–7.
46. Linzer M, Yang EH, Estes NA 3rd, Wang P, Vorperian VR, Kapoor WN. Diagnosing syncope. Part 2: Unexplained syncope. Clinical Efficacy Assessment Project of the American College of Physicians. Ann Intern Med. 1997;127(1):76–86.
47. Sarasin FP, Carballo D, Slama S, Louis-Simonet M. Usefulness of 24-h Holter monitoring in patients with unexplained syncope and a high likelihood of arrhythmias. Int J Cardiol. 2005;101(2):203–7.
48. Croci F, Brignole M, Alboni P, et al. The application of a standardized strategy of evaluation in patients with syncope referred to three syncope units. Europace. 2002;4(4):351–5.
49. Sivakumaran S, Krahn AD, Klein GJ, et al. A prospective randomized comparison of loop recorders versus Holter monitors in patients with syncope or presyncope. Am J Med. 2003;115(1):1–5.
50. Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C. Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators. Circulation. 1999;99(3):406–10.
51. Seidl K, Rameken M, Breunung S, et al. Diagnostic assessment of recurrent unexplained syncope with a new subcutaneously implantable loop recorder. Reveal-Investigators. Europace. 2000;2(3):256–62.
52. Krahn AD, Klein GJ, Yee R, Skanes AC. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. Circulation. 2001;104(1):46–51.
53. Krahn AD, Klein GJ, Yee R, Hoch JS, Skanes AC. Cost implications of testing strategy in patients with syncope: randomized assessment of syncope trial. J Am Coll Cardiol. 2003;42(3):495–501.
54. Assar MD, Krahn AD, Klein GJ, Yee R, Skanes AC. Optimal duration of monitoring in patients with unexplained syncope. Am J Cardiol. 2003;92(10):1231–3.
55. Brignole M, Menozzi C, Moya A, et al. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. Circulation. 2001;104(17):2045–50.
56. Moya A, Brignole M, Menozzi C, et al. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. Circulation. 2001;104(11):1261–7.
57. Menozzi C, Brignole M, Garcia-Civera R, et al. Mechanism of syncope in patients with heart disease and negative electrophysiologic test. Circulation. 2002;105(23):2741–5.
58. Brignole M, Sutton R, Menozzi C, et al. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. Eur Heart J. 2006;27(9):1085–92.
59. Brignole M, Menozzi C, Moya A, et al. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. Circulation. 2012;125(21):2566–71.
60. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61(3):e6–75.
61. Hohnloser SH, Israel CW. Current evidence base for use of the implantable cardioverter-defibrillator. Circulation. 2013;128(2):172–83.
62. Hofsten DE, Wachtell K, Lund B, Molgaard H, Egstrup K. Prevalence and prognostic implications of non-sustained ventricular tachycardia in ST-segment elevation myocardial infarction after revascularization with either fibrinolysis or primary angioplasty. Eur Heart J. 2007;28(4):407–14.
63. Bloch Thomsen PE, Jons C, Raatikainen MJ, et al. Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. Circulation. 2010;122(13):1258–64.
64. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58(25):e212–60.
65. Authors/Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733–79.
66. Buxton AE, Fisher JD, Josephson ME, et al. Prevention of sudden death in patients with coronary artery disease: the Multicenter Unsustained Tachycardia Trial (MUSTT). Prog Cardiovasc Dis. 1993;36(3):215–26.
67. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 1999;341(25):1882–90.
68. Lee KL, Hafley G, Fisher JD, et al. Effect of implantable defibrillators on arrhythmic events and mortality in the multicenter unsustained tachycardia trial. Circulation. 2002;106(2):233–8.
69. Exner DV, Kavanagh KM, Slawnych MP, et al. Noninvasive risk assessment early after a myocardial infarction the REFINE study. J Am Coll Cardiol. 2007;50(24):2275–84.
70. Tokuyama T, Nakano Y, Awazu A, et al. Deterioration of the circadian variation of heart rate variability in Brugada syndrome may contribute to the pathogenesis of ventricular fibrillation. J Cardiol. 2014;64(2):133–8.
71. Sakamoto S, Takagi M, Tatsumi H, et al. Utility of T-wave alternans during night time as a predictor for ventricular fibrillation in patients with Brugada syndrome. Heart Vessels. 2016;31(6):947–5.

Sudden Cardiac Death: Methods of Risk Prediction

6

John Alvin Gayee Kpaeyeh Jr., Dean M. Abtahi, and Michael R. Gold

Abstract

Sudden cardiac death (SCD) is the leading cause of cardiovascular mortality, accounting for more than 50% or greater than 300,000 deaths in the United States annually. As such, this is a major health care problem. Identifying high risk patients that may benefit from preventative strategies has been studied for decades. The implantable cardiac defibrillator (ICDs) has had a major impact on the treatment of SCD. However, this therapy has been largely used in patients with left ventricular dysfunction. A changing epidemiology of SCD with fewer patients having marked reductions in left ventricular ejection fraction (LVEF) has renewed the focus on identifying other high risk populations. This chapter summarizes the current understanding of the diverse clinical, genetic, electrocardiographic and imaging techniques available to detect patients most at risk. Despite many identified risk factors, no single predictor has been shown to have sufficient predictive value to be used to guide preventative therapy and reduce mortality. More recent effort has been directed towards combining markers to increase the sensitivity of identifying high risk cohorts.

Keywords

Sudden cardiac death (SCD) • Risk stratification • Implantable cardioverter defibrillator (ICD) • Ventricular tachycardia (VT) • Genome-wide association studies (GWAS) • Left ventricular ejection fraction (LVEF) • QRS duration • QT interval • Heart rate turbulence • T-wave alternans • Cardiac magnetic resonance imaging (cMRI) • Scar assessment • Sympathetic denervation • Positron emission tomography (PET) • Radioiodinated metaiodobenzylguanidine (mIBG) • Signal Averaged ECG (SAECG) • Electrophysiologic study (EPS) • Holter monitoring

Introduction

Sudden cardiac death (SCD) is most commonly defined as death from unexpected circulatory arrest occurring within an hour of the onset of symptoms or during sleep [1]. In the majority of cases, SCD is triggered by an arrhythmic event, most frequently ventricular tachycardia, ventricular fibrillation and asystole, although recently, pulseless electrical activity has been noted more frequently.

The leading cause of death in the United States, according to the Centers for Disease Control and Prevention, is cardiovascular disease (611,000 deaths annually) [2]. Other

Disclosures: Dr. Gold has received research grants and served as a consultant to Boston Scientific, St Jude and Medtronic.

J.A.G. Kpaeyeh Jr., M.D. • D.M. Abtahi, M.D.
M.R. Gold, M.D., Ph.D. (✉)
Division of Cardiology, Medical University of South Carolina, Charleston, SC 29425, USA
e-mail: kpaeyeh@musc.edu; abtahi@musc.edu; goldmr@musc.edu

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_6

common causes of death include malignancy (584,000), chronic respiratory disease (149,000), accidents (130,000), and strokes (128,000) [2]. Despite a dramatic decline in mortality from heart disease over the past 30 years, SCD remains the leading cause of cardiovascular death. It is estimated that SCD accounts for more than 300,000 deaths in the United States annually and approximately 50% are the first known cardiac event [2, 3]. Even this may be an underestimation, as the majority of patients who suffer out of hospital cardiac arrest never survive the initial event [2].

In order to reduce the burden of SCD, much effort has been directed to identify and better treat those most at risk. It is well described that underlying structural heart disease in the context of ischemia, systolic heart failure and fibrosis often trigger sustained arrhythmias that may lead to cardiovascular collapse and death. However, a broad range of at risk populations for SCD exists, including patients with family history of coronary artery disease, heart failure with reduced ejection fraction (HFrEF), ambient ventricular arrhythmia (PVC, non-sustained ventricular tachycardia (VT), sustained VT), prior cardiac arrest, advanced age, male sex, African American race, left ventricular hypertrophy, congenital heart disease, and cardiac conduction abnormalities, such as bundle branch block. Additionally, patients with underlying channelopathies, including long QT syndrome and Brugada syndrome as well as arrhythmic myopathies, for example arrhythmogenic right ventricular cardiomyopathy, Wolf Parkinson White syndrome and hypertrophic cardiomyopathy, present differently than those with traditional risk from ischemic and non-ischemic cardiomyopathies. Various electrical markers may predict SCD including T-wave alternans, late potentials on signal averaged electrocardiography, inducibility of sustained tachyarrhythmia by programmed electrical stimulation, prolonged QRS and QT intervals, and/or abnormal heart rate variability or turbulence and abnormal baroreflex sensitivity. Additionally, there are further co-morbidities that contribute to and complicate risk stratification including smoking, hypertension, hyperlipidemia, obesity, diabetes mellitus, renal failure, drug abuse, and congenital heart disease. Finally, life style and social factors play a predictive role including activity levels, socioeconomic status, as well as stress (emotional or physical) [1, 4]. Given the complexity and diversity of these factors, it is not surprising that risk stratification of SCD remains a major challenge.

A series of large, multicenter randomized trials demonstrated the benefit of the implantable cardioverter defibrillators (ICD) for preventing sudden death in selected populations [5–7]. This led to a rapid expansion of this therapy, which has likely contributed to a significant decline in incidence of ventricular fibrillation [2, 8, 9] and deaths [8] during out of hospital cardiac arrest. Due to this success and the changing epidemiology of SCD, there has been a renewed focus on risk stratification in this population [3, 10]. However, despite advances in our understanding, SCD remains a significant problem primarily because of a lack of a comprehensive and validated approach to detecting patients at risk. The major risk factors evaluated are presented in Table 6.1 and will be summarized in this chapter.

Table 6.1 Summary of risk stratification tools for sudden cardiac death

History	Post-MI
	Parental history of premature SCD (age < 65)
	VT/VF
	Age
	Male sex
	African American race
	Traditional coronary risk factors
Anatomic abnormalities	Low LVEF
	Myocardial scar
Autonomic abnormalities	Heart rate turbulence: Ambulatory ECG
	Sympathetic denervation: MIBG, PET
ECG abnormalities	
Resting ECG	Prolonged QRS duration
	Prolonged QT interval
	Brugada syndrome: ST-segment elevation and T-wave inversion in V1 and V2
	Arrhythmogenic right ventricular dysplasia: Epsilon waves, prolonged duration of S-wave and T-wave inversion in V1 and V2
	Wolf-Parkinson-White: delta waves, narrow PR and prolonged QRS duration
	Late Potentials on signal averaged ECG
Ambulatory ECG	Ventricular ectopy
	NSVT
	Heart rate turbulence
Exercise ECG	NSVT
	T-wave alternans
EP study	Inducibility of sustained VT

MI myocardial infarction, *LVEF* left ventricular ejection fraction, *SCD* sudden cardiac death, *MIBG* meta-iodobenzylguanidine, *PET* positron emission tomography, *ECG* electrocardiogram, *NSVT* non-sustained ventricular tachycardia

Genetics and Genomics

Multiple population based studies exist suggesting a strong genetic contribution to individual SCD risk, independent of traditional cardiovascular risk factors. The landmark Paris Prospective Study showed increased risk of SCD in middle aged men with parental sudden death (RR 1.80 (95% CI, 1.11–2.88) [11]. Similarly, the Seattle case-controlled study, demonstrated increased risk of SCD (odds ratio (OR) = 2.69, 95% CI = 1.35–5.36) among patients with a parental history of early onset sudden death (age < 65) [12]. Additionally,

family history of sudden death has been shown to be an independent risk factor (OR 2.72, 95% CI 1.84–4.03) for primary ventricular fibrillation in acute myocardial infarction [13]. Despite the multiple studies demonstrating a strong association between family history and SCD, there has yet to be a specific genetic variant or clinical marker identified that has proven effective in predicting individual risk. Furthermore, due to the variability in the mechanism of SCD, there is likely a broad spectrum of heritability of SCD in different populations.

In individuals under 40 years of age, SCD occurs in a Mendelian pattern with cardiomyopathies and electrical disorders being the most prevalent [14]. In individuals above 40 years old, which account for the majority of events, SCD is most commonly caused by ventricular fibrillation in the setting of acute or prior myocardial infarction. To attain a better understanding, genome-wide association studies (GWAS) are now being performed to isolate genetic variants modulating SCD risk, with specific interest in genes that play a role in structural abnormalities, as well as heart rate and ECG indices of slowed conduction and abnormal repolarization [14–18].

GWAS use dense maps of hundreds of thousands of single nucleotide polymorphism (SNP) arrays to identify genotype patterns associated with a particular phenotype [14], in this case SCD. An increasing number of genetic variants are starting to be uncovered with strong associations [19, 20] for SCD, and this approach holds future promise as costs decrease and gene-scanning technologies improve. However, these observations are limited in clinical applicability at this time due to small sample size.

Left Ventricular Ejection Fraction

Left ventricular systolic function, estimated by ejection fraction (LVEF), is the most common studied marker of SCD risk, and it is clearly a powerful predictor of cardiac mortality [21–23]. LVEF is easy to measure, reproducible and predictive in both ischemic and non-ischemic cardiomyopathies. In clinical practice, LVEF has become the primary criterion used for ICD placement. The MADIT II trial demonstrated a significant reduction in SCD and all-cause mortality after ICD placement among patients with previous myocardial infarction and LVEF ≤30% [24]. The SCD-HeFT trial demonstrated decreased all-cause and sudden death mortality after ICD placement in patients with both ischemic and non-ischemic cardiomyopathy, NYHA class II or III functional status and LVEF ≤35% [7]. However, not all studies show a benefit of ICDs among patients with reduced LVEF. The CABG-Patch trial showed no benefit of ICD therapy in patients with EF < 35% undergoing surgical coronary revascularization [25], possibly due to the antiarrhythmic effect or the improved systolic function following revascularization. Similarly, the DINAMIT and IRIS studies showed no benefit of early implantation of ICDs following myocardial infarction despite a reduced ejection fraction [26, 27]. Again, this may be due to improvement in LVEF post MI or competing non-arrhythmic causes of mortality [26]. Hence, the timing of LVEF assessment and of intervention and changes in underlying myocardial status are also important variables to consider. Finally, as noted above, most patients that survive cardiac arrest in more contemporary studies only have mildly depressed or near normal systolic function [5, 28] and the predictive role of LVEF is therefore limited in these populations without significant underlying cardiomyopathy.

Resting Electrocardiogram (QRS and QT Intervals)

The resting electrocardiogram is a non-invasive, inexpensive diagnostic tool that is available in most clinical settings and can provide useful prognostic information. QRS duration represents interventricular conduction time and when prolonged may promote ventricular arrhythmias by altering electrical and mechanical function through abnormal dispersion of depolarization and repolarization and resultant cardiac dyssynchrony. QRS prolongation may also be a marker of more advanced LV dilation and dysfunction. QRS prolongation (≥120 ms) has been shown to predict both overall mortality and SCD in patients with ischemic and non-ischemic cardiomyopathy, independent of LVEF [29]. In a subgroup analysis of the MUSTT trial, QRS duration and the presence of left bundle branch block were found to be independent predictors of overall mortality and SCD in patients with ischemic cardiomyopathy [30]. Despite the above findings, there are a number of conflicting ICD trials that were unable to demonstrate an effect of QRS duration on mortality independent of LVEF [31, 32], limiting its overall predictive value.

The QT interval represents ventricular repolarization, which is routinely corrected for heart rate or RR interval and measured as QTc. A QTc duration greater than 420–440 ms (longer upper limit of normal in females than in males) is associated with a two to threefold increase in cardiac mortality [33–35] among patients with and without coronary artery disease. Applied to the general population, a prolonged QT interval and/or increased QT interval dispersion (the maximal inter-lead QT variance in 12 lead electrocardiogram) predicts increased cardiac and total mortality [36]. However, in patients with advance heart failure, QT interval and interval dispersion were unable to predict mortality independent of LVEF [37], also limiting its clinical applicability in patients with significant underlying cardiomyopathy. Of note, these studies did not include subjects with genetic

Table 6.2 Composite risk scores for SCD in Primary Prevention Cohorts

Prediction model	MADT-II	PAREPET	PACE
	NYHA Class > II	Percentage of denervated myocardium (>37%)	Cr ≥2.0
			Point(s) – 2
	Age > 70 years	LVEDV Index >99 mL/m^2	LVEF ≤ 20%
			Point – 1
	Blood Urea Nitrogen >26	Creatinine >1.49 mg/dL	Age > = 70
			Point – 1
	QRS duration >0.12 s	Lack of angiotensin inhibition	Peripheral artery disease
			Point – 1
	Atrial fibrillation		
Low risk	Zero risk factors	Zero risk factors	
Intermediate risk	Two risk factors	One risk factor	Less than 3 points
High risk	Three or more risk factors	Two risk factors	3 or more points

[94–96]

channelopathies including Long QT syndrome in whom a QTc > 500 ms (or the rarer Short QT syndrome with QTC < 350 ms) is associated with increased risk of SCD independent of structural heart disease [38, 39].

Finally, there are a number of ECG abnormalities recognized that carry an increased incidence of SCD in specific situations including Brugada syndrome, Arrhythmogenic Right Ventricular Dysplasia and Wolf Parkinson White Syndrome (Table 6.2).

Ambulatory Electrocardiogram (Holter Recording of Ventricular Ectopy and Heart Rate Turbulence)

Historically, long term ambulatory electrocardiography by Holter monitoring was used to predict SCD in survivors of myocardial infarction. Patients with complex ventricular ectopy defined as more than 10 premature ventricular beats per hour or non-sustained ventricular tachycardia (NSVT) were shown to have increased mortality [40, 41]. However, in one more recent multivariate analysis performed in the thrombolytic/reperfusion era, complex ventricular ectopy was not shown to be an independent predictor of mortality and the presence of post infarct NSVT no longer predicted mortality or arrhythmic events [42]. Studies evaluating complex ventricular ectopy, specifically NSVT among patients with non-ischemic cardiomyopathy have also had conflicting results [43–45].

Heart rate turbulence is a non-invasive marker of electrical instability that can be assessed on Holter monitor and has been shown to identify patients at high risk for all-cause mortality and sudden death, specifically in post-infarction and congestive heart failure patients [46–49]. Heart rate turbulence is believed to reflect baroreflex sensitivity and is a surrogate marker of cardiac autonomic tone. Under normal conditions, a ventricular premature beat (VPB) results in a transient drop in blood pressure triggering baroreceptor activated inhibition of vagal tone and subsequent increase in heart rate. Increased myocardial contractility following a VPB then results in a transient increase in blood pressure with a decrease in sinus node activity. To analyze, the RR intervals following VPBs are assessed for an initial short acceleration followed by a deceleration of heart rate. Absent or diminished biphasic pattern reflects an abnormal response and increased risk of cardiac arrhythmic death [49].

Exercise Electrocardiogram (NSVT and T-wave Alternans)

Exercise stress testing is a commonly performed, non-invasive test used to detect myocardial ischemia and to evaluate exercise capacity and cardiovascular function. Exercise induced NSVT is associated with increased cardiovascular mortality within the next decades [50]. However, exercise induced NSVT rarely occurs in structurally normal hearts (other than in RVOT ventricular ectopy syndromes) and in otherwise healthy individuals is not associated with an increase in cardiovascular or total mortality [51, 52]. NSVT does not predict long term mortality in patients with myocardial infarction treated with coronary artery reperfusion and beta-blockers or dilated cardiomyopathy, independent of LVEF. However, NSVT does have prognostic significance in patients with hypertrophic cardiomyopathy and certain genetic channelopathies [50].

Microvolt T-wave alternans (TWA) is a beat to beat alternation in the morphology and amplitude of the ST-segment or T-wave that has been associated with increased propensity for sustained ventricular arrhythmias [53]. Only rarely is the variability higher than the microvolt range and actually visible to the eye on routine electrocardiographic strips. The effect of TWA is further augmented by increased heart rate, ventricular premature beats, ischemia from coronary artery

occlusion or reperfusion, adrenergic stimulation and mental stress [53]. The underlying mechanism is believed to involve enhanced sympathetic nerve activity and abnormal calcium handling that disturbs cardiac repolarization in vulnerable myocardium leading to discordant alternans of repolarization of myocytes. Risk stratification is based on peak TWA measured during symptom limiting bicycle or treadmill exercise testing at a target heart rate range of 105–110 beats/min (and during post-exercise recovery) or during 24 h ambulatory ECG recording. Early studies showed that TWA was a powerful electrocardiographic tool in predicting risk of cardiovascular mortality and SCD in patients with myocardial infarction, as well as in cohorts with ischemic and non-ischemic cardiomyopathy. The predictive value of TWA in patients not utilizing beta-adrenergic blockade agents is significantly less than those on beta-adrenergic therapy [53, 54]. This phenomenon is likely the result of the beta-adrenergic blocker's effect on the sympathetic nervous system [53], and indicates that beta blockers should not be withheld before the procedure.

Despite considerable enthusiasm over TWA, subsequent large prospective trials failed to validate the role of TWA for risk stratification in patients with reduced LVEF. The TWA SCD HeFT [55] study showed no predictive value to predict mortality or arrhythmic events among patients in the SCD HeFT trial. In addition, the Master study showed that TWA did not predict appropriate ICD therapy in a large cohort of subjects implanted for standard primary prevention indications [56]. These studies have tempered the enthusiasm for this technique in patients with significant underlying cardiomyopathy. More recently, a different analytic approach was developed to assess T-wave alternans in the absence of exercise. This is a somewhat different measure despite the common name. Ongoing studies are assessing its role in stratifying risk of life threatening arrhythmias and SCD among patients with LVEF >35%, specifically to be used in conjunction with other markers of electrical instability such as signal-averaged ECG, heart rate turbulence or heart rate recovery (see CARISMA and AVID studies under Electrophysiology Study). In this capacity, TWA in the presence of one other factor increased hazard ratios up to 212% and positive predictive value by 78% [53]. In this subgroup of patients, its clinical utility remains undetermined.

Signal Averaged Electrocardiography

Signal averaged electrocardiography (SAECG) is a method of recording and averaging electrocardiographic data with the goal being to detect late potentials [57]. This test was initially found to be a promising marker of sudden cardiac death in patients with ischemic cardiomyopathy and later non-ischemic cardiomyopathy [57–60]. In a study of 182 patients post acute myocardial infarction from 1992 with 14 month follow up, and primary outcome of sustained ventricular arrhythmia or SCD, SAECG was found to be a significant predictor of SCD with a 2.7 fold increase in risk [61]. El-Sherif et all found similar results when they compared SAECG to clinical acumen, ejection fraction, and ventricular arrhythmia and showed that SAECG provided that best predictive criterion [62]. Despite these findings, some studies that have tried to use SAECG was to predict utility of prophylactic ICD implantation in patients with coronary artery disease and depressed ejection fraction at time of elective coronary bypass surgery have shown no survival benefit of ICD implantation if patients with abnormal SAECG [63].

With regard to non-ischemic cardiomyopathy, Mancini et al., in 1993 were able to show that patients with an abnormal SAECG had a significant increase in their risk for sustained ventricular arrhythmias as compared to patients with normal SAECG or bundle branch block (BBB) [57]. Goedel-Meinen et al. in 2001 demonstrated that SAECG was a useful independent prognostic factor for SCD, mortality, and cardiac events [64]. Subsequent studies have shown conflicting and less promising results. A more recent study performed comparing mIBG to SAECG, heart rate variability, and QT dispersion showed that mIGB and not SAECG, heart rate variability or QT dispersion was a predictor of SCD in patients with mild to moderate ejection fraction [65]. It should also be noted that in a study by Brembilla-Perrot et al. showed, that in 128 patients with dilated non-ischemic cardiomyopathy, that in the presence of BBB the predictive value and specificity of SAECG is significantly diminished and that the SAECG itself did could not predict the risk of sudden cardiac death and mortality [66].

A head to head comparison between TWA and SAECG for predicting arrhythmia risk assessment showed that TWA a was more sensitive predictor of ventricular tacharrhythmia and death. It did validate the ability of SAECG to predict risk of spontaneous ventricular arrhythmias though not as well as TWA [67]. Therefore, while an abnormal SAECG may be a marker of risk for SCD, its value, especially as compared to newer modalities, is limited especially when it comes to predicting need for ICD. However, it may be useful in combination but not in isolation.

Electrophysiology Study

Electrophysiology study (EPS) is an invasive procedure designed to diagnose disorders of the cardiac conduction by placing catheters in the right atrium, right ventricle and across the triscupid valve. With this tool and the prospect of delineating high risk patients for sudden cardiac death and malignant ventricular arrhythmias, both the MADIT and the

Multicenter Unsustained Tachycardia Trial (MUSTT) were designed and implemented [68].

In MUSTT, patients with coronary artery disease, left ventricular ejection fraction less than or equal to 40% and asymptomatic non-sustained ventricular tachycardia were enrolled at 85 study sites [68]. Patients who met inclusion criteria and had sustained VT induced by EPS were randomized to cardiac medications only or a strategy of arrhythmia suppression first with antiarrhythmic drugs to suppress the inducibility of VT and if unsuccessful then an ICD. A survival benefit only among patients treated with ICDs and not antiarrhythmic drugs [68]. There was an absolute reduction in risk of cardiac arrest or death from arrhythmia by 7% after 5 years of follow up [68].

The Multicenter Automatic Defibrillator Implantation Trial (MADIT), which enrolled as a similar population with a lower ejection fraction, equal to or less than 35%. In MADIT, patients with inducible VT were randomized to an ICD or to "conventional care" [69]. These trials were followed up by the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II which implanted ICDs in patients with ischemic cardiomyopathy in the absence of EP study for risk stratification [70]. This study included patients with a left ventricular ejection fraction ≤30%. A substudy of MADIT II performed programmed ventricular stimulation through the implanted ICD. This showed that inducible ventricular tachycardia (VT) did correlate with instances of VT but there was an inverse relationship with ventricular fibrillation requiring defibrillation [70]. Interestingly they showed that patients with non-inducible VT had a substantial burden of VT and a higher ventricular fibrillation burden than inducible patients, which casts major doubts on the utility and predictive value of EPS [70].

The above findings are supported by the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial and the Electrophysiologic Study Versus Electrocardiographic Monitoring (EVSEM) trial [70, 71]. The AVID trial included patients with both ischemic and non-ischemic cardiomyopathies [71]. Investigators found that EPS had a limited predictive value for death though it did predict recurrent VT or ventricular fibrillation in patients with inducible VT with rates less than or equal to 200 beats per minute and tended to predict recurrent VT or ventricular fibrillation in patients with coronary artery disease [71]. However, again, EPS tended to miss patients who were at risk for VT or ventricular fibrillation by classifying them as non-inducible [71].

The CARISMA trial was designed to evaluate the predictive value of both invasive and non-invasive strategies of risk assessment for potentially lethal arrhythmias [72]. The study enrolled 5869 patients who had recent myocardial infarctions in ten European countries [72]. The inclusion criteria included left ventricular ejection fraction less than or equal to 40% measured 3–5 days after acute myocardial infarction not undergoing coronary artery bypass surgery [72]. The primary endpoint, unlike earlier studies, was not mortality but rather fatal or near fatal arrhythmias that could have been treated after consensus agreement by a five member committee reviewing the case [72]. Secondary endpoint was all-cause mortality in this study [72]. Monitoring was performed primarily with implantable loop recorders [72]. Risk factors evaluated included LVEF by echocardiography, heart rate variability by Holter Monitoring, TWA, SAECG, EPS, and QT analysis with 12 lead electrocardiogram at index and 6 weeks post acute myocardial infarction [72]. Investigators found that heart rate variability and turbulence at 6 weeks rather than index was the most significant predictor of potential lethal arrhythmia [72]. EPS was a predictor of the primary endpoint but less so than heart rate variability [72]. Interestingly, LVEF and TWA were not found to be a statistically significant predictor of treatable arrhythmia [72]. Another recent study, the ABCD trial, which was designed to evaluate the utility of TWA, EPS or combination, in selecting patients with ischemic cardiomyopathy with an ejection fraction less than or equal to 40% who may benefit from ICD therapy [73]. This study suggested that TWA and EPS were comparable at 1 year and additive in combination in their relative predictive values and might be a tool to help determine patients who would benefit least from ICD therapy in a time dependent way [73]. The utility of EPS may be in these select populations but even so, is limited and not specific enough to be used in a more broad patient population.

Imaging: Assessing Scar Burden

Contrast enhanced cardiac magnetic resonance (cCMR) is an imaging modality that utilizes the power and spatial resolution of MRI images to understand and evaluate cardiac anatomy more accurately [74, 75]. Kim et al. were one of the first groups to demonstrate the potential power of cCMR in that it can distinguish between reversible and irreversible ischemic injury independent of wall motion or infarct age [74]. There are two temporal MRI images that can be used to understand cardiac anatomy and scar burden [74, 75]. The early contrast enhancement phase images are acquired within seconds and reflect perfusion while delayed/late contrast enhancement phase images are captured after several minutes and reflect a myriad of pathophysiological information, including, most importantly, myocardial scar [74, 76].

In 2007, Roes et al. published data that suggested cCMR delineated myocardial scar may be a superior predictor of mortality than LVEF and LV volume in patients with healed myocardial infarction [77]. Despite a number of studies showing a clear association between risk of malignant arrhythmia and myocardial scar, a quantitative continuous relationship has not yet been demonstrated [78]. This suggests

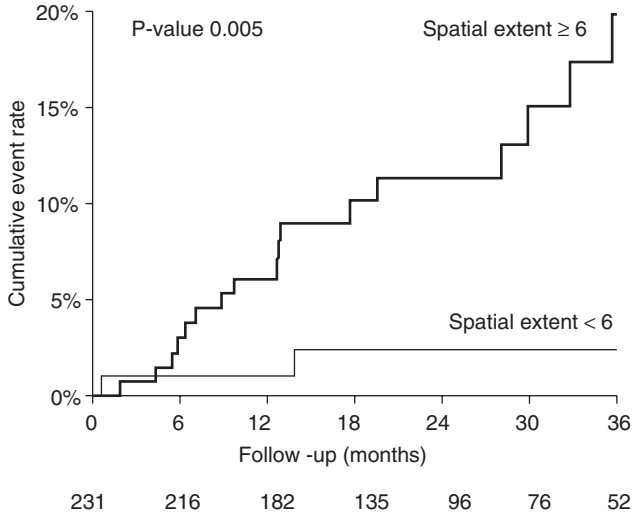


Fig. 6.1 Impact of scar on mortality. Kaplan-Meier curve analysis showing difference in mortality when patients are stratified according to a large extent (>6) vs. a small extent (<6) of scar tissue on contrast enhanced MRI (Reproduced with permission from Roes et al. [77])

that, while scar is an important substrate for VT in patients with ischemic cardiomyopathy, it alone does not correlate with risk for malignant arrhythmia [78] (Fig. 6.1).

In 2009, Kadish et al. designed The Defibrillators To Reduce Risk By Magnetic Resonance Imaging Evaluation study (DETERMINE) as a prospective, multi-center, randomized, clinical trial to investigate the effects of ICD implantation in patients with coronary artery disease (CAD) and mild to moderate LV dysfunction [2, 79]. Their goal was to test the hypothesis that patients with LV infarct mass greater than or equal to 10% of myocardium, by cCMR, on both medical therapy and a functional ICD had a mortality benefit over medical therapy alone [2, 79]. Unfortunately, because of poor enrollment this study was discontinued [2].

Imaging: Assessing Sympathetic Denervation (MIBG)

The autonomic nervous system consists of the sympathetic and parasympathetic components. Under normal circumstances, there is a balance with shifts from one system to the other depending on physiologic requirements. Chronic imbalances may occur in the setting of decreasing LVEF, heart failure and increasing left ventricular end diastolic pressure that may further worsen ventricular dysfunction [2, 80, 81].

In 1993, Mitrani et al. first showed in a small cohort of 18 patients with sympathetic denervation an increase in risk of ventricular tachycardia, even in the absence of coronary artery disease [82]. Ischemic heart disease is a major risk factor for the development of sympathetic denervation, even if only for short durations (minutes) [83]. As part of the remodeling process, denervation leads to increased sympathetic tone resulting in decreased pre-synaptic norepinephrine uptake and post-synaptic beta-adrenoceptors mass in a tachyphylaxis like response resulting in global left ventricular remodeling [84]. The over-stimulation by the sympathetic nervous system results in both supraventricular and ventricular arrhythmias by increasing automatic, triggering automaticity, and reentrance [85, 86].

Computed tomography using radioiodinated metaiodobenzylguanidine (mIBG) is now recognized as a powerful tool to identify inhomogeneity of the sympathetic nervous system within the cardiac myocardium, a potentially important substrate for sudden cardiac death [86–88]. mIBG was initially developed as a marker for adrenal medulla and related adrenergic tumors [87]. It is an analog of norepinephrine that is able to concentrate in sympathetic neurons within the heart [89]. The concentration of mIBG within cardiac neurons directly correlate with the neuronal integrity and function [89]. In 1979, mIBG was first synthesized and tested in both animals and humans [87]. In the human myocardium, mIBG, is preferentially transported by the cardiac neuronal norepinephrine transporter into cardiac sympathetic neurons [87]. mIBG is not metabolized and therefore can be imaged using planar or single photon emission computed tomography after uptake as it is not metabolized as norepinephrine [84]. In a study of 116 patients who underwent mIBG imaging prior to implantation of ICD, Boogers and colleagues showed that this marker was an independent predictor of ventricular arrhythmias that would require ICD therapy [84].

The late heart to mediastinum ratio (HMR) on mIBG has also been found to be an independent predictor of mortality [84]. Early images are typically obtained within an hour of infusion while late images are acquired after 3 h [84]. Late HMR is calculated dividing the regions of interest of the heart mean counts (H) by the regions of interest of the mediastinum mean counts (M) [84]. In the prospective AdreView Myocardial Imaging for Risk Evaluation of Heart Failure (ADMIRE-HF) study of 961 patients with NYHA functional class II/III CHF with an LVEF less than 35%, 237 subjects experienced functional class progression, life threatening arrhythmic events or cardiac death [90]. These investigators compared patients with a late HMR less than 1.6 to those with values greater than or equal to 1.6 [90]. They observed that patients with HMR less than 1.6 were at significant risk for all endpoints including progression of heart failure, arrhythmic events, cardiac death and all-cause mortality (Fig. 6.2), [90]. Multivariable analysis found that HMR, LVEF, BNP, and NYHA class were independent contributors to risk model [90].

Finally, the wash out rate (WR), which assesses the retention of norepinephrine by neurons, has been shown to be a

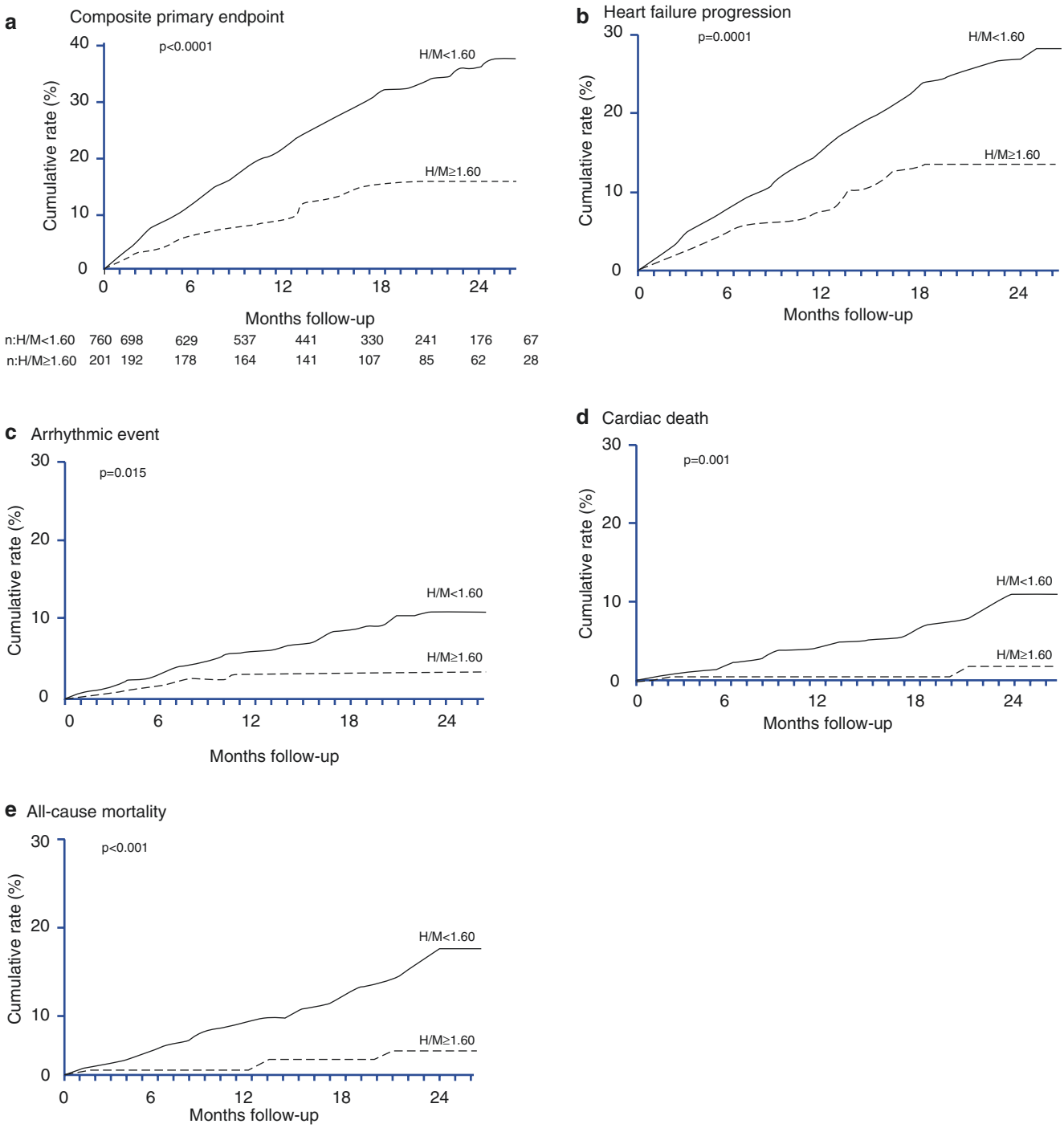


Fig. 6.2 Sympathetic denervation and cardiac outcomes. Cumulative event curves comparing subjects with H/M <1.6 vs. >1.6. (**a**) Composite primary end point; (**b**) heart failure progression; (**c**) arrhythmic event; (**d**) cardiac death; (**e**) all cause mortality. H/M = heart/mediastinum ratio on Computed tomography using radioiodinated metaiobenzylguanidine (mIBG) (Reproduced with permission from Jacobson et al. [90])

potent predictor of sudden cardiac death [84]. Washout is calculated by subtracting the difference between the early H and M by the difference between the late H and M all divided by the difference between early H and M [84]. Tamaki et al. enrolled 106 patients with congestive heart failure, as defined by Framingham criteria, with an LVEF less than 40% [65]. Patients needed to be stable on angiotensin-converting enzyme inhibitor (ACEI), diuretics, and digoxin for at least 3 months [65]. Their exclusion criteria included significant renal failure, insulin dependent diabetes, autonomic neuropathy and beta blockers use [65]. Multivariate analysis showed that abnormal WR (>27%) and depressed LVEF were both

independent predictors of sudden cardiac death. Among patients with LVEF >35%, there was a significantly higher rate of sudden cardiac death in those with abnormal WR [65]. Their results were validated by meta-analysis of 18 studies with a total of 1755 patients by Verberne et al. [91]. WR has also been shown to be a significant independent predictor of MACE in patients with STEMI [92]. The applicability of this approach may be limited as beta blocker use is ubiquitous and a Class I indication among patients with ischemic myocardial infarction.

Imaging: Assessing Sympathetic Denervation (Positron Emission Tomography)

Positron emission tomography (PET) is another imaging modality used in the evaluation of myocardial sympathetic innervation [2]. PET scanners work by detecting the radiation released by isotope emitting positrons after their annihilation within tissues [93]. PET is typically paired with computed tomography or magnetic resonance imaging [93]. In addition to evaluating myocardial sympathetic innervation, PET can also assess myocardial perfusion, metabolism (stunned or hibernating myocardium), and systolic function [93].

[11C]-meta-Hydroxyephedrine (HED) is a radioligand developed for PET to evaluate the sympathetic nervous system. It is a catecholamine analog labeled with 11C with a half-life of approximately 20 min that was developed based on metaraminol [90]. Like mIBG, HED is not metabolized by catechol-O-methyl transferase (COMT) or monoamine oxidase (MAO) [90]. Therefore it can remain in the sympathetic neurons long enough to be imaged. Based on uptake and retention of HED, Luisi et al. were able to show that hibernating myocardium in farm-bred pigs has significant regional reduction in norepinephrine reuptake [88].

The PAREPET trial was a prospective observational trial designed to study the hypothesis that inhomogeneity in human myocardial sympathetic innervation and/or hibernating myocardium could predict risk for arrhythmic death independent of left ventricular function [94]. This study enrolled 204 patients with inclusion criteria of ischemic heart disease and heart failure with LVEF >35% on optimal medical therapy who were not candidates for coronary revascularization and not eligible for primary prevention ICD [94]. Exclusion criteria included patients with prior cardiac arrest or ICD discharge, recent infarction (less than 30 days), or revascularization (PCI within 3 months or bypass grafting within last year) [94]. They also evaluated perfusion, using 13 N–ammonia, and viability using 18F-2deoxyglucose [94].

The primary endpoint of this trial was sudden cardiac arrest, which was defined as arrhythmic death or ICD discharge for ventricular fibrillation or ventricular tachycardia greater than 240 beats per minute over a 4 year follow up period [94]. Infarct volume and LVEF were not predictors of sudden cardiac arrest [94]. However, patients who later suffered from sudden cardiac arrest had a greater sympathetic denervation burden as seen in viable denervated myocardium (33 ± 10% vs. 26 ± % of LV; p = 0.001). Using multivariate analysis they developed a four component prediction system that focused on independent variables that predicted arrhythmic risk [94]. These variables included percentage of denervated myocardium (>37.6%), left ventricular end-diastolic volume index (>99 mL/m^2), creatinine (>1.49 mg/dL), and no angiotensin inhibition therapy (Fig. 6.3). More than 40% of the study population had none of the independent risk factors and an annual rate of sudden cardiac arrest of less than 1%, which is lower than the rate of arrhythmic death in patients with known coronary artery disease and LVEF between 35 and 50% [94]. About 36% of the cohort had only one predictive risk factor and an annual risk of sudden cardiac arrest of approximately 4% [94]. The remainder of the population, approximately 20%, had two or more independent risk factors and an annual rate of sudden cardiac arrest of ~12% [94]. Interestingly, infarct size, left ventricular ejection fraction, BNP and other variables did not improve their predictive model.

Despite these encouraging results, the multivariate analysis was post hoc so it needs to be replicated to strengthen this observation. Other limitations include the use of HED, which has a short half-life requiring close proximity to cyclotron, and exclusions of patients with recent myocardial infarction, non-ischemic cardiomyopathy and patients with more preserved left ventricular systolic function. Of note, 18-Flourine labeled norepinephrine analogs may improve clinic utility of PET because of improved half-life as compared to HED.

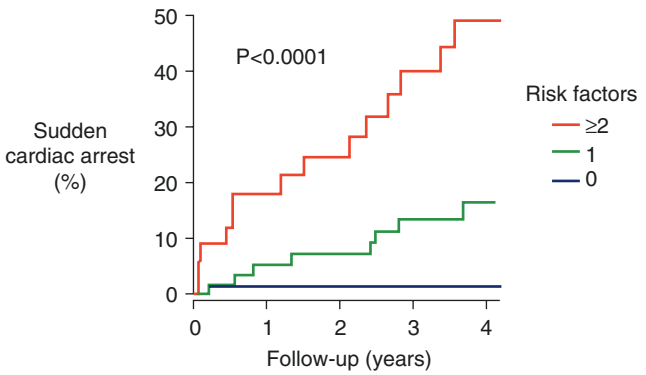


Fig. 6.3 PET Scan and other Clinical Factors to Predict SCD. Kaplan-Meier curves illustrating significant differences in the incidence of sudden cardiac arrest (SCA) in relation to the number of risk factors present ($p < 0.0001$). Subjects with no risk factors had an annual rate of SCA < 1%; 1 risk factor had an annual rate of ~4% and 2 or more risk factors had an annual risk of ~12% (Reproduced with permission from Fallavollita et al. [94])

Table 6.3 Patient subgroup evaluations for primary prevention ICD placement

Patient population	History	Imaging	Other tests
CAD	>40 days post MI	LVEF ≤30%	
		LVEF 35–40%	EPS
CHF	3 months post onset of symptoms	LVEF ≤35%	
	Medical therapy optimized		
	NYHA II, III and ambulatory IV		
LQTS	QTc > 500 ms		Genetic testing optional
	Syncope on beta blocker		
HCM	Syncope	IVS ≥ 30 mm	Stress test for hemodynamic response
	FH SCD		Holter monitor
Brugada Syndrome	Syncope		ECG
	FH SCD		EPS optional
Sarcoidosis	Syncope	MRI or PET	EPS
	Pacemaker indication		

Summary

SCD remains a major health care problem, particularly in western cultures. Early studies identified LVEF, ischemic heart disease, heart failure and ambient arrhythmias as predictors of events. This led to large multicenter trials establishing the role of the ICD for primary prevention of SCD. However, a changing epidemiology of SCD has confirmed an unmet need for risk stratification. In addition, there is interest in improved risk stratification of ICD eligible patients. In this regard, newer imaging, advanced electrocardiographic and genetic techniques raise hope that specific markers or a combinations of tests will allow identification of high risk subjects who can benefit from specific antiarrhythmic therapy, including those with uncommon arrhythmia substrates. A summary of risk stratification approaches for different groups at risk for SCD is summarized in Table 6.3. However, despite these newer techniques and promising markers of SCD, most studies remain observational with frequent posthoc analysis. Accordingly, contemporary risk stratification and guidelines for therapy have changed little over the past decade to address the unmet need of prevention of SCD.

Beyond clinical interest, the cost and practicality of risk stratification strategies and ICD implantation is significant. The cost of genetic testing, ejection fraction evaluation, resting electrocardiograms, exercise electrocardiogram, ambulatory electrocardiogram, SAECG, EPS, imaging of myocardial scar, and innervation studies is significant. It is unlikely that funding aimed at limiting testing and device therapy could be funded any other way than by public means, which is on the decline. However understanding both the cost and benefit of evaluation of SCD should of major importance to governments, institutions, providers and patients as medical costs continue to rise. Thus far there has been no cost benefit and cost effectiveness studies looking at SCD that could help guide a reasonable and appropriate approach to SCD risk stratification wide scale. Studies of this nature would need to compare cost of strategy to cost of devices and patient benefit indices. While this would be a daunting task, it would also be an extremely worthwhile and immensely beneficial enterprise.

References

1. European Heart Rhythm Association, Heart Rhythm Society, Zipes DP, Camm AJ, Borggrefe M, Buxton AE, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48(5):e247–346.
2. Goldberger JJ, Basu A, Boineau R, Buxton AE, Cain ME, Canty JM Jr, et al. Risk stratification for sudden cardiac death: a plan for the future. Circulation. 2014;129(4):516–26.
3. Johnson CC, Spitz MR. Childhood nervous system tumours: an assessment of risk associated with paternal occupations involving use, repair or manufacture of electrical and electronic equipment. Int J Epidemiol. 1989;18(4):756–62.
4. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001;345(20):1473–82.
5. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337(22):1576–83.
6. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML, et al. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol. 2004;43(8):1459–65.
7. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225–37.

8. Hulleman M, Berdowski J, de Groot JR, van Dessel PF, Borleffs CJ, Blom MT, et al. Implantable cardioverter-defibrillators have reduced the incidence of resuscitation for out-of-hospital cardiac arrest caused by lethal arrhythmias. Circulation. 2012;126(7):815–21.
9. Bunch TJ, White RD, Friedman PA, Kottke TE, LA W, Packer DL. Trends in treated ventricular fibrillation out-of-hospital cardiac arrest: a 17-year population-based study. Heart Rhythm. 2004;1(3):255–9.
10. Stecker EC, Reinier K, Marijon E, Narayanan K, Teodorescu C, Uy-Evanado A, et al. Public health burden of sudden cardiac death in the United States. Circ Arrhythm Electrophysiol. 2014;7(2):212–7.
11. Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population: the Paris Prospective Study I. Circulation. 1999;99(15):1978–83.
12. Friedlander Y, Siscovick DS, Arbogast P, Psaty BM, Weinmann S, Lemaitre RN, et al. Sudden death and myocardial infarction in first degree relatives as predictors of primary cardiac arrest. Atherosclerosis. 2002;162(1):211–6.
13. Dekker LR, Bezzina CR, Henriques JP, Tanck MW, Koch KT, Alings MW, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. Circulation. 2006;114(11):1140–5.
14. Kolder IC, Tanck MW, Bezzina CR. Common genetic variation modulating cardiac ECG parameters and susceptibility to sudden cardiac death. J Mol Cell Cardiol. 2012;52(3):620–9.
15. Arking DE, Junttila MJ, Goyette P, Huertas-Vazquez A, Eijgelsheim M, Blom MT, et al. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. PLoS Genet. 2011;7(6):e1002158.
16. Hong KW, Lim JE, Kim JW, Tabara Y, Ueshima H, Miki T, et al. Identification of three novel genetic variations associated with electrocardiographic traits (QRS duration and PR interval) in East Asians. Hum Mol Genet. 2014;23(24):6659–67.
17. Arking DE, Reinier K, Post W, Jui J, Hilton G, O'Connor A, et al. Genome-wide association study identifies GPC5 as a novel genetic locus protective against sudden cardiac arrest. PLoS One. 2010;5(3):e9879.
18. Aouizerat BE, Vittinghoff E, Musone SL, Pawlikowska L, Kwok PY, Olgin JE, et al. GWAS for discovery and replication of genetic loci associated with sudden cardiac arrest in patients with coronary artery disease. BMC Cardiovasc Disord. 2011;11:29.
19. Albert CM, MacRae CA, Chasman DI, VanDenburgh M, Buring JE, Manson JE, et al. Common variants in cardiac ion channel genes are associated with sudden cardiac death. Circ Arrhythm Electrophysiol. 2010;3(3):222–9.
20. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell. 2001;104(4):569–80.
21. Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med. 1983;309(6):331–6.
22. Huikuri HV, Tapanainen JM, Lindgren K, Raatikainen P, Makikallio TH, Juhani Airaksinen KE, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. J Am Coll Cardiol. 2003;42(4):652–8.
23. Grimm W, Christ M, Bach J, Muller HH, Maisch B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg Cardiomyopathy Study. Circulation. 2003;108(23):2883–91.
24. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877–83.
25. Suliman FA. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. N Engl J Med. 1998;338(17):1228.
26. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004;351(24):2481–8.
27. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, et al. Defibrillator implantation early after myocardial infarction. N Engl J Med. 2009;361(15):1427–36.
28. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000;101(11):1297–302.
29. Iuliano S, Fisher SG, Karasik PE, Fletcher RD, Singh SN, Department of Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. QRS duration and mortality in patients with congestive heart failure. Am Heart J. 2002;143(6):1085–91.
30. Zimetbaum PJ, Buxton AE, Batsford W, Fisher JD, Hafley GE, Lee KL, et al. Electrocardiographic predictors of arrhythmic death and total mortality in the multicenter unsustained tachycardia trial. Circulation. 2004;110(7):766–9.
31. Singh JP, Hall WJ, McNitt S, Wang H, Daubert JP, Zareba W, et al. Factors influencing appropriate firing of the implanted defibrillator for ventricular tachycardia/fibrillation: findings from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). J Am Coll Cardiol. 2005;46(9):1712–20.
32. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004;350(21):2151–8.
33. Peters RW, Byington RP, Barker A, Yusuf S. Prognostic value of prolonged ventricular repolarization following myocardial infarction: the BHAT experience. The BHAT Study Group. J Clin Epidemiol. 1990;43(2):167–72.
34. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. Circulation. 1991;84(4):1516–23.
35. Karjalainen J, Reunanen A, Ristola P, Viitasalo M. QT interval as a cardiac risk factor in a middle aged population. Heart. 1997;77(6):543–8.
36. Elming H, Holm E, Jun L, Torp-Pedersen C, Kober L, Kircshoff M, et al. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. Eur Heart J. 1998;19(9):1391–400.
37. Brendorp B, Elming H, Jun L, Kober L, Malik M, Jensen GB, et al. Qt dispersion has no prognostic information for patients with advanced congestive heart failure and reduced left ventricular systolic function. Circulation. 2001;103(6):831–5.
38. Berul CI. Congenital long-QT syndromes: who's at risk for sudden cardiac death? Circulation. 2008;117(17):2178–80.
39. Patel C, Yan GX, Antzelevitch C. Short QT syndrome: from bench to bedside. Circ Arrhythm Electrophysiol. 2010;3(4):401–8.
40. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation. 1984;69(2):250–8.
41. Maggioni AP, Zuanetti G, Franzosi MG, Rovelli F, Santoro E, Staszewsky L, et al. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era. GISSI-2 results. Circulation. 1993;87(2):312–22.
42. Hohnloser SH, Klingenheben T, Zabel M, Schopperl M, Mauss O. Prevalence, characteristics and prognostic value during long-term follow-up of nonsustained ventricular tachycardia after myocardial infarction in the thrombolytic era. J Am Coll Cardiol. 1999;33(7):1895–902.

43. Grimm W, Christ M, Maisch B. Long runs of non-sustained ventricular tachycardia on 24-hour ambulatory electrocardiogram predict major arrhythmic events in patients with idiopathic dilated cardiomyopathy. Pacing Clin Electrophysiol. 2005;28(Suppl 1):S207–10.
44. Zecchin M, Di Lenarda A, Gregori D, Merlo M, Pivetta A, Vitrella G, et al. Are nonsustained ventricular tachycardias predictive of major arrhythmias in patients with dilated cardiomyopathy on optimal medical treatment? Pacing Clin Electrophysiol. 2008;31(3):290–9.
45. de Sousa MR, Morillo CA, Rabelo FT, Nogueira Filho AM, Ribeiro AL. Non-sustained ventricular tachycardia as a predictor of sudden cardiac death in patients with left ventricular dysfunction: a meta-analysis. Eur J Heart Fail. 2008;10(10):1007–14.
46. Kusmirek SL, Gold MR. Sudden cardiac death: the role of risk stratification. Am Heart J. 2007;153(4 Suppl):25–33.
47. Berkowitsch A, Zareba W, Neumann T, Erdogan A, Nitt SM, Moss AJ, et al. Risk stratification using heart rate turbulence and ventricular arrhythmia in MADIT II: usefulness and limitations of a 10-minute holter recording. Ann Noninvasive Electrocardiol. 2004;9(3):270–9.
48. Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet. 1999;353(9162):1390–6.
49. Cygankiewicz I. Heart rate turbulence. Prog Cardiovasc Dis. 2013;56(2):160–71.
50. Katritsis DG, Zareba W, Camm AJ. Nonsustained ventricular tachycardia. J Am Coll Cardiol. 2012;60(20):1993–2004.
51. Fleg JL, Lakatta EG. Prevalence and prognosis of exercise-induced nonsustained ventricular tachycardia in apparently healthy volunteers. Am J Cardiol. 1984;54(7):762–4.
52. Marine JE, Shetty V, Chow GV, Wright JG, Gerstenblith G, Najjar SS, et al. Prevalence and prognostic significance of exercise-induced nonsustained ventricular tachycardia in asymptomatic volunteers: BLSA (Baltimore Longitudinal Study of Aging). J Am Coll Cardiol. 2013;62(7):595–600.
53. Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner DV, Hohnloser SH, et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility—consensus guideline by International Society for Holter and Noninvasive Electrocardiology. J Am Coll Cardiol. 2011;58(13):1309–24.
54. Chan PS, Gold MR, Nallamothu BK. Do Beta-blockers impact microvolt T-wave alternans testing in patients at risk for ventricular arrhythmias? A meta-analysis. J Cardiovasc Electrophysiol. 2010;21(9):1009–14.
55. Gold MR, Ip JH, Costantini O, Poole JE, McNulty S, Mark DB, et al. Role of microvolt T-wave alternans in assessment of arrhythmia vulnerability among patients with heart failure and systolic dysfunction: primary results from the T-wave alternans sudden cardiac death in heart failure trial substudy. Circulation. 2008;118(20):2022–8.
56. Chow T, Kereiakes DJ, Onufer J, Woelfel A, Gursoy S, Peterson BJ, et al. Does microvolt T-wave alternans testing predict ventricular tachyarrhythmias in patients with ischemic cardiomyopathy and prophylactic defibrillators? The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial. J Am Coll Cardiol. 2008;52(20):1607–15.
57. Mancini DM, Wong KL, Simson MB. Prognostic value of an abnormal signal-averaged electrocardiogram in patients with nonischemic congestive cardiomyopathy. Circulation. 1993;87(4):1083–92.
58. Simson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. Circulation. 1981;64(2):235–42.
59. Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardial infarction: natural history and prognostic significance. Circulation. 1986;74(6):1280–9.
60. Gomes JA, Winters SL, Stewart D, Horowitz S, Milner M, Barreca P. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction: based on signal-averaged electrocardiogram, radionuclide ejection fraction and Holter monitoring. J Am Coll Cardiol. 1987;10(2):349–57.
61. Steinberg JS, Regan A, Sciacca RR, Bigger JT Jr, Fleiss JL. Predicting arrhythmic events after acute myocardial infarction using the signal-averaged electrocardiogram. Am J Cardiol. 1992;69(1):13–21.
62. el-Sherif N, Denes P, Katz R, Capone R, Mitchell LB, Carlson M, et al. Definition of the best prediction criteria of the time domain signal-averaged electrocardiogram for serious arrhythmic events in the postinfarction period. The Cardiac Arrhythmia Suppression Trial/Signal-Averaged Electrocardiogram (CAST/SAECG) Substudy Investigators. J Am Coll Cardiol. 1995;25(4):908–14.
63. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med. 1997;337(22):1569–75.
64. Goedel-Meinen L, Hofmann M, Ryba S, Schomig A. Prognostic value of an abnormal signal-averaged electrocardiogram in patients with nonischemic dilated cardiomyopathy. Am J Cardiol. 2001;87(6):809–12. A9
65. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. J Am Coll Cardiol. 2009;53(5):426–35.
66. Brembilla-Perrot B, Terrier de la Chaise A, Jacquemin L, Beurrier D, Houplon P. The signal-averaged electrocardiogram is of limited value in patients with bundle branch block and dilated cardiomyopathy in predicting inducible ventricular tachycardia or death. Am J Cardiol. 1997;79(2):154–9.
67. Gold MR, Bloomfield DM, Anderson KP, El-Sherif NE, Wilber DJ, Groh WJ, et al. A comparison of T-wave alternans, signal averaged electrocardiography and programmed ventricular stimulation for arrhythmia risk stratification. J Am Coll Cardiol. 2000;36(7):2247–53.
68. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 1999;341(25):1882–90.
69. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996;335(26):1933–40.
70. Daubert JP, Zareba W, Hall WJ, Schuger C, Corsello A, Leon AR, et al. Predictive value of ventricular arrhythmia inducibility for subsequent ventricular tachycardia or ventricular fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. J Am Coll Cardiol. 2006;47(1):98–107.
71. Brodsky MA, Mitchell LB, Halperin BD, Raitt MH, Hallstrom AP, AVID Investigators. Prognostic value of baseline electrophysiology studies in patients with sustained ventricular tachyarrhythmia: the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. Am Heart J. 2002;144(3):478–84.
72. Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, Hartikainen J, Virtanen V, Boland J, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. Eur Heart J. 2009;30(6):689–98.

73. Costantini O, Hohnloser SH, Kirk MM, Lerman BB, Baker JH 2nd, Sethuraman B, et al. The ABCD (Alternans Before Cardioverter Defibrillator) Trial: strategies using T-wave alternans to improve efficiency of sudden cardiac death prevention. J Am Coll Cardiol. 2009;53(6):471–9.
74. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999;100(19):1992–2002.
75. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med. 2000;343(20):1445–53.
76. Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. Circulation. 2006;113(23):2733–43.
77. Roes SD, Kelle S, Kaandorp TA, Kokocinski T, Poldermans D, Lamb HJ, et al. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. Am J Cardiol. 2007;100(6):930–6.
78. Lee DC, Goldberger JJ. CMR for sudden cardiac death risk stratification: are we there yet? JACC Cardiovasc Imaging. 2013;6(3):345–8.
79. Kadish AH, Bello D, Finn JP, Bonow RO, Schaechter A, Subacius H, et al. Rationale and design for the Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) trial. J Cardiovasc Electrophysiol. 2009;20(9):982–7.
80. Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. Eur Heart J. 2015;36(30):1974–82b.
81. Kishi T. Heart failure as an autonomic nervous system dysfunction. J Cardiol. 2012;59(2):117–22.
82. Mitrani RD, Klein LS, Miles WM, Hackett FK, Burt RW, Wellman HN, et al. Regional cardiac sympathetic denervation in patients with ventricular tachycardia in the absence of coronary artery disease. J Am Coll Cardiol. 1993;22(5):1344–53.
83. Inoue H, Zipes DP. Time course of denervation of efferent sympathetic and vagal nerves after occlusion of the coronary artery in the canine heart. Circ Res. 1988;62(6):1111–20.
84. Carrio I, Cowie MR, Yamazaki J, Udelson J, Camici PG. Cardiac sympathetic imaging with mIBG in heart failure. JACC Cardiovasc Imaging. 2010;3(1):92–100.
85. Zipes DP. Sympathetic stimulation and arrhythmias. N Engl J Med. 1991;325(9):656–7.
86. Klein T, Dilsizian V, Cao Q, Chen W, Dickfeld TM. The potential role of iodine-123 metaiodobenzylguanidine imaging for identifying sustained ventricular tachycardia in patients with cardiomyopathy. Curr Cardiol Rep. 2013;15(5):359.
87. Raffel DM, Wieland DM. Development of mIBG as a cardiac innervation imaging agent. JACC Cardiovasc Imaging. 2010;3(1):111–6.
88. Luisi AJ Jr, Suzuki G, Dekemp R, Haka MS, Toorongian SA, Canty JM Jr, et al. Regional 11C-hydroxyephedrine retention in hibernating myocardium: chronic inhomogeneity of sympathetic innervation in the absence of infarction. J Nucl Med. 2005;46(8):1368–74.
89. Sisson JC, Shapiro B, Meyers L, Mallette S, Mangner TJ, Wieland DM, et al. Metaiodobenzylguanidine to map scintigraphically the adrenergic nervous system in man. J Nucl Med. 1987;28(10):1625–36.
90. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol. 2010;55(20):2212–21.
91. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. Eur Heart J. 2008;29(9):1147–59.
92. de Benedictis FM, Bush A. Rhinosinusitis and asthma: epiphenomenon or causal association? 1999. Chest. 2009;136(5 Suppl):e30.
93. Anagnostopoulos C, Georgakopoulos A, Pianou N, Nekolla SG. Assessment of myocardial perfusion and viability by positron emission tomography. Int J Cardiol. 2013;167(5):1737–49.
94. Fallavollita JA, Heavey BM, Luisi AJ Jr, Michalek SM, Baldwa S, Mashtare TL Jr, et al. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. J Am Coll Cardiol. 2014;63(2):141–9.
95. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol. 2008;51(3):288–96.
96. Kramer DB, Friedman PA, Kallinen LM, Morrison TB, Crusan DJ, Hodge DO, et al. Development and validation of a risk score to predict early mortality in recipients of implantable cardioverter-defibrillators. Heart Rhythm. 2012;9(1):42–6.

Electrophysiologic Testing and Cardiac Mapping

7

Jackson J. Liang and David J. Callans

Abstract

The electrophysiologic study (EPS) is an invasive test that examines the heart's electrical properties via recording electrical signals (intracardiac electrograms) and pacing protocols with multiple strategically placed intracardiac catheters. EPS is the gold standard diagnostic study for the evaluation of many arrhythmias. With EPS, electrophysiologists are able to examine the components of the conduction system in patients with bradycardia or conduction defects, differentiate between mechanisms of tachycardias, and risk-stratify patients to rule out potentially dangerous arrhythmias. EPS is frequently performed as a diagnostic study before, during, and after catheter ablation of arrhythmias, often in conjunction with imaging modalities such as electroanatomical mapping (EAM) and intracardiac echocardiography (ICE).

Keywords

Electrophysiology • Cardiac mapping • Catheter ablation • Supraventricular tachycardia • Ventricular tachycardia • Intracardiac echocardiography • Heart block • Syncope • Sinus node dysfunction • Atrial fibrillation

Indications

EPS is most frequently performed for diagnostic evaluation of unexplained syncope, palpitations, documented or suspected narrow or wide complex tachycardia, or to risk stratify patients with Wolf Parkinson White syndrome, prior myocardial infarction, or structural heart disease. It allows for the definitive differentiation between AV nodal reentry tachycardia (AVNRT), AV reentry tachycardia (AVRT), and atrial tachycardia (AT) in patients presenting with narrow complex tachycardia. It can differentiate between aberrancy, pre-excitation, and ventricular arrhythmias in wide QRS tachycardias. EPS can also be therapeutic when performed in conjunction with catheter ablation. While it is extremely helpful in several scenarios, the sensitivity and specificity of EPS should be considered in context with the clinical picture and the protocol used.

In patients with structural heart disease and syncope, inducible ventricular tachycardia (VT) or ventricular fibrillation (VF) at EPS warrants implantation of an implantable cardioverter defibrillator (ICD) [1]. EPS may be diagnostic in patients with syncope which is preceded immediately by palpitations, suspected sinus node dysfunction, or if bifascicular or trifascicular block patterns are present on the electrocardiogram [2]. In patients with indeterminate 2:1 AV block, EPS can easily delineate whether the site of conduction delay is supra or infrahisian, thus guiding the decision to implant a permanent pacemaker [1].

EPS is helpful to risk stratify specific patient population and should be considered in all survivors of sudden cardiac death and idiopathic VF when the etiology remains unclear after noninvasive testing [3, 4]. In survivors of myocardial infarction who have depressed LVEF (<40%) and nonsustained

J.J. Liang, D.O.
Clinical Cardiac Electrophysiology Fellow Hospital of the University of Pennsylvania, Philadelphia, USA
e-mail: Jackson.Liang@uphs.upenn.edu

D.J. Callans, M.D. (✉)
Electrophysiology Section, Division of Cardiovascular Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA
e-mail: david.callans@uphs.upenn.edu

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_7

monomorphic VT, EPS is helpful to identify high risk individuals who may benefit from ICD [1, 5]. It can also be used to stratify the risk of sudden death in patients with conditions such as WPW or cardiac sarcoidosis [6, 7]. Of note, although EPS is quite useful for both diagnostic and prognostic purposes in the setting of suspected reentrant arrhythmias, it has limited sensitivity and specificity in conditions which predispose to non-reentrant arrhythmia, such as Long-QT Syndrome, Short-QT Syndrome, and catecholaminergic polymorphic VT.

Recently, EPS (usually in conjunction with the use of an electroanatomic mapping system) has also been reported to be useful to guide endomyocardial biopsy in patients with nonischemic cardiomyopathy and suspected cardiac sarcoidosis or myocarditis. Since these disease processes classically manifest patchy myocardial involvement, standard fluoroscopically guided right ventricular septal endomyocardial biopsy results in a low diagnostic yield. Recent studies have shown that endomyocardial biopsy targeting low voltage areas with fractionated electrograms may result in increased diagnostic yield [8, 9].

Contraindications

According to the 2006 ACC/AHA consensus statement, absolute contraindications to invasive EPS include active unstable angina, bacteremia or septicemia, acute decompensated heart failure not thought to be caused by arrhythmia, and major bleeding diathesis [10]. Also, ipsilateral femoral vein cannulation should be avoided in the presence of acute lower extremity deep vein thrombosis. While these contraindications should certainly be considered in patients presenting on an elective basis, emergent EPS may be justifiable and should not be withheld in patients who are suffering from incessant arrhythmia. In these cases the risks and benefits of EPS should be weighed [10].

Potential Complications

While EPS is generally a safe procedure, complications occur in approximately 2% of cases [11]. When ablation procedures are performed concordantly with diagnostic testing, the incidence of complications increases [12, 13]. Most major complications are related to vascular access (bleeding, vascular injury, infection), thromboembolism (pulmonary emboli with venous access; formation of intracardiac thrombi possibly resulting in stroke/TIA or systemic emboli when accessing the left-sided cardiac chambers), infection, or cardiac perforation (possibly resulting in hemopericardium or cardiac tamponade). Other possible complications include adverse drug reactions, unintended or refractory ventricular and supraventricular arrhythmias, heart block (AV block, RBBB, or LBBB), hypotension, respiratory decline, myocardial infarction, and even death. These potential complications should be discussed with all patients while obtaining informed consent for EPS.

Electrophysiology Laboratory Requirements

EPS should be performed in a dedicated electrophysiology laboratory equipped with fluoroscopy. An electrophysiologic stimulator such as the Bloom stimulator (Fischer Medical Technologies; Broomfield, CO) permits the operator to pace the heart at constant pacing intervals, and allows for programmed single or multiple timed extrastimuli after sensed or paced beats. Since intracardiac electrograms recorded by catheters are usually very small (<10 mV amplitude), they must be amplified to be interpretable. Additionally, since there may be significant noise and artifact in the electrophysiology lab, digital filters are necessary to remove unwanted signals. Generally, high-pass filters are set to remove low frequency components below 30 Hz, while low-pass filters are set to remove those signals greater than 500 Hz for intracardiac signals (or 200 Hz for surface electrocardiogram signals). Notch filters can also be set to remove signals at a specific frequency, such as the Mains interference (electric hum) which is typically 60 Hz. However, it is important to recognize that Notch filters may alter the true intracardiac signals. After signals are amplified, filtered, and digitized, they are displayed real-time on a monitor and stored for off-line analysis by a recording system, such as the Prucka CardioLab system (General Electric Healthcare; Piscataway Township, NJ). The sweep speed can be adjusted based on operator preference.

Procedural Preparation

We attempt to hold all AV-nodal blocking agents and antiarrhythmic drugs for at least five half-lives prior to the procedure unless testing their effects. Due to its extensive tissue distribution and long half-life, amiodarone should be discontinued beforehand at a particularly long interval. Before the procedure, a pregnancy test should be performed in all women of childbearing age due to radiation exposure. Patients are usually kept NPO after midnight the night before the procedure such that they are fasting for at least 8 h beforehand.

The electrophysiology laboratory should be equipped with a 12-lead electrocardiographic monitoring system, a non-invasive blood pressure cuff, supplemental oxygen, a suction device, intubation equipment, and continuous pulse oximetry. Defibrillation pads should be placed on the patient's chest and two external defibrillators (one as a back-up) should be present in the room for easy access during the case if required. There should always be a code cart nearby with medications for Advanced Cardiac Life Support and management

of specific arrhythmias such as intravenous preparations of adenosine, beta blockers and antiarrhythmic drugs.

Intravenous access is obtained prior to the procedure for administration of drugs. Since general anesthetic medications often suppress arrhythmias (especially those due to abnormal automaticity), conscious sedation with short-acting benzodiazepines and opiate medications are preferred if sedation is needed. Sedation can interfere with assessment of tolerance of an induced arrhythmia.

Vascular Access

The femoral veins (and femoral arteries, when access to the left-sided cardiac chambers is necessary) are the usual sites of access for EPS at our institution. In general, our approach to vascular access for EPS begins with prepping and draping the patient in a sterile manner. Vascular ultrasound is preferred by some operators and can be helpful, but is not required for obtaining vascular access. The inguinal ligament, which runs from the iliac crest to the pubic symphysis should be identified. The femoral artery is usually easily palpated along the medial third of the inguinal ligament. Typically, the femoral vein runs superficial to and approximately 1 cm medial to the femoral artery. Once the region of vascular access has been identified, a local anesthetic agent such as lidocaine is injected into the subcutaneous tissue at the area of intended access. Using Seldinger technique, multiple venous accesses (typically three to four for routine EPS) are obtained. It is important that when multiple accesses within the same vessel are required, that the sheaths not be passed over the wires until all guide wires have been inserted. This prevents the possibility of inadvertent puncture/transection (with possible embolization) of catheters which have already been advanced into the vessel.

After venous access has been obtained, femoral artery access can proceed, if necessary. Direct palpation of the femoral artery at the level of the inguinal ligament allows for identification of the vessel location. Using an introducer needle, successful arterial puncture should result in pulsatile arterial flow. When pulsatile flow is seen, a soft J-tip guidewire is passed through the needle which is subsequently replaced by an arterial sheath. It is important to remember that sheaths should always be one French size larger than the size of the catheter to be inserted if simultaneous administration of fluids through the sheaths is planned.

Catheter Selection and Location

For routine EPS in our laboratory, we typically use four catheters, placed at the high right atrium (HRA), His bundle, coronary sinus (CS), and RV apex under fluoroscopic guidance (Fig. 7.1). Additional catheters at alternative locations may be used as the clinical scenario necessitates. For conduction system assessment only, the CS catheter is usually not needed. Likewise if the study is only to assess ICD function or serial drug testing.

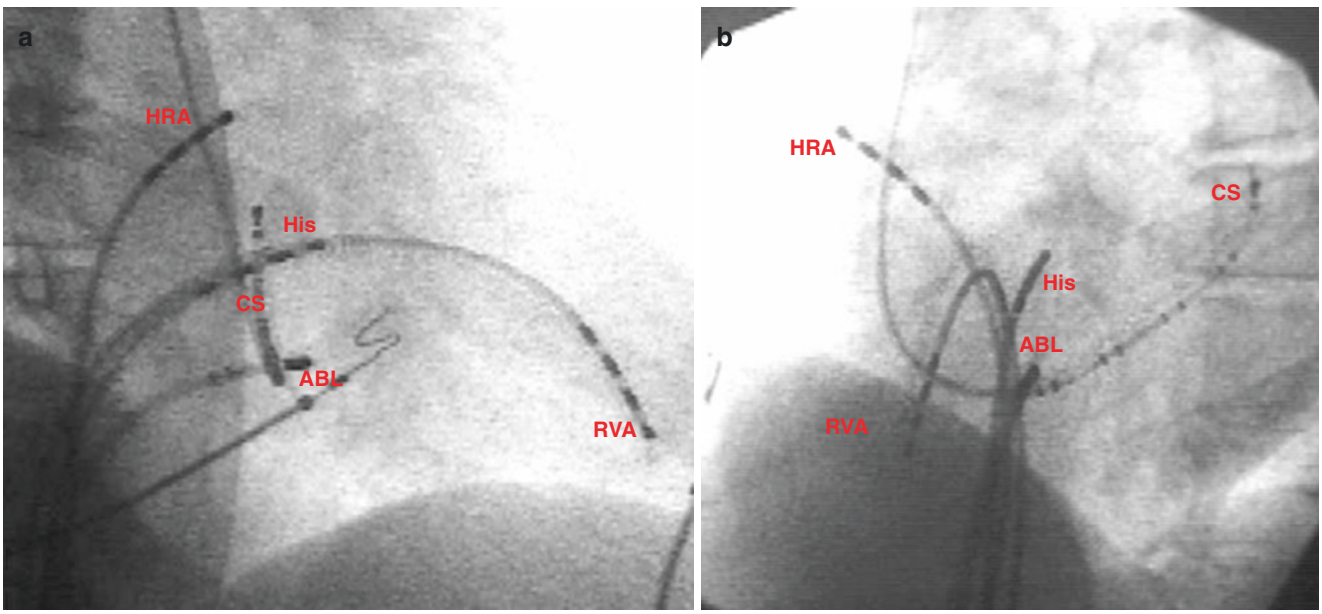


Fig. 7.1 Standard placement of catheters during routine EPS. RAO (A) and LAO (B) fluoroscopic views demonstrating standard placement of catheters during a routine EPS: high right atrium (HRA), His, coronary sinus (CS), and right ventricular apex (RVA). An ablation catheter (ABL) is positioned in the slow pathway region for ablation of AV nodal reentry. *Note that the CS catheter is placed from above using an internal jugular approach*

HRA catheter: A quadrapolar (four-electrode) catheter is inserted through the femoral vein up into the area of the high posterolateral wall of the RA, near the sinus node. Optimally, the catheter tip should be on the lateral wall of the right atrium near the junction of the superior vena cava and RA junction. Some labs place it in the right atrial appendage for stable pacing.

His bundle catheter: A quadrapolar catheter is advanced across the tricuspid valve, against the RV septum at the area of the His bundle. When correctly placed, this catheter should record a sharp His bundle electrogram (HBE) between the atrial and ventricular electrograms, which are both usually seen as well on the His catheter (larger and sharper atrial electrogram in the more proximal electrodes, and larger and sharper ventricular electrogram in the distal electrodes). Ideally, the most proximal His bundle signal is recorded.

RV catheter: A quadrapolar catheter may be advanced from the femoral vein across the tricuspid valve into the RV. The RV catheter can be maneuvered to different sites for recording and pacing (i.e. RV apex or RV outflow tract) as needed.

CS catheter: The CS ostium lies in the inferior aspect of the interatrial septum in the RA, between the IVC and tricuspid valve. The CS runs leftward along the AV groove between the LA and LV, and therefore a catheter in the CS has the capability to pace and record LA intracardiac signals without actually being in the LA. Since the CS usually runs more atrially than ventricularly, the atrial signals are typically sharper and larger in amplitude. The CS catheter allows for detection of the LA activation sequence, and we prefer to use a decapolar (ten electrode) catheter. Of note, access to the CS can be obtained both from above (via an internal jugular or subclavian vein) or below (via a femoral vein).

Basic EPS Protocol

While specific EPS protocols are dependent on the clinical problem or arrhythmia under evaluation, it is important that certain baseline measurements, intervals, and refractory periods are measured during each study to assure comprehensive evaluation.

Electrophysiologists typically report intervals in cycle length (CL) rather than heart rate (HR). The formula to convert HR to CL is as follows: CL (ms) = 60,000/HR (bpm). For example, a HR of 100 bpm is equivalent to a CL of 600, while a HR of 150 bpm is equal to a CL of 400.

Once the catheters are placed in the correct positions in the heart, conduction and refractoriness can be assessed. Baseline intervals (basic CL, PR interval, QRS duration, and QT interval measured on the surface electrocardiogram) are measured at the beginning of the EPS while in sinus rhythm, if possible (Fig. 7.2).

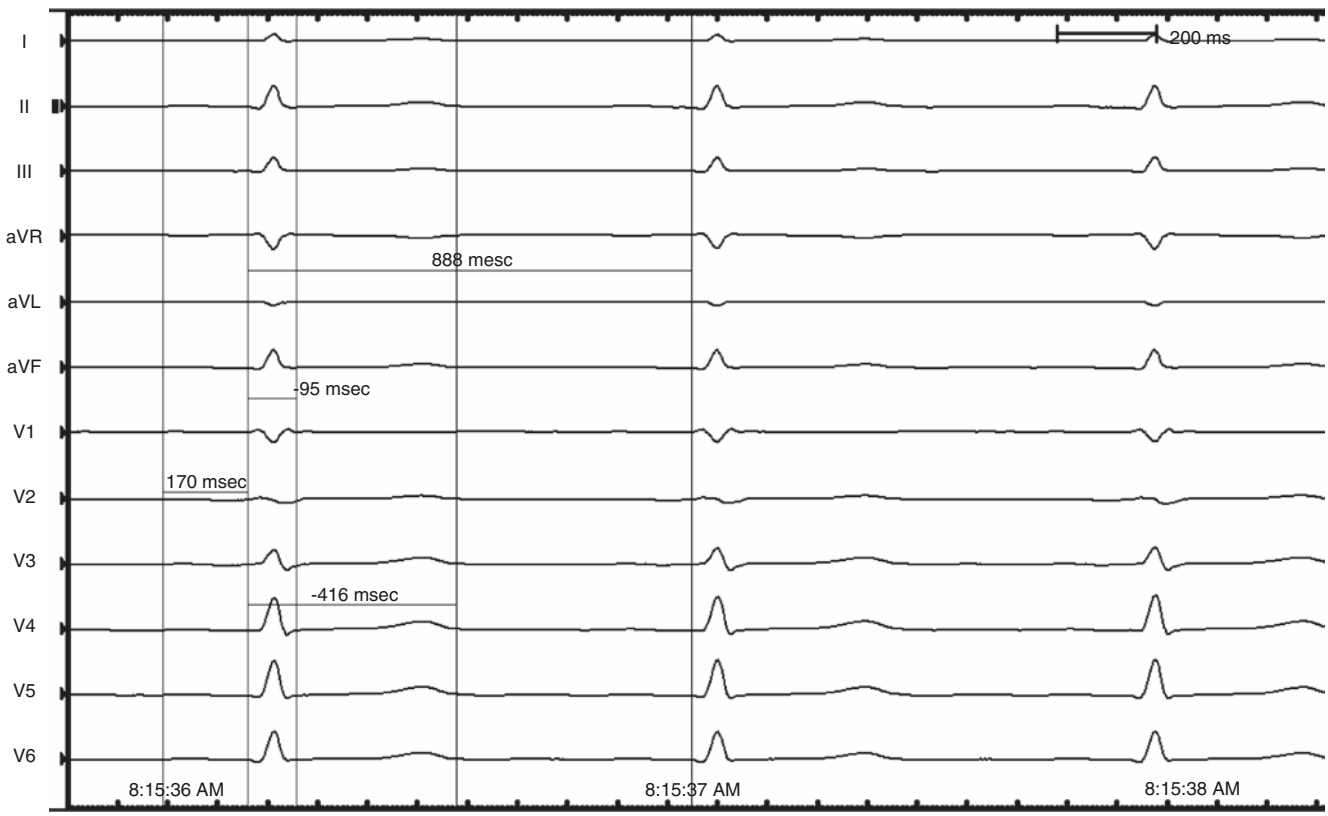


Fig. 7.2 Baseline intervals. Surface measurements of the basic cycle length (888 ms), PR interval (170 ms), QRS duration (95 ms), QT interval (416 ms) during sinus rhythm

Baseline Conduction Intervals

PA interval: The PA interval is measured from the onset of the P-wave on the surface electrocardiogram to the atrial electrogram recorded from the His catheter and represents intra-atrial conduction time.

His Bundle electrogram duration: The interval between first and last components of HBE on the His catheter recording should be recorded. Duration and morphology of HBE are important to detect disease in the His bundle. The HBE is usually <30 ms in duration. If longer, or if a split His signal is present (two separate components), one must suspect that significant intra-His delay may be present.

AH interval: The AH interval represents the AV nodal conduction time, or the time it takes for an electrical impulse to travel through the AV node. It is measured from the earliest atrial signal on the His bundle to the beginning of the HBE (Fig. 7.3). A normal AH interval is generally between 55 and 125 ms. The AH interval is particularly susceptible to alteration by medications (including anesthetic agents used for sedation) and autonomic tone. Due to the decremental properties of AV node, it is normal for the AH interval to increase as the atrial paced CL (PCL) decreases.

HV interval: The HV interval represents conduction through the infranodal (His-Purkinje) conduction system. It is measured from the earliest His deflection to the earliest surface or intracardiac ventricular activation (Fig. 7.3). A normal HV interval is 35–55 ms. When the HV interval is <35 ms, one must consider that an accessory pathway is present. Contrarily, when the HV interval is >55 ms, His-Purkinje disease may be present. An HV interval > 70 ms is consistent with severe His-Purkinje disease. The HV interval is less prone to alteration by autonomic tone than the AH interval.

Assessment of Sinus Node Function

To assess for sinus node dysfunction, overdrive pacing is performed from the HRA catheter for >30 s. Upon cessation of pacing, the time it takes for the next spontaneous sinus beat to occur is the sinus node recovery time (SNRT). The longest value after repeated measurements over a range of drive cycles should be recorded as the maximal SNRT. A normal SNRT is ≤1500 ms. Since the SNRT is directly related to the underlying heart rate, it must be corrected (CSNRT) to take into account the baseline sinus CL prior to pacing. The formula for the corrected sinus node recovery time (CSNRT) = SNRT—baseline cycle length (BCL). A normal value for CSNRT is ≤525 ms. SNRT >1500 ms or CSNRT >525 ms signifies the presence of sinus node dysfunction. Of note, it usually takes 5–6 beats for the SA node

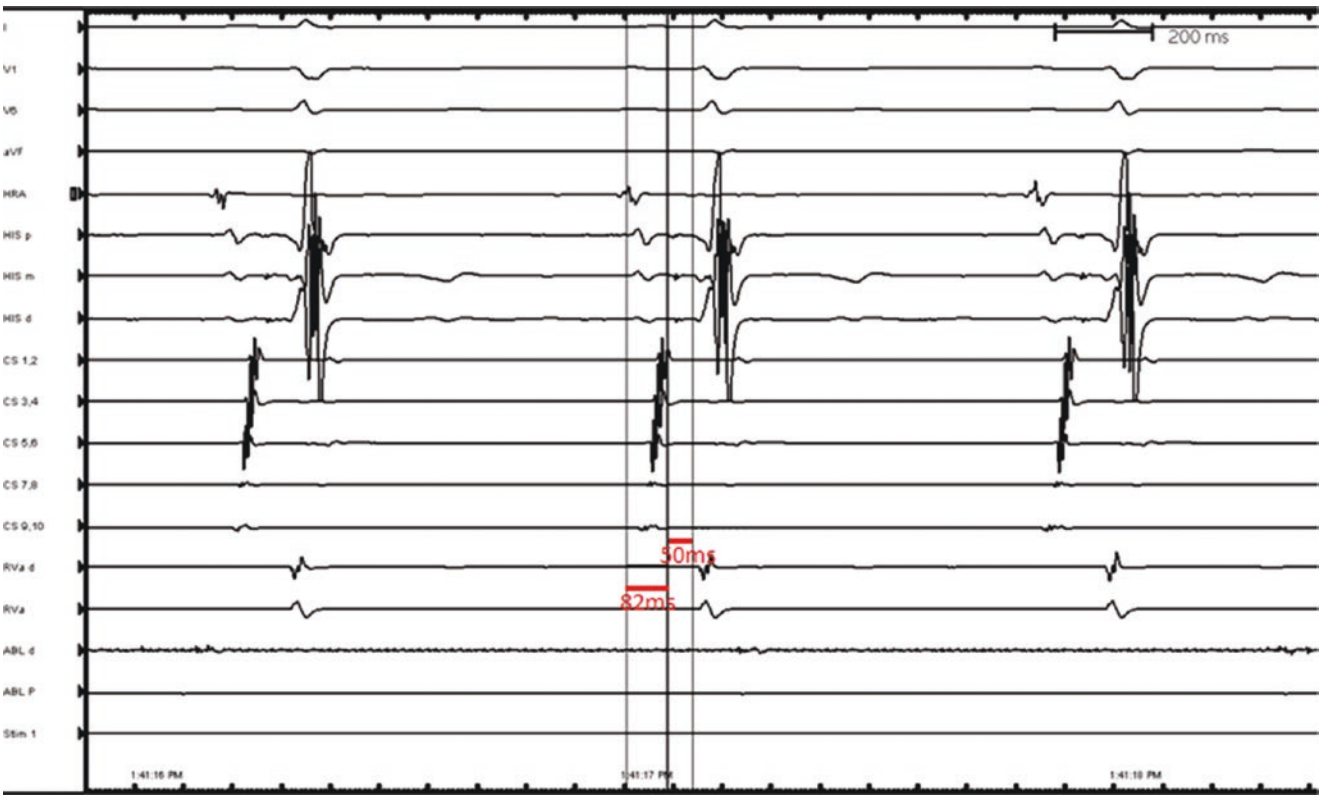


Fig. 7.3 AH and HV intervals. Measurement of the AH (82 ms) and HV (50 ms) intervals in a patient undergoing routine EP study. A normal AH interval is 55–125 ms and a normal HV interval is 35–55 ms

to recover to baseline after cessation of overdrive pacing. Falsely short SRTs may occur if atriosinus entrance block is present. More detailed assessment of the sinus node also includes determining the peak paced cycle length (PCLP) of the longest CSRT, which can reveal the status of atriosinus conduction during SRT testing, and indirect sinoatrial conduction time (SACT) using premature atrial extrastimuli or direct SACT measurement on a recorded sinus node electrogram (refs) Sinus node dysfunction can be manifest as disorders of automaticity, conduction, or both.

Programmed Stimulation

Evaluation of Refractoriness and Conduction

Programmed atrial and ventricular stimulation are useful methods to evaluate the refractoriness and conduction of the cardiac conduction system. To perform programmed atrial stimulation, an atrial paced drivetrain at a fixed CL (S1) is followed by a premature extrastimulus (S2). This is repeated with progressively premature extrastimuli (shortening by 10 ms intervals). Atrial extrastimulus testing can be used to evaluate atrial, AV nodal, and occasionally ventricular refractoriness. As the coupling interval of a premature atrial stimulus is shortened, there is progressive delay in AV nodal conduction, due to its decremental properties. Mobitz 1 block occurs once the Wenkebach CL has been reached (typically ≤450 ms). Atrial pacing should be performed down to the AV Wenkebach CL (or 300 ms, whichever occurs first) to measure the AV Wenkebach CL.

Programmed ventricular stimulation is performed (usually at the RV apex) in a similar fashion as programmed atrial stimulation, with a ventricular-paced drivetrain followed by ventricular extrastimuli at progressively shorter intervals until ventricular refractoriness is reached. This is performed to assess retrograde VA conduction and ventricular refractoriness. Typically this is done at drive cycles of 600–400 ms. Furthermore, progressive ventricular pacing down to the VA Wenkebach CL (or 300 ms, whichever occurs first) can be performed when VA conduction is present to determine the VA Wenkebach CL. When retrograde conduction through the AV node is present (in contrast to eccentric VA conduction over an accessory pathway), the earliest atrial activation is midline (on the His bundle catheter) and decremental with increasing drive rates or extrastimulus prematurity.

Effective Refractory Period: The effective refractory period (ERP) is the longest premature coupling interval of an extrastimulus which fails to conduct through a tissue. The atrial ERP is the longest S1-S2 coupling interval which fails to depolarize the atria. The AV nodal ERP is the longest A1-A2 interval which is not followed by an H2. The His-Purkinje ERP is the longest H1-H2 which fails to result in ventricular activation. The ventricular ERP is the longest S1-S2 coupling interval which fails to depolarize the ventricle.

Relative Refractory Period: The relative refractory period (RRP) is the longest premature coupling interval that results in prolonged conduction of the premature impulse compared with conduction during the basic drive train. The atrial RRP is the longest S1-S2 coupling interval which results in prolongation of the S2-A2 interval (compared with the S1-A1 interval). The AV nodal RRP is the longest A1-A2 at which the A2-H2 interval exceeds the A1-H2 interval. The His-Purkinje RRP is the longest H1-H2 interval for which H2-V2 exceeds H1-V2.

Functional Refractory Period: The functional refractory period (FRP) actually represents tissue conduction rather than refractoriness. It is the shortest interval between two impulses conducted through a tissue. The atrial FRP is the shortest A1-A2 interval following any S1-S2 interval. The AV nodal FRP is the shortest H1-H2 interval following any A1-A2 interval. The His-Purkinje FRP is the shortest V1-V2 following any H1-H2.

In addition to ascertaining anterograde (AV) and retrograde (VA) conduction through the AV node, programmed stimulation can detect the presence of dual AV nodal physiology or accessory pathways. When gradually incremental atrial pacing or decreasing premature atrial extrastimulus coupling intervals (at 10 ms intervals) results in an abrupt "jump" in the AH interval (>50 ms increase), the presence of dual AV nodal physiology is likely (Fig. 7.4). This is explained by block in the "fast" AV nodal pathway (which has a longer refractory period) and conduction down the "slow" pathway. It is important to note that while an "AH jump" suggests the presence of dual AV nodal physiology as a potential cause of a supraventricular tachyarrhythmia, it does not necessarily implicate that the cause of arrhythmia is definitely due to AVNRT.

Accessory pathways can usually be detected due to the presence of an "eccentric" atrial activation sequence when pacing from the ventricle. In patients with intact VA conduction, the normal atrial activation sequence from the AV node goes from medial to lateral in the LA- demonstrating a "concentric" atrial activation pattern on the CS catheter with activation sequence from proximal to distal. As such, changes in activation sequence with ventricular pacing suggest the presence of an accessory pathway (Fig. 7.5), and specific techniques such as Para-Hisian pacing are helpful to exclude a septal accessory pathway.

Induction of Tachycardia

While some patients may present to the EP lab in tachycardia, those with paroxysmal symptoms often present in sinus rhythm. Atrial and ventricular stimulation can be useful

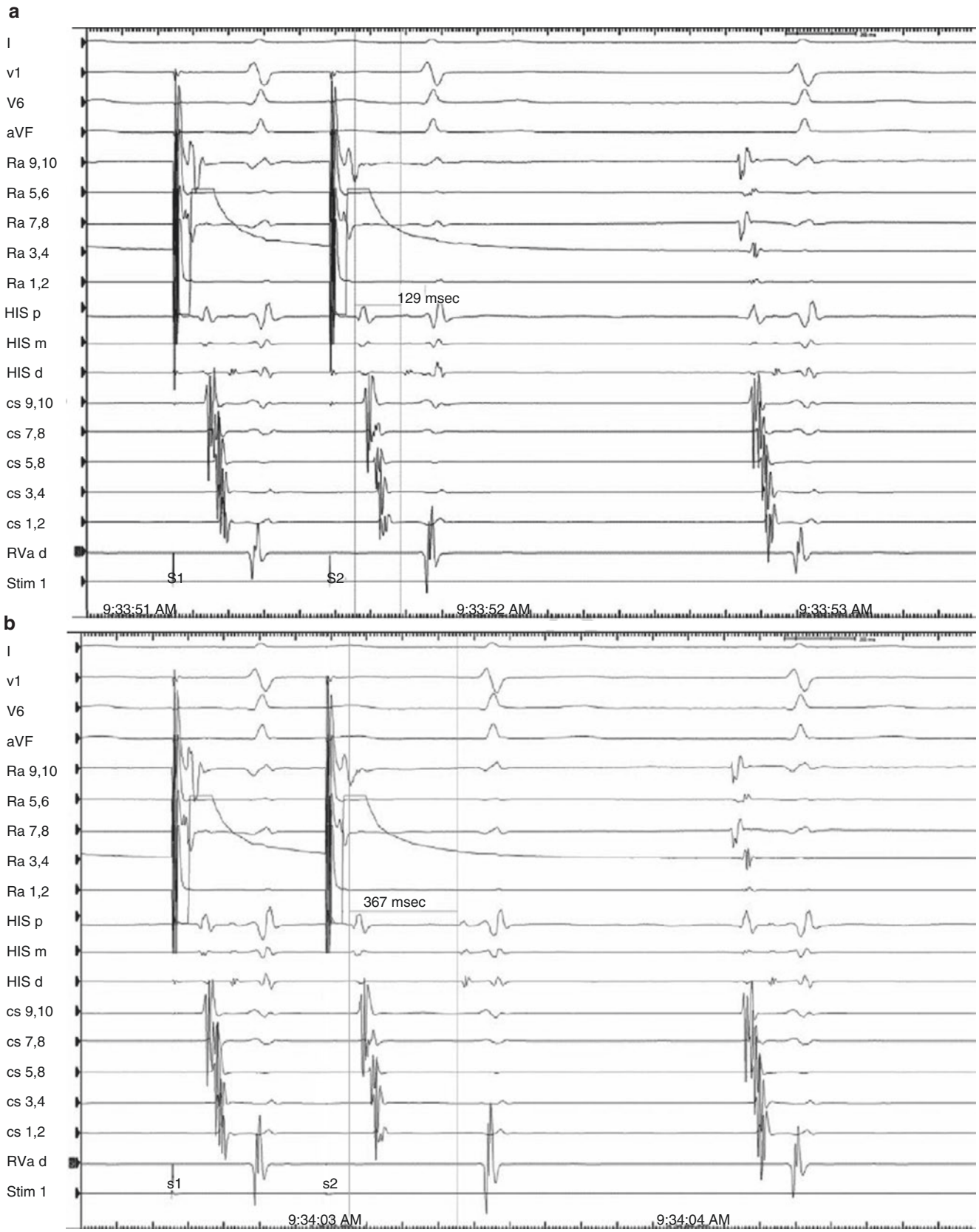


Fig. 7.4 AH Jump. (**a**) While pacing at a drivetrain with S1 at 700 ms, a programmed atrial extrastimulus (S2) at a coupling interval of 440 ms is introduced with a subsequent AH interval of 129 ms(**b**) Shortening the coupling interval of S2 by 10 ms (to 430 ms) results in prolongation of the AH interval (305 ms), suggesting the presence of dual AV nodal physiology

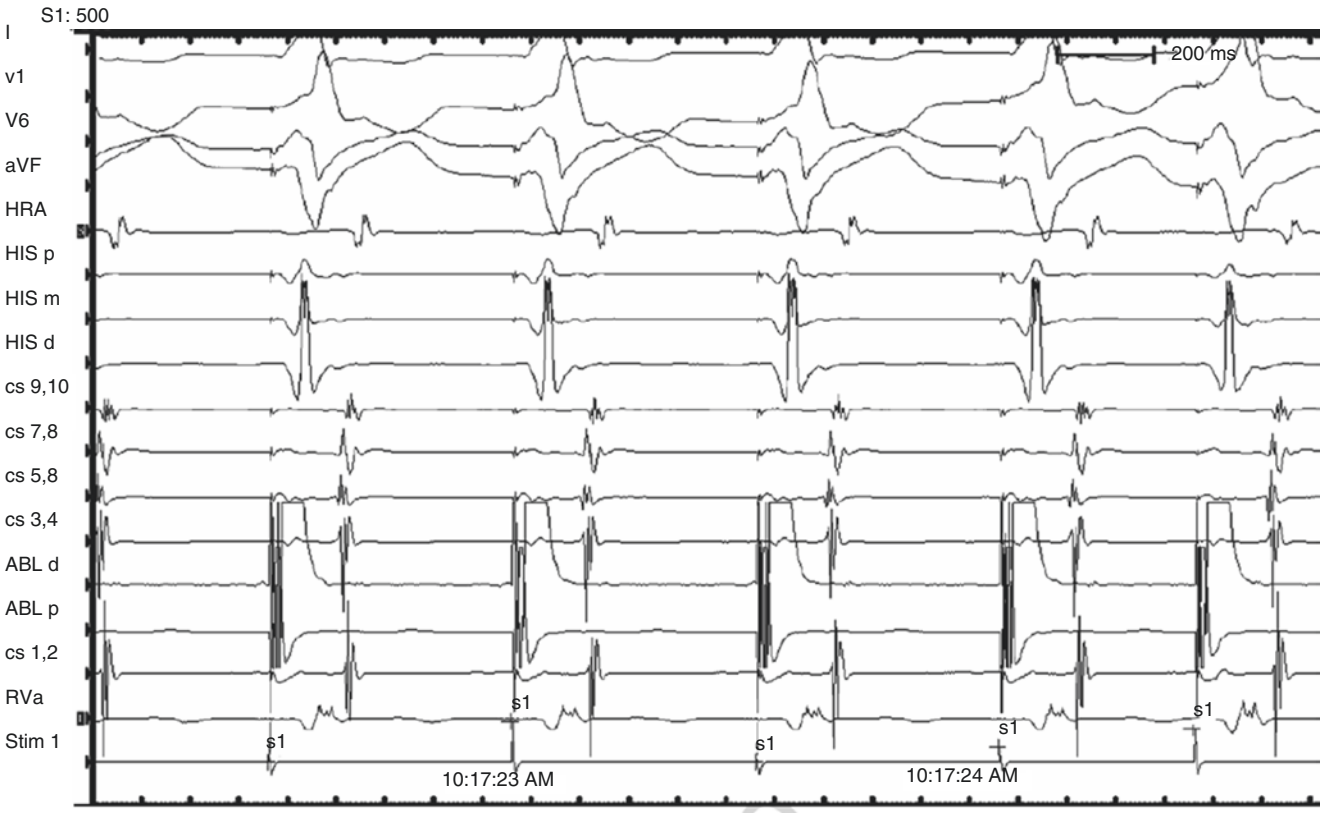


Fig. 7.5 Atrial activation sequence. Pacing from the left ventricle results in an "eccentric" retrograde activation sequence. Note that C3,4 and C5,6 are earliest and the atrial activation proceeds from lateral to medial in the left atrium. This is an extranodal response and is consistent with the presence of a left lateral accessory pathway

to initiate tachycardia in these patients. Catecholamine stimulation using isoproterenol can be an effective method to provoke arrhythmia as well. Supraventricular tachycardias such as AVNRT and AVRT can be induced by both atrial and ventricular programmed stimulation, while atrial tachycardia, atrial flutter, and atrial fibrillation are often inducible only with atrial extrastimuli or rapid atrial pacing. Meanwhile, protocols for induction of VT include stimulation with single, double, and triple extrastimuli from at least two locations (usually RV apex and RVOT).

Cardiac Mapping Techniques

The key intracardiac mapping techniques for evaluation of cardiac arrhythmias are activation mapping, pace mapping, and entrainment mapping. Additionally, computerized mapping (also referred to as substrate mapping) using three-dimensional mapping systems allows for visualization of scar and anatomic barriers which may be targeted for substrate ablation. Each of these techniques will be briefly discussed.

Activation mapping: Activation mapping helps to localize the site of earliest endocardial activation and to identify the activation sequence during tachycardia (Fig. 7.6). It is particularly helpful to identify the site of origin of focal arrhythmias.

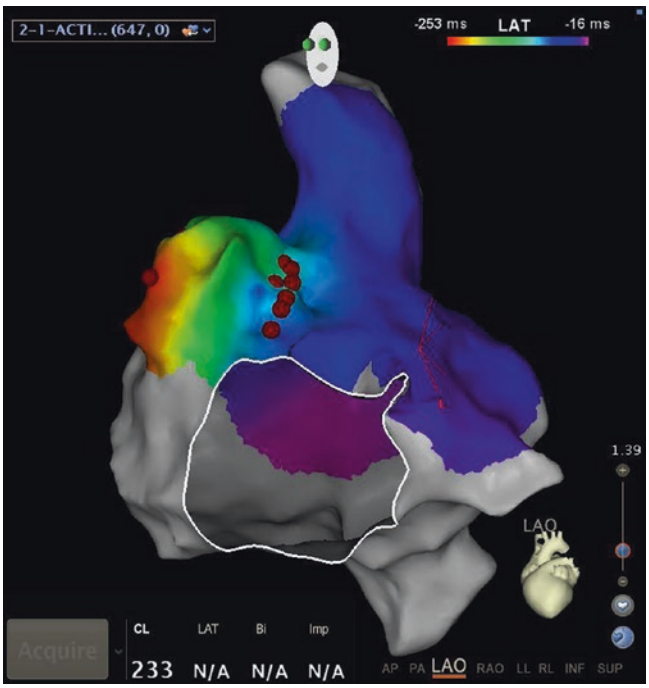


Fig. 7.6 Activation mapping. Activation map (LAO view) created using the Carto system depicting the activation sequence of the left ventricle in a patient undergoing PVC ablation. The red sites on the left of the image represent the earliest site of activation, and are the likely site of origin of the PVCs

The earliest activation site and potential site of origin is often the area of the heart which has electrograms that precede the onset of the P-wave or QRS complex during tachycardia. It is important to recognize that, unlike focal arrhythmias, macroreentrant arrhythmias by definition have ongoing intracardiac activity throughout the entire cardiac cycle, therefore it is impossible to pinpoint a single "earliest" site.

Entrainment mapping: Entrainment is a well-described pacing maneuver which is helpful to identify reentry as the mechanism of arrhythmia and to localize the reentrant circuit. While a thorough discussion of entrainment is beyond the scope of this chapter, we will discuss the basic principles. Entrainment mapping is particularly helpful for the diagnosis and treatment of macroreentrant arrhythmias since it can define the critical isthmus of a circuit for targeted ablation. Briefly, entrainment involves continuous resetting of a reentrant circuit with an excitable gap by pacing stimuli. With entrainment, pacing at a faster CL than the intrinsic tachycardia accelerates the tachycardia to the paced rate, with resumption of the prior tachycardia following termination of pacing. For manifest entrainment to exist, the paced beats must exhibit constant fusion at a fixed CL and progressive fusion with a shorter pacing CL. While entrainment is a useful way to determine whether pacing sites are in the arrhythmia circuit, one must be cognizant of the potential pitfalls of interpretation, including failure to capture with pacing or obscuration of the return electrogram by the pacing stimulus, among others [14, 15].

Pacemapping: Pacemapping involves pacing at various sites near the suspected origin of a tachycardia and examining the degree of concordance between the paced P-wave or QRS compared with that of the arrhythmia. Although generally pacemapping should be used in conjunction with activation and entrainment mapping, this is not always possible. When arrhythmias are paroxysmal or noninducible in the EP laboratory, activation and entrainment mapping may be difficult or impossible. In this situation pacemapping can be performed to suggest the site of origin (for focal arrhythmias) or exit site (for reentrant arrhythmias). Optimal pace maps should match in all 12 surface electrocardiogram leads with the clinical tachycardia (Fig. 7.7).

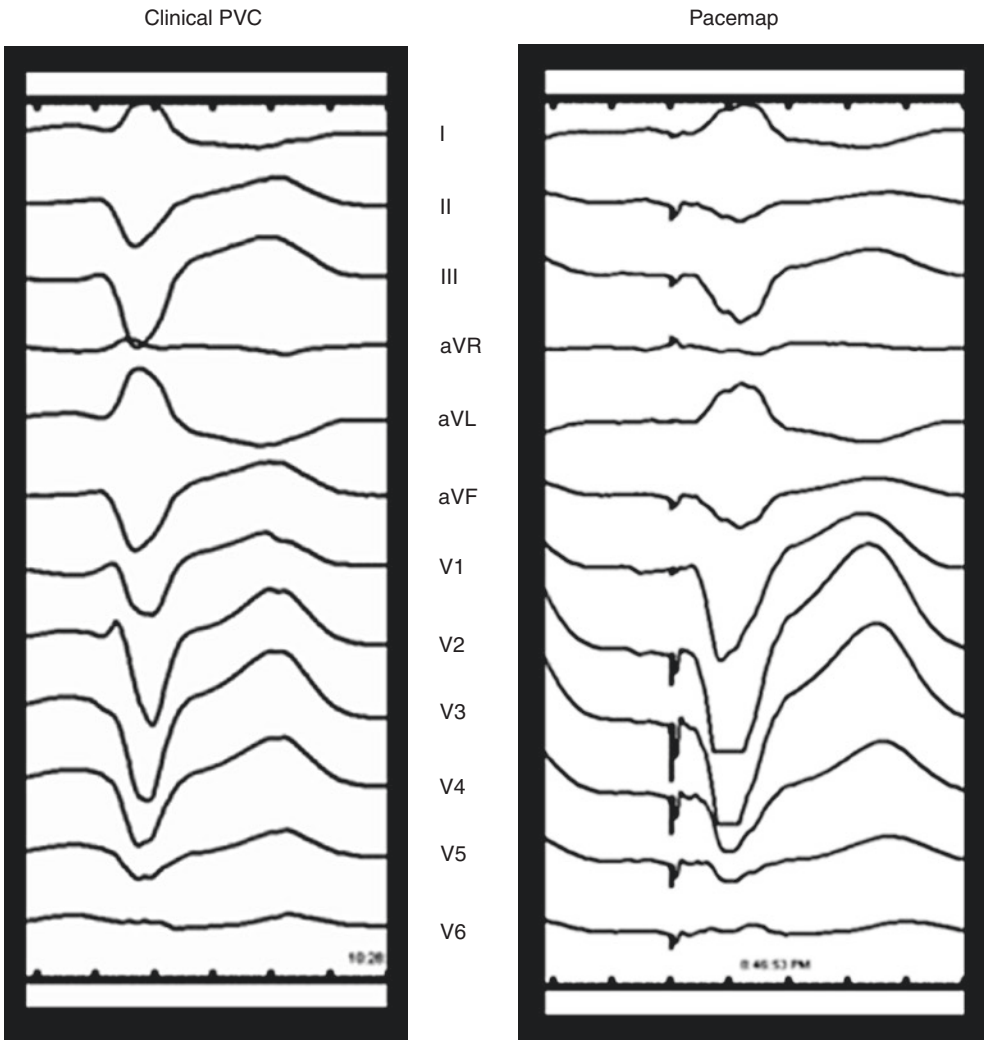


Fig. 7.7 Pacemapping. Pacing on a papillary muscle to identify the closest pacematch for a PVC in a patient with PVC-triggered VF. Ablation at this site successfully abolished the PVC

Advanced Computerized Mapping

While fluoroscopy has long been the cornerstone imaging modality for EPS, non-fluoroscopic three-dimensional electroanatomic mapping systems and Intracardiac (catheter based) echocardiography ICE are being increasingly utilized, especially for patients undergoing catheter ablation. Both of these adjunctive modalities increase the precision of catheter ablation and may help to reduce fluoroscopy exposure.

Three-Dimensional Electroanatomic Mapping Systems

Mapping systems which create three dimensional electroanatomic maps can accurately localize catheter position within the heart while minimizing the need for fluoroscopy. These systems are able to merge anatomic information obtained from computed tomography, magnetic resonance imaging, or ICE to create a three-dimensional geometric reconstruction of the cardiac chambers. The two most commonly used mapping systems are the CARTO and EnSite NavX systems, which will be briefly discussed.

One of the major benefits of nonfluoroscopic mapping systems is their ability to display both activation sequences and electrogram voltages on three-dimensional electroanatomic maps.

The CARTO (Biosense Webster Inc.; Diamond Bar, CA) system uses a magnetic field to reconstruct three-dimensional electroanatomic maps (Fig. 7.8). Using a certain fixed electrode on the table below the patient as a reference, electrodes on mapping and ablation catheters with magnetosensors can be localized in real-time as they are moved throughout the heart. By touching the myocardium at various areas of the heart in a point-by-point manner, unipolar and bipolar signals are obtained and stored, allowing for the creation of maps depicting voltages and activation sequence. Multipolar catheters are frequently used and allow for rapid acquisition of electroanatomic and voltage information.

With the EnSite NavX (St. Jude Medical; St. Paul, MN) system, surface electrode patches placed on the patient's body serve as a reference, allowing for localization of catheters as they are moved in a patient's heart. The electrogram signals obtained by the mapping catheters are transmitted to the patches and vice versa for creation of three-dimensional electroanatomic maps (Fig. 7.9).

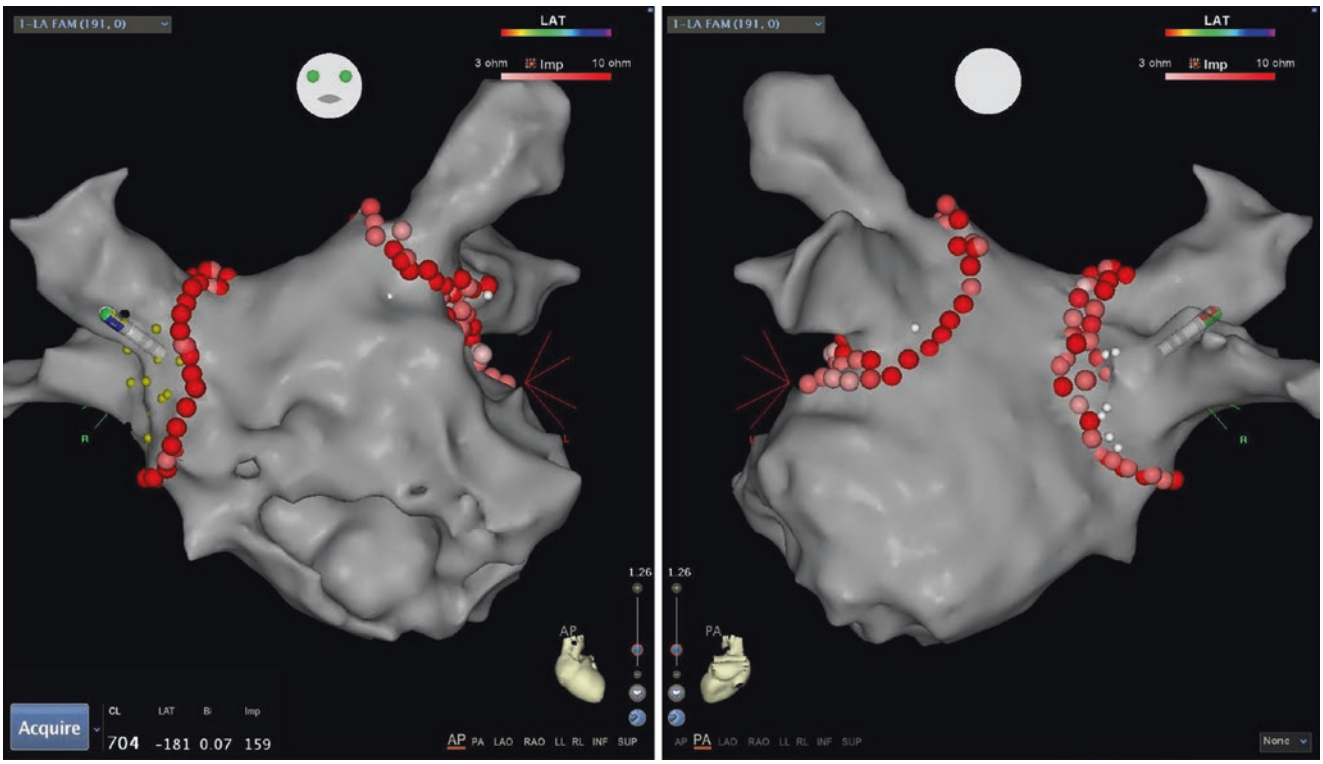


Fig. 7.8 CARTO mapping system. PA (*left*) and AP (*right*) views of an electroanatomic map created with the CARTO system during an atrial fibrillation ablation procedure

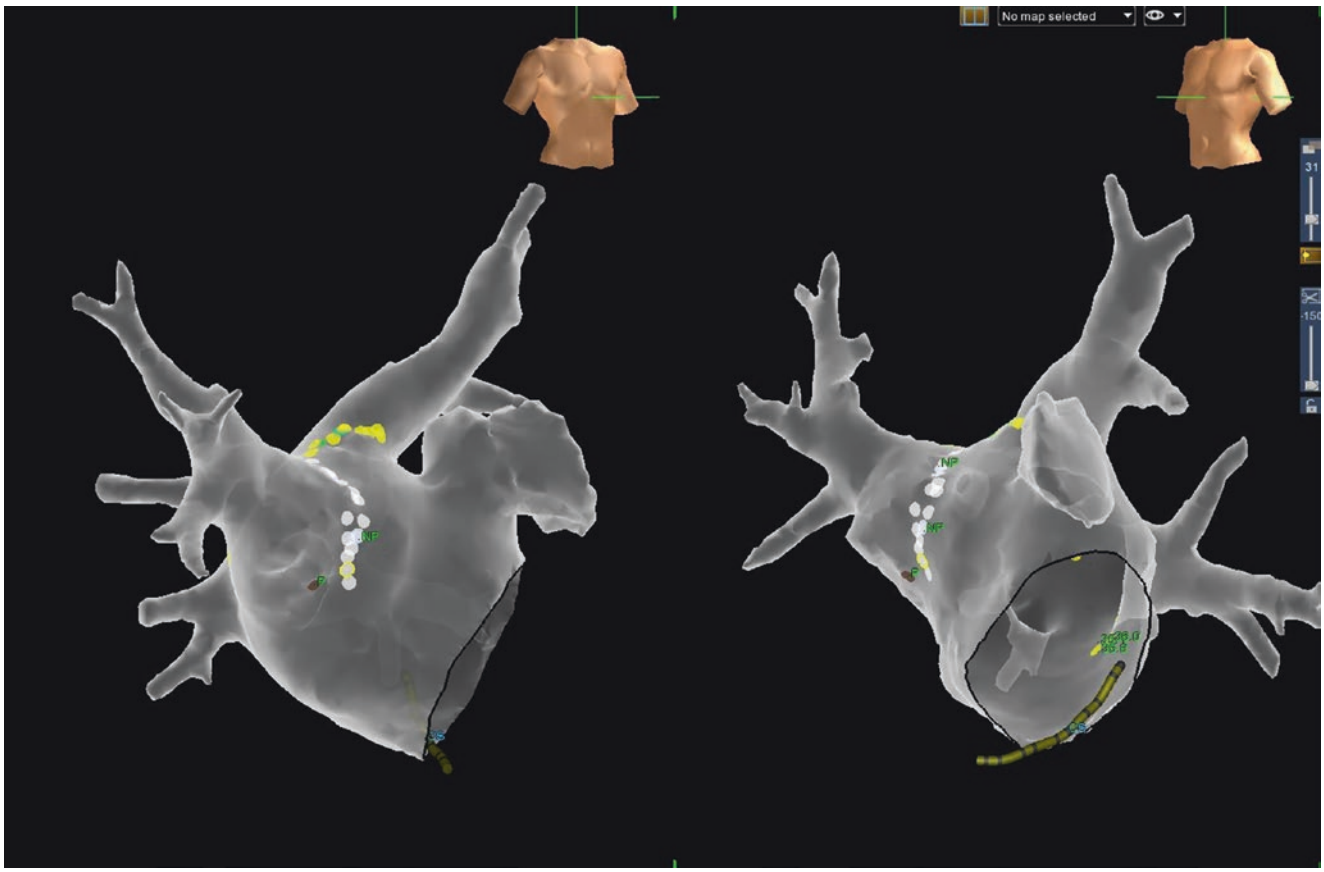


Fig. 7.9 NavX electoranatomic mapping. RAO (*left*) and LAO (*right*) views of an electroanatomic map created using the NavX system during an atrial fibrillation ablation procedure

In addition to point-by-point contact mapping, the Ensite Array (St. Jude Medical; St. Paul, MN) catheter is a multi-electrode noncontact mapping catheter which can gather thousands of electrical points per heart beat when placed in a chamber of interest. This technology is particularly helpful to rapidly map nonsustained or hemodynamically intolerable arrhythmias.

Imaging Modalities for EPS and Ablation

Intracardiac Echocardiography

Intracardiac echocardiography is an adjunctive imaging modality which may increase both safety and efficacy of catheter ablation. ICE allows for direct, real-time visualization of catheters before, during, and after catheter ablation. It is especially helpful in aiding transseptal puncture when accessing the left-sided cardiac chambers, as for pulmonary vein isolation for AF (Fig. 7.10). In these patients it can also identify the esophagus to allow for safe ablation of the posterior LA [16].

With ICE, operators are able to immediately identify procedural complications such as cardiac perforation, damage to

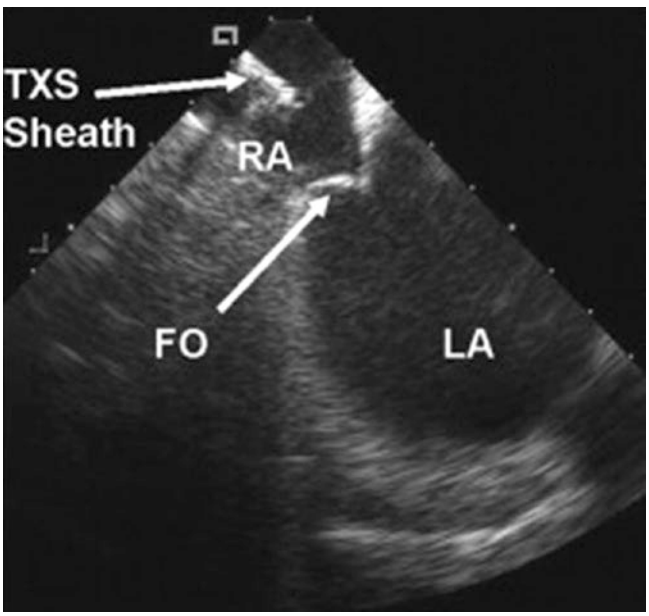


Fig. 7.10 Intracardiac ultrasound to guide transseptal puncture during ablation for atrial fibrillation. Indentation of the foramen ovale (FO) by the transseptal sheath (TXS) before transseptal puncture (*Reproduced, with permission from: Callans DJ, Wood MA. How to use intracardiac echocardiography for atrial fibrillation procedures. Heart Rhythm. 2007;4(2):242–5*)

intracardiac structures, pericardial effusion, myocardial air embolization, esophageal injury, formation of intracardiac thrombi, and PV stenosis in real time such that corrective action can be undertaken right away [17–19]. Furthermore, images obtained from ICE can be merged with an EAM to reconstruct three-dimensional geometrical representations of a patient's cardiac anatomy.

Summary

EPS is a valuable diagnostic and prognostic tool for patients with unexplained syncope or suspected arrhythmia. Although invasive, it is a generally safe procedure which allows electrophysiologists to examine the conduction and refractoriness of various components of the cardiac conduction system. EPS can be therapeutic when used in conjunction with cardiac mapping techniques and advanced imaging modalities, as catheter ablation is a potentially curative treatment option for patients with certain arrhythmias.

References

1. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61:e6–75.
2. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30:2631–71.
3. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10:1932–63.
4. Khairy P, Van Hare GF, Balaji S, et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). Heart Rhythm. 2014;11:e102–65.
5. Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 2000;342:1937–45.
6. Cohen MI, Triedman JK, Cannon BC, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). Heart Rhythm. 2012;9:1006–24.
7. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014;11:1305–23.
8. Liang JJ, Hebl VB, DeSimone CV, et al. Electrogram guidance: a method to increase the precision and diagnostic yield of endomyocardial biopsy for suspected cardiac sarcoidosis and myocarditis. JACC Heart Fail. 2014;2:466–73.
9. Casella M, Pizzamiglio F, Dello Russo A, et al. Feasibility of combined unipolar and bipolar voltage maps to improve sensitivity of endomyocardial biopsy. Circ Arrhythm Electrophysiol. 2015;8:625–32.
10. Tracy CM, Akhtar M, DiMarco JP, et al. American College of Cardiology/American Heart Association 2006 update of the clinical competence statement on invasive electrophysiologystudies, cat heterablation,andcardioversion: a report of the American College of Cardiology/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training developed in collaboration with the Heart Rhythm Society. J Am Coll Cardiol. 2006;48:1503–17.
11. Dimarco JP, Garan H, Ruskin JN. Complications in patients undergoing cardiac electrophysiologic procedures. Ann Intern Med. 1982;97:490–3.
12. Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3:32–8.
13. Palaniswamy C, Kolte D, Harikrishnan P, et al. Catheter ablation of postinfarction ventricular tachycardia: ten-year trends in utilization, in-hospital complications, and in-hospital mortality in the United States. Heart Rhythm. 2014;11:2056–63.
14. Knight BP, Ebinger M, Oral H, et al. Diagnostic value of tachycardia features and pacing maneuvers during paroxysmalsupraventricular tachycardia. J Am Coll Cardiol. 2000;36:574–82.
15. Stevenson WG, Khan H, Sager P, et al. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. Circulation. 1993;88:1647–70.
16. Ren J-F, Marchlinski FE, Callans DJ. Real-time intracardiac echocardiographic imaging of the posterior left atrial wall contiguous to anterior wall of the esophagus. J Am Coll Cardiol. 2006;48:594.
17. Ren JF, Marchlinski FE, Callans DJ. Left atrial thrombus associated with ablation for atrial fibrillation: identification with intracardiac echocardiography. J Am Coll Cardiol. 2004;43:1861–7.
18. Ren JF, Marchlinski FE. Utility of intracardiac echocardiography in left heart ablation for tachyarrhythmias. Echocardiography. 2007;24:533–40.
19. Ren JF, Marchlinski FE. Early detection of iatrogenic pericardial effusion: importance of intracardiac echocardiography. JACC Cardiovasc Interv. 2010;3:127. author reply 127-8

Antiarrhythmic Drug Management of Atrial Fibrillation

8

A. John Camm and Irina Savelieva

Abstract

Rhythm control indicated for patients with atrial fibrillation who remain symptomatic despite adequate rate control. Usually antiarrhythmic agents are chosen as a first attempt to restore or maintain sinus rhythm, and ablation is reserved for patients who do not respond to simple medical therapy. Antiarrhythmic drugs are usually effective, at least in part, and may provide sufficient symptomatic relief but they may be complicated by proarrhythmia, especially in patients with underlying structural heart disease because of their potential arrhythmogenic, and negative inotropic and chronotropic effects.

There are just six antiarrhythmic agents that are frequently used to treat atrial fibrillation (flecainide, propafenone, amiodarone, sotalol dofetilide, and dronedarone). In some countries disopyramide cibenzoline, antazoline, bepridil and others are less frequently used. The choice of an antiarrhythmic is usually made on the basis of the underlying cardiovascular status. In patients with heart failure only dofetilide and amiodarone are considered, and in patients with coronary artery disease disopyramide, flecainide and propafenone are avoided. Dronedarone must be avoided if there is a high likelihood of the arrhythmia progressing to a permanent for of AF.

Antiarrhythmic agents may also be used as hybrid therapy in combination with other antiarrhythmic agents or catheter ablation. A significant proportion of patients will respond favourably to antiarrhythmic agents after ablation whereas they were refractory to these drugs prior to ablation. The combination of antiarrhythmic agents is poorly researched but often used in clinical practice.

Very few antiarrhythmic agents have been introduced into the clinic in the last several decades. Vernakalant (outside the USA) and ibutilide are used for restoration of acute onset atrial fibrillation. Dronedarone is an agent that seems to reduce cardiovascular hospitalizations in patients with high risk intermittent atrial fibrillation but was associated with increased mortality when given, often together with digoxin, to patients with permanent atrial fibrillation.

Ranolazine is not approved as an antiarrhythmic agent for managing patients with atrial fibrillating, but is often used "off-label" for resistant cases. It may be particularly effective in combination with other dronedarone or amiodarone, but there is insufficient clinical trial data to recommend these combinations.

A.J. Camm, M.D., F.R.C.P. (✉) • I. Savelieva
Clinical Sciences Division, St George's University of London,
Cranmer Terrace, London SW17 0RE, UK
e-mail: jcamm@sgul.ac.uk

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_8

Keywords

Antiarrhythmic drugs • Atrial fibrillation • Pharmacology • Pharmacokinetics • Proarrhythmia • Electrical cardioversion of atrial fibrillation • Amiodarone • Sotalol • Rate vs. rhythm control of atrial fibrillation • Post-operative atrial fibrillation

Introduction

The management of atrial fibrillation (AF) requires comprehensive and effective therapy for co-morbidities that may underlie the development of AF or its complications such as stroke or heart failure. When necessary, specific protection against thromboembolic risks must be initiated. A strategic decision should be taken about whether the treatment approach will involve rate- or rhythm-control. Several trials have demonstrated that there is no survival advantage associated with the rhythm control strategy [1–3], but persistent symptoms may require antiarrhythmic therapy (Fig. 8.1). In general, appropriate candidates for rhythm control are: young, active and highly symptomatic presenting with early onset AF, AF with a transient or reversible cause, little or no structural heart disease, or AF which remains symptomatic despite adequate rate control.

When rhythm control is selected, it may be necessary to restore sinus rhythm (cardioversion) and/or to prevent recurrences or AF. Both therapeutic goals may be achieved using pharmacological or non-drug based interventions. Antiarrhythmic drugs may be used independently or in a hybrid setting, together with electrical cardioversion or left atrial ablation, to achieve these objectives.

Antiarrhythmic drugs are effective rhythm control therapies for patients with intermittent forms of AF, but their safe use is compromised by proarrhythmic complications, negative inotropic, chronotropic and dromotropic effects, drug-drug interactions and problems with drug elimination. No antiarrhythmic agent has been shown to improve survival, and a trend towards an increased mortality has been demonstrated in several instances. In general, antiarrhythmic drug therapy is specifically aimed at reducing symptoms and possibly improving the quality but not the length of life.

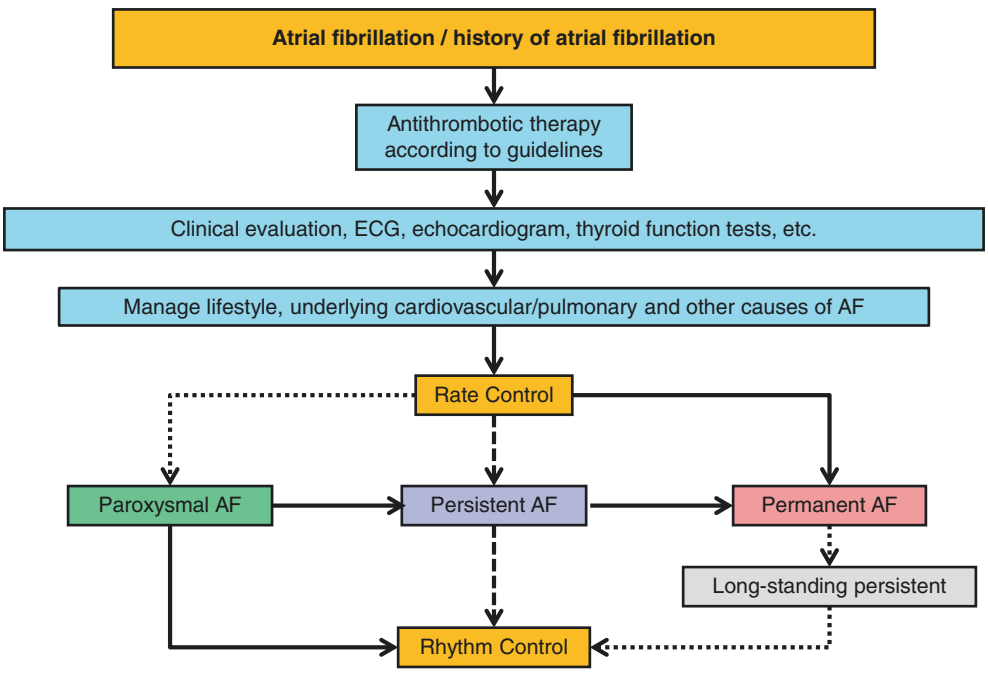


Fig. 8.1 The initial evaluation of a patient with AF involves assessment of the cardiovascular system and potential causes of AF, provision of antithrombotic protection if needed, attention to life style and treatment of underlying co-morbidities. The main decision then concerns rate versus rhythm control that is influenced by the temporal pattern of the AF, the extent of cardiac and comorbid disease and the symptomatic status of the patient

Clinical AF is often preceded by short asymptomatic runs of atrial tachyarrhythmia/fibrillation (silent AF) [4] which may then progress towards more sustained episodes of AF (clinical AF) persistent AF may terminate spontaneously (paroxysmal AF) or continue until an active intervention is used to terminate the arrhythmia (persistent AF). Persistent AF often becomes more difficult to terminate, or may recur so rapidly, that the physician and/or patient may decide that it is best to remain "stable" in AF (permanent AF) [5]. This process is described as "progression" which occurs at a rate of between 5 and 15% per year [6]. It is related to atrial remodelling at an electrophysiological (shortened atrial action potentials, atrial conduction delay or block) and structural level (essentially, development of fibrosis, myocyte degeneration, fatty metamorphosis and increasing atrial size), which is partially related to the AF itself ("atrial fibrillation begets atrial fibrillation") [7], or the effects on the atrium of age or co-morbidities such as heart failure or hypertension. AF progression is also a potential target for antiarrhythmic drug therapy, and early aggressive rhythm control may therefore be an appropriate approach, but his has not yet been convincingly demonstrated.

Principles or Antiarrhythmic Drug Therapy for Maintaining Sinus Rhythm

The use of an antiarrhythmic drug is primarily for symptom reduction since there is no evidence that rhythm control leads to an increase of lifespan. The efficacy of antiarrhythmic drug therapy to cardiovert AF or to maintain sinus rhythm is modest. However, failure of one antiarrhythmic drug does not imply that others may not be successful and a significant reduction of burden of the arrhythmia (frequency or duration of episodes) may be a valuable and often sufficient clinical response. The choice of a specific antiarrhythmic drug is usually empiric, but may be theoretically rationalised by using the concept of explicit vulnerable parameters which can be targeted by specific antiarrhythmic drugs [8]. This Sicilian Gambit approach [9] is still more theoretical than practical, and because the adverse complications of antiarrhythmic drug therapy are not uncommon the choice of an antiarrhythmic drug often revolves around the likelihood of adverse events rather than potential efficacy alone [10].

Antiarrhythmic drugs remain classified according to the scheme proposed by Vaughan-Williams: class I drugs predominantly impair conduction (IA associated with delayed repolarisation, class IB with shortening of repolarisation and class IC with no effect on repolarisation), class IIK, antiadrenergic drugs, mostly beta blockers, class III agents which prolong repolarisation and Class IV agents, notably the non-dihydropyridine calcium antagonists [11].

Goals of Antiarrhythmic Drug Therapy

Antiarrhythmic drugs may be used to cardiovert patients from AF to sinus rhythm, to maintain sinus rhythm by preventing or delaying recurrences, to prevent the onset of the arrhythmia in specific circumstances such a peri cardiothoracic surgical procedures, or to reduce symptoms such as palpitations, chest pain, breathlessness or anxiety by reducing the duration of the arrhythmia or slowing the ventricular rate response. Rhythm control with antiarrhythmic drugs remains essential part of AF management. Antiarrhythmic therapy may result in the reduction of AF burden and improvement of quality of life, and may also decrease the rate of progression of AF and its complications such as left ventricular dysfunction.

Antiarrhythmic drugs can be used to facilitate electrical cardioversion and to prevent early recurrence of AF. The beneficial effects include prolongation of atrial refractoriness, conversion of fibrillation AF to a more organized atrial rhythm (e.g. flutter) which may be cardioverted with less energy, and suppression of atrial premature beats that may re-initiate AF. Evidence for such "synergistic" action of antiarrhythmic drugs has largely come from the small studies with short-acting intravenous formulations and is limited with oral agents [12].

In patients who underwent left atrial ablation, antiarrhythmic drugs, often a lower dose, may constitute part of "hybrid therapy" to achieve complete suppression of the arrhythmia. Although intuitively, effective long-term maintenance of sinus rhythm can reduce risk of stroke, anticoagulation should not be discontinued in patients with risk factors on the assumption that AF has been successfully suppressed.

Pharmacologic Cardioversion of Atrial Fibrillation

Antiarrhythmic drug therapy is used to cardiovert AF to sinus rhythm directly, to facilitate electrical cardioversion or to maintain sinus rhythm immediately post cardioversion. It is an alternative approach to electrical cardioversion which can generally be initiated early following symptomatic AF onset since it does not require anesthesia and an appropriately prepared patient. However, when the arrhythmia is sustained beyond 48 h it is usually necessary to initiate effective anticoagulation and the success of drug-induced cardioversion decreases and electrical cardioversion is then preferred.

The usual technique is to monitor the ECG and blood pressure and to infuse an intravenous formulation of an antiarrhythmic drug. Apart from dofetilide and dronedarone the drugs used for oral AF prophylaxis have intravenous counterparts which are be mostly widely available, but some such

as intravenous propafenone, flecainide and vernakalant are not available in the USA but are elsewhere whereas ibutilide is available in the USA but not everywhere outside the USA.

The choice of antiarrhythmic drug depends on underlying comorbidities such as significant structural heart disease, particularly heart failure and the speed of response that is needed (Fig. 8.2). While amiodarone is highly effective and can be used even in patients with heart failure, it characteristically results in early ventricular rate slowing and delayed cardioversion. Flecainide and propafenone act rapidly but cannot be given to patients with significant structural heart disease. Vernakalant also acts quickly and can be given to patients with mild heart failure, hypertension and coronary disease [13]. Patients with haemodynamically significant aortic stenosis should be avoided. Some drugs are more effective in terminating flutter, e.g., ibutilide whilst other drugs are ineffective in this setting e.g., vernakalant. The properties of the drugs used to convert atrial fibrillation are listed in Table 8.1.

When electrical direct current cardioversion completely fails, or AF rapidly resumes after a brief spell in sinus rhythm, a further attempt at electrical cardio version can be at rescheduled after a course of oral antiarrhythmic or after an intravenous infusion of an antiarrhythmic agent. In many centers it is routine to prescribe antiarrhythmic pre-treatment in patients who have failed a previous cardioversion, patients who have relapsed into AF when antiarrhythmic support has been withdrawn, or patients with less chance of successful cardioversion, e.g. associated left ventricular dysfunction or enlarged left atrium.

Pill-in-the-Pocket Approach

When an antiarrhythmic treatment is commenced during ongoing AF the arrhythmia may convert to sinus rhythm within several days or weeks, even when the AF has been present for some time. It is never clear whether the arrhythmia would have stopped spontaneously, and this is not therefore a common clinical strategy. If an antiarrhythmic is started during AF it is usual to plan a subsequent cardioversion. However, administration of a single high dose of a class

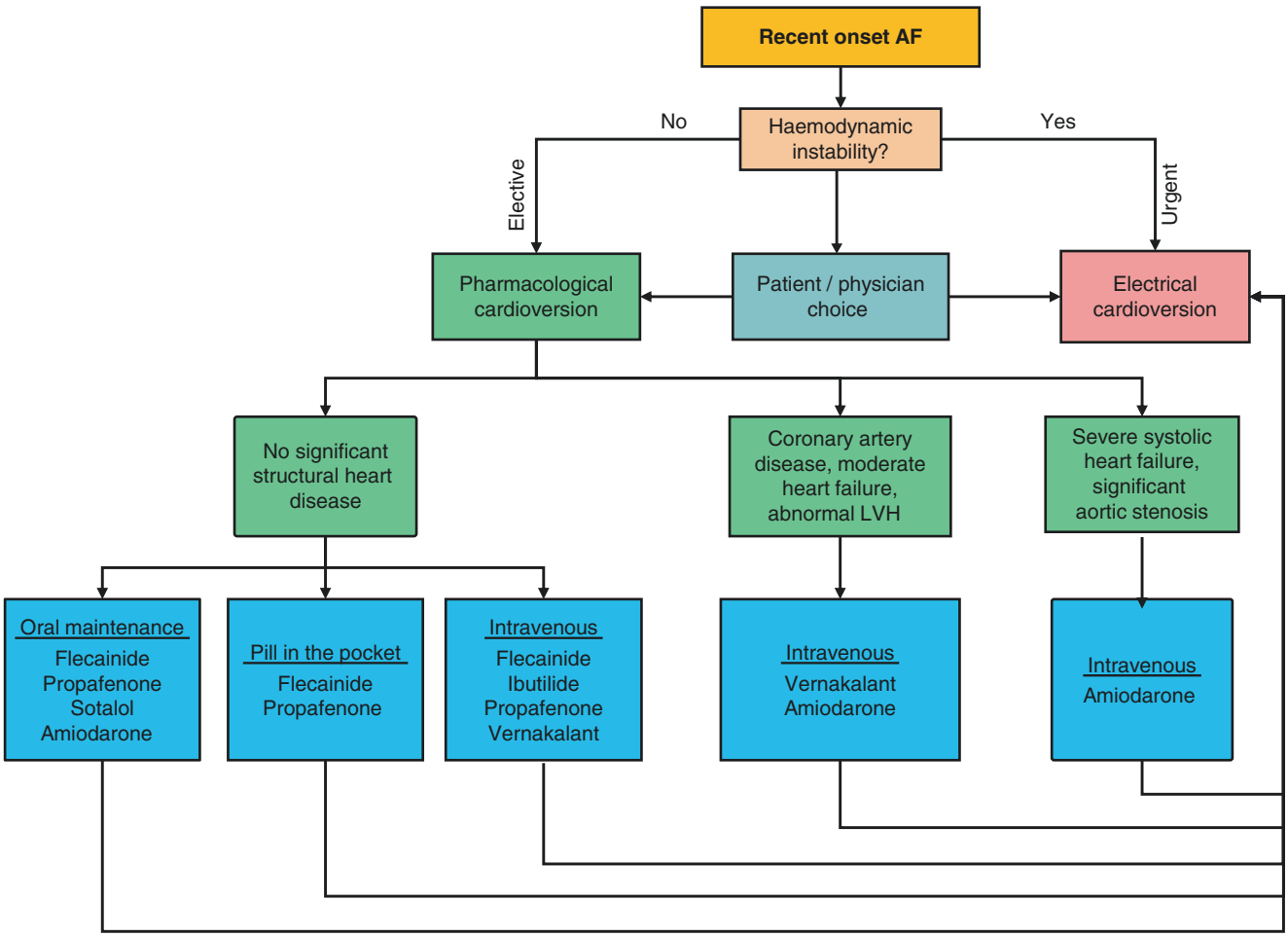


Fig. 8.2 Electrical and pharmacologic cardioversion - the choice of techniques. *LVH* left ventricular hypertrophy

Table 8.1 Antiarrhythmic drugs for pharmacologic cardioversion

Drug	Route of administration	Dose	Contraindications/precautions
Flecainide	IV	1.5–2 mg/kg over 10 min	Avoid in coronary disease associated with ischemia, or in heart failure with left ventricular dysfunction, or other relevant structural heart disease
	Oral	200–300 mg in a single dose	Complications include hypotension, QRS widening, QT prolongation, and rarely atrial flutter with 1:1 conduction, ventricular tachycardia
Propafenone	IV	1.5–2 mg/kg over 10 min	Avoid in coronary disease associated with ischemia, or in heart failure with left ventricular dysfunction, or other relevant structural heart disease
	Oral	450–600 mg in a single dose	Complications include hypotension, QRS widening, QT prolongation, and rarely atrial flutter with 1:1 conduction, ventricular tachycardia
Amiodarone	IV	5–7 mg/kg over 1-2 h, then 50 mg/h to a maximum 1.0 g for 24 h)	Complications include phlebitis (large bore cannula or central line should be used for infusion), hypotension, AV block and bradycardia
			Rapid control of ventricular rate but relatively delayed cardioversion
Ibutilide	IV	1 mg over 10 min, then wait for 10 min, then 1 mg over 10 min	Avoid when low LVEF, QT interval prolongation, or significant LVH
			QT prolongation and polymorphic VT (TdP) may occur
			ECG monitoring for 4 h after administration
Vernakalant	IV	3 mg/kg over 10 min, then wait for 10 min and then 2 mg/kg over 10 min	Avoid in significant aortic stenosis, dehydration, hypotension (SBP<100mmHg), recent ACS (< 30 days), severe heart failure (NYHA III-IV), or prolonged QT (QT uncorrected > 440ms)
			Complications include: hypotension, QT prolongation, QRS widening or non-sustained VT
			ECG monitoring for at least 4 h after administration

IV intravenous, *AV* atrioventricular, *ECG* electrocardiogram, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *TdP* torsade de pointes, *NYHA* New York Heart Association, *VT* ventricular tachycardia. Modified from the 2016 European Society of Cardiology Guidelines on the management of patients with of atrial fibrillation [14]

I antiarrhythmic may quickly convert AF to sinus rhythm. This is known as the pill-in-the-pocket technique [15].

This treatment is often employed in Europe but is relatively rarely used in the United States. It is endorsed by European Society of Cardiology and NICE guidelines. In patients with clear symptomatic episodes of AF but no or minimal structural heart disease and relatively infrequent (less than 12 per year) episodes of arrhythmia, a high single dose of propafenone (450–600 mg) or flecainide (200–300 mg) can be used to terminate AF. The drug is not taken on a regular basis but only when the arrhythmia occurs, thereby avoiding long-term exposure to adverse effects Studies have shown that AF terminated in 50–60% patients at 3 h and 70–80% patients at 8 h following the ingestion of a single oral loading dose of propafenone or flecainide compared with 18 and 39% on placebo [16, 17]. A tenfold reduction in the monthly number of visits to emergency was noted in a proof-of-concept study [18].

It is important that the effectiveness and safety of this technique is first tested in-hospital and it is not appropriate to use the technique in patients who are also taking antiarrhythmic therapy prophylactically [19]. If 1:1 atrial flutter, ventricular arrhythmias or AV block are not provoked and if post termination sinus pauses or significant QT prolongation do not occur the patient may use the technique as a self-initiated therapy outside the hospital setting within a short time of arrhythmia onset.

Selection of an Antiarrhythmic Drug

Antiarrhythmic drugs are ion channel blockers that principally influence atrial or junctional automaticity or refractoriness in such a way to suppress the triggers of AF, such as frequent atrial premature beats, short bursts of rapid atrial tachycardia (common) or junctional reciprocating tachycardias (rare). These drugs also modulate the substrate for AF by decreasing excitability and conduction velocity, or lengthening refractoriness of atrial tissue and therefore discourage re-entry (multiple wavelets or spiral waves). Some antiarrhythmic drugs may also change the balance of autonomic stimulation of the atrial myocardium by suppression of sympathetic (e.g. beta-blockers, amiodarone or dronedarone) or muscarinic activity (e.g. disopyramide).

The choice between antiarrhythmic drugs is usually based on side effect profiles and safety which is determined by the presence and nature of underlying heart disease rather than any specific efficacy in particular patients [10]. However, it is generally true that the most effective drugs also have the greatest propensity to cardiovascular adverse effects such as proarrhythmia (bradycardia and tachycardia) and negative inotropic effects, particularly on left ventricular function. Many patients who resort to rhythm control have already been exposed to beta-blockers for the treatment of underlying cardiovascular problems or for AF ventricular rate control, but if not, a trial of beta-blocker is the initial approach to

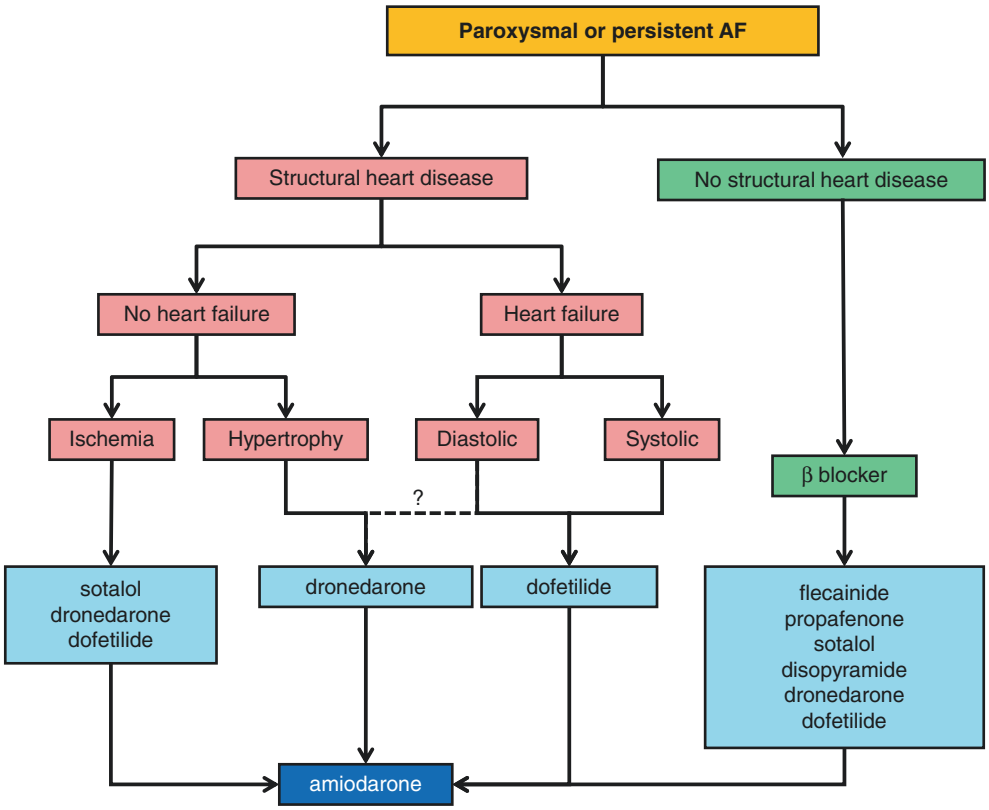


Fig. 8.3 Choice of antiarrhythmic drug for the prevention of recurrences of atrial fibrillation. It remains unclear whether a patient with mild heart failure with preserved ejection fraction can be safely treated with dronedarone

rhythm control, in almost every circumstance. If optimal beta-blockade fails to be effective, is contra-indicated, or is associated with adverse effects, a specific antiarrhythmic drug may be used. At this stage, it is very important to consider associated cardiovascular disease. Patients are generally divided into those with no or minimal structural cardiovascular disease (lone AF), hypertensive heart disease (with or without associated significant left ventricular hypertrophy), ischaemic heart disease, or heart failure (mild or moderate to severe) (Fig. 8.3). Alternatively, a classification based on left ventricular function [normal, depressed but left ventricular ejection fraction (LVEF) ≥ 35%, or <35%] can form the primary basis for the choice of an antiarrhythmic drug.

Any of the antiarrhythmic agents can be given to patients with little or no underlying heart disease, when the choice depends on local tradition, the expense and convenience of therapy, non-cardiovascular co-morbidities or the adverse effect profile of the drug (Table 8.2). Generally amiodarone is deferred until the last resort, and sotalol is avoided because of the need for hospitalisation or precautions related to the presence of AF or acquired long QT syndrome. Dofetilide and dronedarone are kept back because of monitoring and expense issues. Flecainide or propafenone are the most usual first-line drugs. Patients with hypertension can be treated similarly if there is no significant left ventricular hypertrophy or likelihood of co-existing coronary heart disease.

In the presence of significant left ventricular hypertrophy sotalol and dofetilide should be avoided because of the risk of QT prolongation and torsades de pointes, especially if potassium-wasting diuretics are also being used, for example to manage hypertension, or if sinus node dysfunction is present. Conventionally flecainide and propafenone are not used because of a fear of proarrhythmia extrapolated from the results of CAST (Cardiac Arrhythmia Suppression Study) [20]. Thus, only dronedarone and amiodarone are available to treat these patients and when hypertrophy is severe as in hypertrophic cardiomyopathy there has only been sufficient clinical experience to be confident about the use of amiodarone.

Flecainide and propafenone are clearly contra-indicated in coronary artery disease because of increased mortality seen in the CAST study when post myocardial infarction patients with active ischemia were exposed to this type of drug. Sotalol, dronedarone and amiodarone are possible treatments; each is anti-ischemic and antiarrhythmic. Some physicians avoid sotalol and dofetilide because of the proarrhythmic risk and others prefer not to use dronedarone because of concerns related to progression to permanent AF and the burden of monitoring liver function. In the USA dofetilide can be used but it is generally relegated until last because of the hurdles of QT interval and potassium monitoring, and the paperwork involved.

Only amiodarone and dofetilide can be considered for all grades of heart failure [21]. In the USA dronedarone can be used in patients with any class of heart failure of heart failure and dronedarone can be given to patients with mild to moderate heart failure but not to those with recently unstable,

Table 8.2 Characteristics of drugs used on a chronic oral basis for the control of recurrent atrial fibrillation

Drug	Dose	Average efficacy at 1 year	Main contraindications and precautions	Monitoring
Disopyramide	100–250 mg t.i.d.	54%	Left ventricular systolic dysfunction, sinus node dysfunction, second and third degree heart block without a pacemaker	ECG: PR, QRS, QTc intervals
			Caution when using concomitant medication with QT-prolonging drugs, intraventricular conduction delay, angle-close glaucoma, prostate enlargement	
Flecainide	100–200 mg b.i.d.	up to 77%	Coronary artery disease with evidence of myocardial ischemia, previous myocardial infarction, left ventricular systolic dysfunction	ECG (baseline and days 1, 2-3, and after dose increase): PR, QRS, QTc intervals, organization into atrial flutter. Consider lower dose or stopping if QRS increase> 25%
Flecanide XL	200 mg o.d.			
			Caution in the presence of conduction system disease and renal impairment (CrCL< 50 ml/min), presence of CYP2D6 inhibitors	Holter: atrial flutter with 1:1 or 2:1 AV conduction
				Renal function, particularly in the elderly patients and those with known CKD
				New onset myocardial ischemia
Propafenone	150–300 mg t.i.d.	40–75%	Coronary artery disease with evidence of myocardial ischemia, previous myocardial infarction, left ventricular systolic dysfunction	ECG (baseline and days 1, 2-3, and after dose increase): PR, QRS, QTc intervals, organization into atrial flutter. Consider lower dose or stopping if QRS increase> 25%
Propafenone SR	225–425 mg b.i.d.			
			Caution in the presence of conduction system disease, renal impairment (CrCL< 50 ml/min) or liver impairment	Holter: atrial flutter with 1:1 or 2:1 AV conduction
			Increases concentration of digitalis and warfarin	New onset myocardial ischemia
d,l-Sotalol	80–160 mg b.i.d.	30–50%; in earlier studies up to 70%	Contraindicated in the presence of significant left ventricular hypertrophy, systolic heart failure, pre-existing QT prolongation, hypokalemia, significant renal dysfunction	ECG (baseline and days 1, 2-3, and after dose increase): QTc interval, heart rate: ventricular tachyarrhythmias, transient repolarization abnormalities (e.g. QT prolongation, abnormal U waves). Consider lower dose or stopping if QT > 500 ms)
			Caution when using concomitantly with QT prolonging drugs, heart failure	Renal function and electrolytes, particularly in the elderly patients and those with known CKD
			Moderate renal dysfunction requires dose titration	
Dofetilide	125–500 mcg b.i.d.	40–65%	Contraindicated in the presence of pre-existing QT prolongation, history or risk of torsade de pointes, creatinine clearance <20 mL/min, hypokalemia, hypomagnesemia	ECG (baseline and days 1, 2-3, and after dose increase) or continuous monitoring for 48 h: ventricular tachyarrhythmias, transient repolarization abnormalities (e.g. QT prolongation, abnormal U waves)
			Caution when using concomitantly with QT prolonging drugs, heart failure	Renal function and electrolytes including magnesium every 6 months
			Dose should be adjusted in accordance with creatinine clearance	
Amiodarone	200 mg in t.i.d. for 4 weeks, 200 mg b.i.d. for 4 weeks, then 100–200 mg daily	52–70%	Caution when using concomitantly with QT prolonging drugs, heart failure, or pre-existing liver disease	ECG: PR, QTc intervals, heart rate
			Dose of warfarin and digoxin may require adjustment (reduction)	Holter: heart rate, transient repolarization abnormalities (e.g. QT prolongation, abnormal U waves)
			Moderate P-Gp inhibitor; caution with NOACs	Creatinine. liver enzymes, thyroid hormones (every 6 months)
				Lung function tests (yearly), chest X-rays if abnormality is detected

(continued)

Table 8.2 (continued)

Drug	Dose	Average efficacy at 1 year	Main contraindications and precautions	Monitoring
Dronedarone	400 mg b.i.d.	33–40%	Contraindicated in the presence of systolic heart failure NYHA class III-IV or unstable or recently decompensated heart failure, pre-existing QT prolongation, significant renal dysfunction	ECG (Baseline, 1 week, 4 weeks or after dose increase): PR, QTc intervals, heart rate
			Caution when using concomitantly with QT prolonging drugs	Creatinine at 7–14 days after the start of treatment and periodically thereafter
			Contraindicated with strong CYP3A4 inhibitors (azole antifungals or protease inhibitors; caution with moderate inhibitors: verapamil and diltiazem	Liver enzymes at 7 days after the start of treatment, monthly during the first 6 months, then at 9 and 12 months; periodically thereafter (1–2 times a year)

CrCl creatinine clearance, *CKD* chronic kidney disease, *AV* atrioventricular, *P-Gp* P glycoprotein, *NOACS* non-vitamin K antagonist oral anticoagulants, *NYHA* New York Heart Association. Modified from the 2016 European Society of Cardiology Guidelines on the management of patients with of atrial fibrillation [14]

NYHA Class IV heart failure patients, especially when the left ventricular ejection fraction is <35%. However, in Europe the use of dronedarone is discouraged in all patients with a history of, or current heart failure or depressed left ventricular function. There is some concern about the use of amiodarone in NYHA class III patients, but there is little or no medical alternative in Europe. In patients with heart failure the risk of negative inotropic and proarrhythmic effects are intensified. Optimal treatment of the haemodynamic aspects of heart failure is crucial.

When there is a strong autonomic background to paroxysms of AF other consideration may apply. For example, antiarrhythmic drugs with anti-muscarinic effects, such as disopyramide or quinidine, can be considered for vagotonic AF (predominantly in the setting of relative bradycardia, in the evening or at week-ends, after meals and associated with alcohol). Drugs with strong anti-sympathetic actions, such as beta-blockers, dronedarone or amiodarone, can be used for patients with paroxysms related to sympathetic stimulation (during mental or physical stress, against a background of relative sinus tachycardia).

Initiation of Antiarrhythmic Drug Therapy

Because of the possibility of a proarrhythmic effect or a deleterious effect on left ventricular function it is important to monitor patients closely during the initiation and maintenance of antiarrhythmic drug therapy [22, 23]. ECGs should be recorded pre-therapy and at appropriate intervals after treatment is started or the dose is increased. Slowing of heart rate, PR interval prolongation, QRS complex widening QT interval prolongation, the development of ST segment elevation or the emergence of late potentials (epsilon waves) are of particular interest. Although it is not very practical to hospitalise patients for the initiation of antiarrhythmic drug treatment it is important to consider this for high-risk patients, or when drugs with a high likelihood of provoking ventricular arrhythmias such as torsades de pointes are used, for example dofetilide. In most instances, initial prescription of low dose therapy and careful outpatient dose titration using trans-telephonic monitoring or repeated 12-lead ECGs can be safely undertaken. When left ventricular function is impaired it is sensible to monitor patients with follow-up echocardiograms at regular interval or whenever symptoms suggestive of heart failure develop or worsen.

In the absence of proarrhythmic concerns and formal labeling, convenience and cost-effectiveness favour out-hospital initiation, particularly if the patient is in sins rhythm. Amiodarone, dronedarone, and sotalol, due to their AV blocking effect and low risk of fast ventricular rates should AF organize into atrial flutter, can be initiated during ongoing atrial fibrillation on an outpatient basis. It is acceptable to initiate propafenone and flecainide out-of-hospital in patients with lone AF after adequate AV blockade with a beta-blocker or a rate-slowing calcium channel blocker has been prescribed—see also "pill in the pocket" approach.

Assessment of Rhythm Control

It seems straightforward to follow patients with symptomatic AF because the occurrence of symptoms suggests recurrence of the arrhythmia. However, experience with intensive ECG monitoring of patients enrolled in drug studies or following ablation procedures has demonstrated that there is often little association between symptoms and AF episodes. In many cases there are far more asymptomatic than symptomatic recurrences and in some patients recurrences are almost always asymptomatic. Therefore, it is important to consider

prolonged monitoring if the recurrence of asymptomatic episodes is important to therapeutic decisions. Usually, in patients who are adequately anticoagulated silent recurrences of AF are unimportant, but if a physician intends to base decisions relating to anticoagulation or to supplementary rate control on the presence or absence of AF episodes intensive ECG monitoring is needed, for example 48-h to 7-day Holter or patch monitoring every 2 or 3 months, or even continuous monitoring with an implantable loop recorder. This form of ECG data collection is also frequently needed for research studies.

When a patient has intermittent symptoms and the likelihood of recurrence is high, but undocumented, the physician should resort to Holter ECG monitoring if the recurrences are sufficiently frequent (1 or 2 attacks per day when 24-h monitoring is contemplated and 1 or 2 attacks per week when 7-day ECG monitoring is proposed). Less frequent recurrences are best documented with event recorders or long-term (2–4 week) patch ECG recorders. Increasingly patients and physicians are turning to the use of smart phones with modifications to allow ECG recording and transmission to the physician or third party vendor. When paroxysms are identified the physician should explore the mechanism of AF initiation, the stability or otherwise of the arrhythmia and the ventricular rate during episodes of AF. Appropriate revision of treatment can then be designed.

Comparative Efficacy of Antiarrhythmic Drugs

The superiority of one antiarrhythmic drug over another has long been debated, mainly due to a relatively small number and sub-optimal design of direct comparison studies and their inconsistent results as well as enrolment of patients with different underlying cardiovascular pathologies. A recent Cochrane review provides a systematic analysis of efficacy, mortality and proarrhythmia associated with antiarrhythmic drugs [24] (Fig. 8.4).

Beta-Blockers

There is no evidence in patients with AF that treatment with beta blockers reduces mortality, even when heart failure is present. Beta blockers are modestly effective in preventing AF (~30–50%) and are mainly used for rate control. An exception is adrenergically-mediated AF, AF caused by thyrotoxicosis, and AF after cardiac surgery, in which case beta-blockers may be a first-line therapy. Nevertheless, metoprolol was superior to placebo [25], and bisoprolol was effective as sotalol [26] for prevention of recurrent AF.

Some beta-blockers such as carvedilol may be more potent antiarrhythmics because of their direct effects on

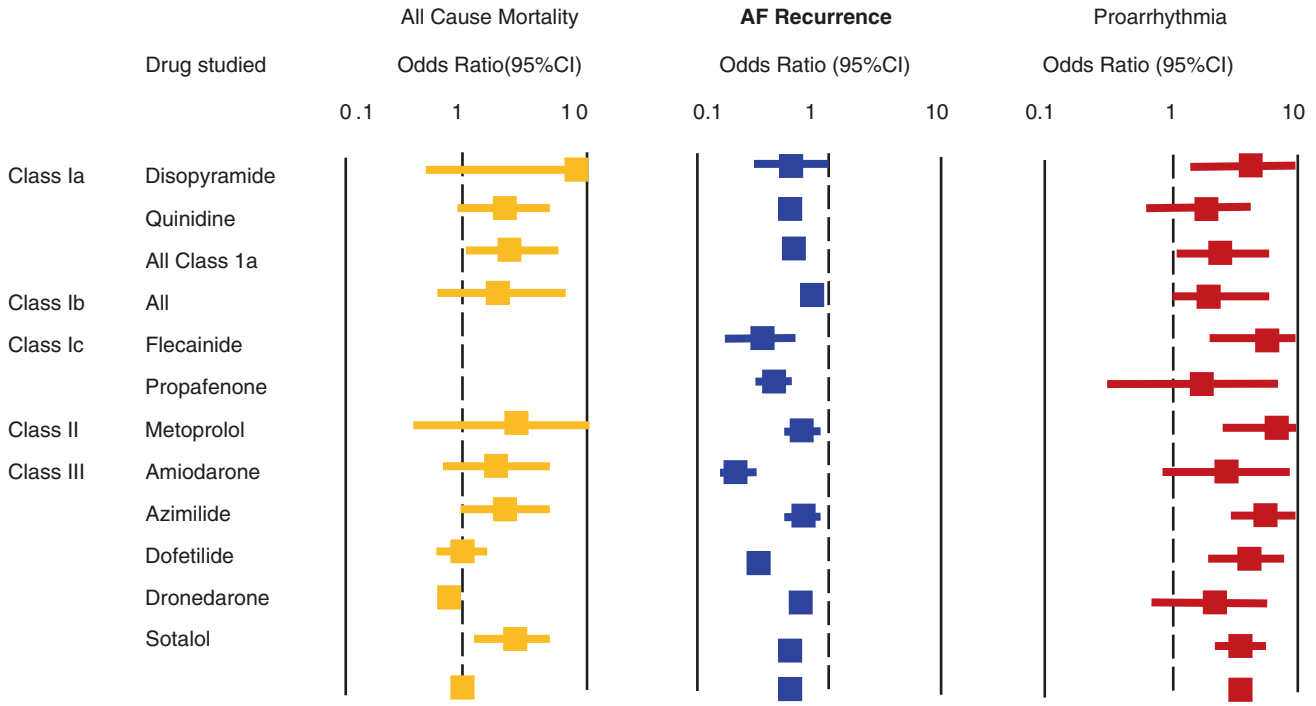


Fig. 8.4 Mortality, AF recurrences and proarrhythmia associated with antiarrhythmic drug therapy for maintenance of sinus rhythm in patients with AF. The data are taken from Cochrane systematic reviews conducted by LaFuente-LaFuente C. et al. (see references)

cardiac ion channels beyond their anti-adrenergic action. In addition, carvedilol has antioxidant activity and may protect the atrial myocardium from oxidative injury caused by fast atrial rates and ischemia. In direct comparisons, carvedilol demonstrated no benefit over bisoprolol, although a higher proportion of patients treated with carvedilol completed the 1-year study in sinus rhythm [27].

Disopyramide

Disopyramide is rarely used for treatment of AF, mainly because of its negative inotropic effect and poor tolerance due to anti-muscarinic properties as well as proarrhythmias. However, the use of disopyramide is advocated in patients with lone, vagally-mediated AF. The efficacy of disopyramide was reported to be 70% at 1 month, 67% at 6 months, and 54% at 1 year after electrical cardioversion [28, 29].

Propafenone and Flecainide

Propafenone and flecainide are recommended as first-line therapy for AF in patients without significant structural heart disease such as heart failure, hypertension with left ventricular hypertrophy, previous myocardial, or coronary artery disease with documented myocardial ischemia. Both propafenone and flecainide reduced the recurrence rate by two-thirds, with no advantage of one drug over the other. In direct comparisons, flecainide and propafenone prevented AF in 77% and 75% patients, respectively [30]. In a meta-analysis of propafenone, the incidence of recurrent AF was 55.4% (51.3–59.7%) at 6 months and 56.8% (52.3–61.3%) at 1 year [31]. All-cause mortality associated with propafenone was 0.3%. Both agents are available in modified-release formulations (Propafenone-SR and Flecainide-XL). Because of the danger of organization of AF into atrial flutter with 1:1 or 2:1 conduction (Fig. 8.5), concomitant use of AV slowing agents such as beta-blockers and calcium channel blockers are recommended.

Sotalol

Sotalol has proven an effective and safe prophylactic antiarrhythmic drug in patients with AF and stable coronary artery disease in the absence of previous myocardial infarction and left ventricular systolic dysfunction, and patients with hypertension without evidence of left ventricular hypertrophy. Because of its beta-blocking effect, sotalol offers the additional benefit of ventricular rate slowing during recurrences.

However, in CTAF (Canadian Trial of Atrial Fibrillation), sotalol was significantly inferior to amiodarone for the long-term maintenance of sinus rhythm (37% vs. 65%) [32]. In SAFE-T (Sotalol Amiodarone Atrial Fibrillation Efficacy Trial), sotalol was also less effective than amiodarone post-cardioversion for persistent AF (the median time to a recurrence was 6 days on placebo, 74 days of sotalol, and 487 days on amiodarone) [33]. At 2 years, approximately 30% of patients treated with sotalol remained in sinus rhythm compared with 60% of patients on amiodarone and 10% of patients on placebo. The efficacy of sotalol was like that of class I antiarrhythmic drugs and inferior to that of amiodarone in the AFFIRM substudy (48%, 45%, and 66%, respectively) [34].

Hypotension and bradycardia are the most common cardiovascular adverse effects of sotalol with the incidence of 6–10%. Proarrhythmias associated with QT interval prolongation were observed in 1–4% of patients, usually within 72 h after the first dose.

Dofetilide

Unlike propafenone, flecainide, and sotalol, dofetilide is safe to use in patients with previous myocardial infarction and/or heart failure. In the DIAMOND (Danish Investigations of Arrhythmia and Mortality ON Dofetilide) AF substudy of DIAMOND-CHF and DIAMOND-MI trials, 506 patients with AF at baseline were more likely to remain in sinus rhythm on treatment with dofetilide 500 mg twice daily compared with placebo (79% vs. 42%) [35].

In the dose-ranging SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) study of

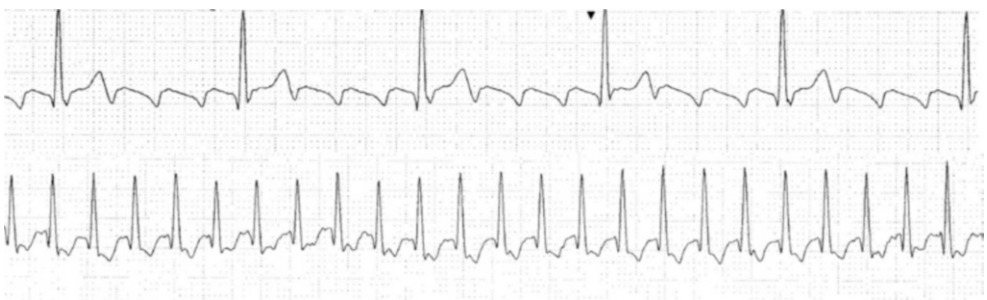


Fig. 8.5 Monitored ECG recordings from a patient receiving therapy with a class IC antiarrhythmic drug. Atrial flutter *upper trace* is slowed and conducts 1:1 to the ventricles leading to an increase in the ventricular rate *lower trace*

325 patients with persistent AF or flutter for 2–26 weeks, dofetilide exhibited a dose-related effect: 40%, 37%, and 58% patients receiving 250, 500, and 1000 mg of dofetilide, respectively, were in sinus rhythm after 1 year compared with 25% in the placebo group [36].

The major safety concern about dofetilide is its torsadogenic potential which is dose-related and often occurs within the first 48–72 h after the start of treatment in up to 3.3% of patients. This made the in-hospital initiation of dofetilide mandatory.

Amiodarone

The potential of amiodarone to maintain sinus rhythm in patients with AF and a relative cardiac safety in patients with significant structural heart disease has been repeatedly shown in observational and prospective, randomized, controlled studies. Data from the CHF-STAT (Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy) substudy showed that patients who received amiodarone had fewer recurrences of AF and were twice as less likely to develop new AF compared with placebo [37]. The safety of amiodarone was indirectly demonstrated in the AF-CHF study [3].

Amiodarone has a low torsadogenic potential (<1%). Given its neutral effect on all-cause mortality, amiodarone should be considered a drug of choice for management of AF in patients with congestive heart failure, hypertrophic cardiomyopathy and hypertension with significant left ventricular hypertrophy. However, there was a warning from the recent subgroup analysis of SCD-HeFT (SCD-Sudden Cardiac Death in Heart Failure Trial) which has suggested that amiodarone was associated with excess mortality in patients with NYHA III heart failure [38].

Dronedarone

The antiarrhythmic potential of dronedarone has been studied in two high quality, medium size efficacy and safety trials. The EURIDIS (EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm) and its American-Australian-African equivalent ADONIS, have shown that dronedarone was superior to placebo in prevention of recurrent paroxysmal and persistent AF and was also effective in controlling ventricular rates [39].

ANDROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate to severe heart failure Evaluating morbidity DecreAse), which was conducted in patients with severe congestive heart failure, was stopped prematurely after 627 patients out of the 1000 planned were enrolled, because an interim safety analysis revealed an excess of deaths in the dronedarone arm compared with placebo (8% vs. 13.8%; hazard ratio 2.13, 95% CI, 1.07–4.25; p = 0.027) [40]. Although ANDROMEDA clearly defined a population that should not receive dronedarone, it did little else to clarify the safety profile of the drug.

The post hoc analysis of the EURIDIS and ADONIS studies showed that patients treated with dronedarone had a 27% reduction in relative risk of hospitalization for cardiovascular causes and death (22.8% vs. 30.9% on placebo). Subsequently, the ATHENA (A placebo controlled, double blind Trial to assess the efficacy of dronedarone for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation and flutter) trial in 4628 high-risk patients has demonstrated that therapy with dronedarone prolonged time to first cardiovascular hospitalization or death from any cause (the composite primary endpoint) by 24% compared with placebo [41]. This effect was driven by the reduction in cardiovascular hospitalizations (25%), particularly hospitalizations for AF (37%). All-cause mortality was similar in the dronedarone and placebo groups (5% and 6%, respectively); however, dronedarone significantly reduced deaths from cardiovascular causes. Post hoc analysis suggested that stroke might also have been reduced by treatment with dronedarone.

In the ATHENA study, there were 473 patients who seemed to remain in AF throughout the study. A retrospective analysis of these patients showed that fewer of these patients were in the dronedarone group (178 vs. 295), and that those treated with dronedarone had a similar reduction of the primary ATHENA endpoint (HR = 0.76) as for the trial population in general [42]. Subsequently, the PALLAS (Permanent Atrial fibriLLAtion outcome Study) in patients with AF and risk factors was instigated, but was stopped prematurely due to excess of adverse events in the dronedarone arm [43].

PALLAS enroled patients over 64 years of age with at least a 6-month history of permanent atrial fibrillation and risk factors for major vascular events and randomised them to receive dronedarone or placebo. After enrolment of 3236 patients, the study was stopped because the primary outcomes occurred in significantly more patients receiving dronedarone than those receiving placebo. There were 21 deaths from cardiovascular causes in the dronedarone group and 10 in the placebo group (hazard ratio, 2.11; 95% CI, 1.00 to 4.49; P = 0.046), including death from arrhythmia in 13 patients and 4 patients, respectively (hazard ratio, 3.26; 95% CI, 1.06 to 10.00; P = 0.03). The exceed in deaths were confined to patients who were also taking digoxin, suggesting the possibility of a drug-drug interaction. In contrast to ATHENA stroke also occurred more commonly in the dronedarone group (23 patients vs. 10) and hospitalization for heart failure was also seen in more patients treated with dronedarone. The patients in PALLAS were very largely in

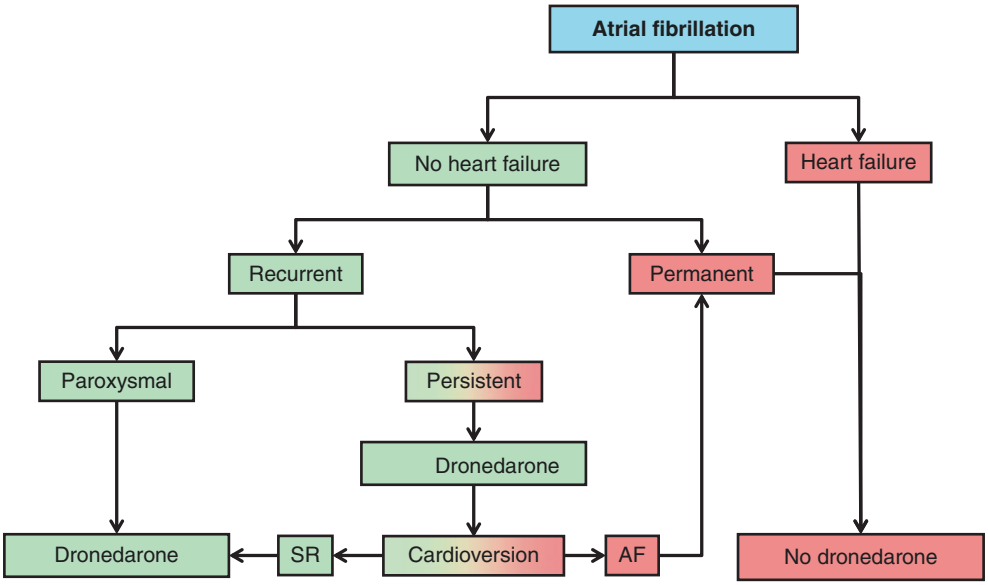


Fig. 8.6 Flow chart explaining the decision process regarding the use of dronedarone for symptom control in patients with intermittent AF

permanent AF, whereas most patients in ATHENA had recurrent forms of AF and many were in sinus rhythm for most the trial. Any advantage from achieving sinus rhythm was not possible in PALLAS [44].

Since PALLAS the results of the HESTIA study (The Effects of Dronedarone on Atrial Fibrillation Burden in Subjects with Permanent Pacemakers) have been reported. 112 AF patients fitted with pacemakers were randomized to dronedarone or placebo. During a 12-week study period, AF burden decreased by 54.4% (0.22) ($P = 0.0009$) with dronedarone and increased by 12.8% (0.16) ($P = 0.450$) with placebo [45].

A study based on the United States Department of Defense Electronic Health Record database compared new initiators of DR and "other AADs" using 1:2 propensity matching to reduce selection bias. There were no differences in cardiovascular hospitalizations (8.4 vs. 7.8%, respectively; hazard ratio = 1.16 [CI, 0.96–1.40; p = 0.117]) or cardiovascular death rates (both 0.1%; hazard ratio = 1.62 [CI, 0.17–15.6; p = 0.677]). The study showed was that there was no increased risk of cardiovascular deaths/hospitalizations associated with dronedarone [46].

A recently reported systematic review also showed that real-life evidence of dronedarone use was not associated with increased all-cause mortality [OR (Odds Ratio) 1.36, 95% CI 0.79–2.33; p = 0.732, I2 = 57.0%] or cardiovascular mortality [OR 1.51 95%CI 0.74–3.08; p = 0.860, I2 = 64.4%]. Only two variables, co-administration with digoxin and the prevalence of non-permanent AF accounted for the heterogeneity of results. The conclusion was that the use of dronedarone for prophylaxis of AF recurrences is not associated with an increased risk of death, but that combination with digoxin should be avoided [47].

Dronedarone is currently recommended for reducing the need for hospitalization for cardiovascular events in at-risk patients with paroxysmal AF or after conversion of persistent AF, but should not be used in patients with permanent AF or advanced or recently decompensated heart failure (Fig. 8.6). Co-administration with digoxin should be avoided.

Optimizing the Use of Antiarrhythmic Drugs: Special Situations

Shortening the Duration of Therapy

Systematic reviews of antiarrhythmic drug treatment in AF demonstrate convincing evidence of efficacy, but also underscore the risk of adverse effects, including proarrhythmia and increased mortality [48–50]. One approach to mitigate this problem is to restrict the drug dose and period of treatment. The reason to explore this strategy is that antiarrhythmic drug suppression of AF for a few weeks or months following conversion to sinus rhythm may give enough time for reverse atrial electrical remodelling to occur, so that AF recurrence would then be less likely, even after cessation of antiarrhythmic drug treatment.

A few trials have investigated this possibility. The Flec-SL (Flecainide Short Long) trial in 635 patients has shown that short-term antiarrhythmic drug therapy limited to 4 weeks after cardioversion resulted in less, but clinically relevant antiarrhythmic effect on AF recurrence, about 80% of the effect of long-term treatment over the first 6 months post cardioversion [51]. However, the follow-up was short, and it may be that long-term treatment is

necessary because simply reducing AF-induced atrial remodelling may not be enough to counteract reversal of the electrophysiological and structural effects due to age and underlying heart disease [52]. Another study with intermittent amiodarone treatment was not as effective as continuous amiodarone in terms of a composite outcome including efficacy and safety events [53].

These trials suggest that it may be worthwhile restricting antiarrhythmic therapy to a short period after cardioversion for patients at high risk of adverse effects due to antiarrhythmic drug treatment but that in most cases long term therapy will be needed.

Postoperative Atrial Fibrillation

AF may complicate cardiac or thoracic surgery and usually occurs on the 2nd to 4th postoperative day. Following cardiac surgery AF may occur in up to 30% of patients. It is thought to be largely due to inflammation (sterile pericarditis), but other factors such as the cessation of protective therapies prior to surgery, e.g. beta-blockers, underlying heart or lung disease, surgical trauma, exposure to anaesthetics and inotropes, electrolyte disturbances, oxidative stress and postoperative infections may all play a role. Antiarrhythmic drugs may be used to prevent the development of postoperative AF or to manage the arrhythmia once it has presented. At this point, however, because of its potentially transient and self-limiting nature short term rate control may be all that is needed. Other factors that may have contributed to the emergence of the arrhythmia must also be actively managed.

Beta blockers such as bisoprolol or metoprolol, and antiarrhythmic drugs for example sotalol and amiodarone have been shown to reduce the likelihood of postoperative AF [54–56]. Magnesium therapy, perhaps by reducing electrolyte abnormalities has been found to be helpful [57]. Anti-inflammatory strategies with colchicine and corticosteroids have also been explored. Most of these approaches are not employed. However, it is particularly important that patients should not stop regular treatment with beta-blockers prior to surgery.

When postoperative AF occurs it may be managed expectantly or with rate control, usually with beta-blockers. A recent trial 523 patients were randomized after cardiac surgery to rate or rhythm control. There were no significant differences in the rates of death (P = 0.64) or overall serious adverse events (24.8 per 100 patient-months in the rate-control group and 26.4 per 100 patient-months in the rhythm-control group, P = 0.61), including thromboembolic and bleeding events [58]. When needed, amiodarone is the most frequently used antiarrhythmic and has the advantage of also slowing the ventricular rate. Vernakalant is approved in Europe for post-operative management of AF [59] and there are reports of the successful use of ranolazine, although it is not approved for this purpose.

Proarrhythmia

The recognition of proarrhythmia came to the fore with the publication cases of syncope in patients taking quinidine which were shown to be due to polymorphic ventricular tachycardia occurring against a background of quinidine induced QT interval prolongation [60]. This arrhythmia subsequently became known by the French term “torsades de pointes” [61]. Many drugs which reduce outward repolarising current, for example IKr and IKs or increase inward depolarising currents such as INaL may induce prolongation of ventricular myocardial action potential duration and dispersion of the duration of repolarisation in different myocardial layers (epicardium, mid-myocardium, endocardium and Purkinje tissue) giving rise to early after depolarisations which induce ventricular arrhythmia in the disturbed ventricular electrophysiologic substrate. The most powerful drugs that may cause this arrhythmia are those designed and developed as antiarrhythmic agents, particularly class IA (e.g., quinidine and disopyramide) [62] and Class III (e.g., sotalol) [63] This arrhythmia is more likely to occur in specific settings, such as when drug elimination is compromised, or when bradycardia, hypokalemia, or hypomagnesemia occur. The potential of this form of proarrhythmia to impair survival was well illustrated in the SWORD (Survival With Oral D-sotalol) trial when d-sotalol was given to patients with left ventricular dysfunction following myocardial infarction [64]. Immediately following cardioversion of AF is an especially vulnerable period.

Ventricular proarrhythmia may also occur when ventricular myocardial conduction is slowed or blocked or when Brugada syndrome electrophysiological circumstances are provoked. Class IC (e.g., flecainide, propafenone, or pilsicainide) and Class IA antiarrhythmic dugs (e.g., ajmaline or procainamide) may induce these circumstances. This proarrhythmia is more likely to occur when ventricular scarring or Brugada physiology due to underlying genetic polymorphisms are present. J waves or early repolarisation may be seen on the ECG, even before drug administration. The powerful proarrhythmic potential of Class IC drugs was first demonstrated in the Cardiac Suppression Trial (CAST), and the Cardiac Arrest Study Hamburg (CASH) [65] when fatal arrhythmias or cardiac arrest occurred more frequently when patients were treated with, for example flecainide.

Proarrhythmia may also occur at the atrial level. Sinus node dysfunction may be aggravated and AV conduction impaired by most antiarrhythmic drugs including class I and class III antiarrhythmic agents. AF may be converted to slow atrial flutter with 1:1 AV conduction and a resulting rapid

ventricular rate. This may occur in about 10% of patients in whom pharmacologic cardioversion is attempted. For this reason, it is advised to co-prescribe an agent which impairs AV nodal conduction such as a beta blocker or a non-dihydropyridine calcium channel antagonist whenever a class IA or IC drugs is used to restore or maintain sinus rhythm in patients with atrial fibrillation.

Ablation

Interventional techniques are highly effective therapies for patients who remain symptomatic despite optimal medical therapy. AV nodal ablation and pacemaker implantation may be considered if the heart rate during AF cannot be adequately controlled and there is little likelihood of restoring and maintaining sinus rhythm even with left atrial ablation. This procedure is suitable for older patients, but should generally be avoided in the young if alternative strategies such as left atrial ablation are available.

If antiarrhythmic drugs fail to prevent symptomatic recurrences of paroxysmal AF, particularly if several drugs alone and in combination have been tried, it is useful to undertake left atrial ablation, usually pulmonary vein isolation. This is a relatively straightforward and effective technique, but is complicated by a small incidence of stroke, atrio-esophageal fistula, major bleeding and vascular damage. Guidelines strongly recommend this approach, and in some instances advocate considering the use of left atrial ablation prior to trials of antiarrhythmic drug therapy. Guidelines are generally less enthusiastic about recommending let atrial ablation for persistent or long-standing persistent AF, but the technique is frequently employed for this indication.

There have been several randomised trials comparing antiarrhythmic drugs and left atrial ablation as first-line therapy for intermittent, usually paroxysmal AF [66, 67]. Both studies have shown that left atrial ablation is not worse than antiarrhythmic drugs at delaying the time to recurrence of AF or reducing the burden of the arrhythmia [68], although they were not large enough to show conclusive non-inferiority. Not all studies have convincingly demonstrated superiority of left atrial ablation over antiarrhythmic drugs, but generally the results have shown less recurrences of AF after ablation.

Often, LA ablation is not completely successful at eradicating all episodes of AF and the administration of antiarrhythmic drugs is deemed necessary. It seems that short term antiarrhythmic drug therapy in the immediate post-ablation period may decrease AF recurrences but this reduced AF burden does little to prevent long-term recurrences or encourage reversal of atrial remodelling. Post ablation continued antiarrhythmic drug therapy may be successful when prior to ablation it had not helped to control the arrhythmia. For example, a recent database study showed that treatment with antiarrhythmic drugs following catheter ablation was associated with a decrease in hospital readmissions within 90 days (11.6% vs. 16.2%) [69].

The 5A Trial AntiArrhythmics After Ablation of Atrial Fibrillation) enroled 110 patients (age 55 ± 9 years, 71% male), and 53 were randomized after left atrial ablation to antiarrhythmic therapy and 57 to no antiarrhythmics. In the short-term post ablation period AF occurred in 19% of those treated with antiarrhythmics versus 42% ($p < 0.005$) who had no such treatment [70]. However, in the long-term, at 6 months, there was no difference between the groups [71]. Similarly AMIO-CAT (AMIOdarone after CATheter ablation for AF) which randomized 212 patients showed a reduction in atrial tachyarrhythmias in the blanking period when treated with amiodarone but there was no difference between the groups at 6 months [72]. Finally the Kansai Plus Atrial Fibrillation (KPAF) trial randomised 2120 patients and confirmed the results of these major but smaller trials by showing no difference between groups in the recurrence of atrial tachyarrhythmias at 1-year with a blanking period of 90 days post ablation [73].

Again, the major reason for using antiarrhythmic drugs after ablation is purely to reduce the symptoms associated with arrhythmia recurrences.

New Antiarrhythmic Drugs

There are many attempts to identify new drug targets and to develop new antiarrhythmic medications. Many dugs have been shown active in tissue preparations and effective in the animal laboratory but have not been successfully developed because of non-cardiac adverse effects, proarrhythmia or clinical ineffectiveness. Some compounds remain very promising and are undergoing further development.

Ranolazine

Recently, ranolazine, an agent developed to treat chronic stable angina, which selectively inhibits predominantly the late component of the sodium current (INa) [74], has been shown to improve the success of electrical cardioversion or cardioversion in response to amiodarone, and possibly to delay recurrence of AF in patients post cardioversion [75]. The RAFFAELLO (Ranolazine in Atrial Fibrillation Following An ELectricaL CardiOversion) study was a prospective, randomized, double-blind, placebo-control dose-ranging trial involving 241 patients with persistent AF after successful electrical cardioversion who were randomised to placebo, or one of several doses of ranolazine. Ranolazine was safe and well tolerated. No dose of the drug significantly prolonged time to AF recurrence but overall AF recurrence

in the combined higher dose groups was borderline significant. The study was limited by its small size and the restriction to a top dose of 750 mg bid [76].

Ranolazine seems to be effective and safe when used in a "pill-in-the-pocket" strategy even in patients with underlying heart disease [77]. Ranolazine is approved for the treatment of chronic stable angina and for long QT3, but is not approved for the treatment of AF.

Studies in the laboratory and in the clinic suggest that ranolazine may work synergistically with amiodarone or dronedarone [78]. The HARMONY trial tested dronedarone and amiodarone independently and two combination of dronedarone and ranolazine against placebo in 134 patients with recurrent AF who were fitted with implanted pacemakers capable of logging the onset and duration of AF. Over a 3-month observation period neither placebo nor either drug alone significantly reduced AF but both ranolazine/dronedarone combinations reduced AF (lower dose by 43% [P = 0.072) and higher dose by 59% vs. placebo [P = 0.008]) and were well tolerated [79]. Further development of a fixed dose combination is awaited, and until then using a combination of these drugs (or amiodarone plus ranolazine) may prove hazardous because the doses available to the clinician are untested and potentially hazardous because of drug-drug interactions.

Eleclazine, another and more specific slow INa inhibitor, has recently been tested in experimental animals [80, 81]. The results suggest that this drug will prove an effective antiarrhythmic agent for treatment of AF, but clinical results are not yet available. Since the drug has not proven successful at preventing ventricular arrhythmias it may not be further developed.

Budiodarone

Budiodarone, a mixed ion channel inhibitor, is an analogue of amiodarone which is engineered to retain the antiarrhythmic effects of amiodarone but to be rapidly metabolised by serum and cellular esterase enzymes and avoid tissue accumulation. The iodine moieties are retained and the drug may be expected to have the same effects on thyroid function as amiodarone. The drug has been evaluated in one small proof of concept study in six AF patients with implanted pacemakers and showed a significant reduction in the burden of AF [82]. A larger study, PASCAL (Paroxysmal Atrial fibrillation Study with Continuous Atrial fibrillation Logging) in 72 pacemaker patients was a randomised study of three doses of budiodarone versus placebo over a period of 4 months (1 month baseline and 3 months treatment). Sixty-one patients completed the study and pacemaker logs demonstrated a median reduction of AF by up to 74% ($p < 0.001$) with the highest dose of dronedarone with a significant dose-response ($p < 0.001$) [83]. This drug seemed very promising but was complicated by gastro-intestinal side effects and still awaits phase 3 development.

Atrial Repolarisation Delaying Agents (ARDAs)

Atrial specific ion channel inhibitors, such as IKACh blockers (e.g., BMS 914392 or NTC 801 [84]) and IKur antagonists (e.g., BMS-919373 or D0103 [85]) are being developed because they have little effect on ventricular electrophysiology whilst causing significant prolongation of atrial refractoriness in animal and human tissues. It is anticipated that these drugs will not provoke ventricular proarrhythmia whilst being effective antiarrhythmic agents for AF suppression. Unfortunately, so far phase II trials involving pacemaker patients with AF have not shown significant clinical efficacy [86], but other studies continue with some compounds.

Small-Conductance Calcium-Activated Potassium Channels

Specific SK blocking compounds (e.g., NS8593 [87]) are under development. Small-conductance calcium-activated potassium channels are widely expressed in the nervous system, vascular endothelium, skeletal muscle, smooth muscle, and cardiac myocytes. In animal studies (canines and rodents) SK-current blockers have been shown to increase atrial action potential duration and atrial refractoriness, and have demonstrated clear in vivo anti-AF effects. They have not yet been studied in humans and there are some concerns related to ventricular proarrhythmia.

Conclusions

The current estimate of the global prevalence of AF suggests that over 30 million patients suffer from the arrhythmia. Life-style factors and underlying heart disease seem to account for most these cases, and the physician should give much attention to rectifying these causative factors. Some of the treatment for underlying disease, such as angiotensin receptor antagonists for hypertension, may specifically act as an upstream form of therapy suppressing AF. Once thromboembolic issues have been assessed and treated most patients will require rate or rhythm control to reduce the symptomatic burden. Although rate control is preferred and satisfactory for many patients others will need rhythm control. Left atrial ablation may eradicate AF in some, and help many by reducing the frequency or duration of attacks. Antiarrhythmic drugs are needed for most rhythm control patients but only a few agents are available. These drugs are potentially complicated by

adverse effects, particularly proarrhythmia which may explain why, despite their antiarrhythmic efficacy, they are not associated with improved survival and may in some circumstances lead to increased mortality. There is a constant search for new antiarrhythmic agents with a better benefit-risk ratio, and several new drugs, at present waiting in the wings, may fulfil this promise.

References

1. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825–33.
2. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347:1834–40.
3. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358:2667–77.
4. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. J Interv Card Electrophysiol. 2000;4:369–82.
5. De Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, van den Heijkant AC, Allessie MA, Crijns HJ. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. J Am Coll Cardiol. 2010;55:725–31.
6. Nattel S, Guasch E, Savelieva I, Cosio FG, Valverde I, Halperin JL, et al. Early management of atrial fibrillation to prevent cardiovascular complications. Eur Heart J. 2014;35:1448–56.
7. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92(7):1954–68.
8. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH, ESC Committee for Practice Guidelines. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010;12(10):1360–420. doi:10.1093/europace/euq350.
9. The 'Sicilian Gambit'. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. The Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. Eur Heart J. 1991;12(10):1112–31.
10. Camm AJ. Safety considerations in the pharmacological management of atrial fibrillation. Int J Cardiol. 2008;127:299–306.
11. Vaughan Williams EM. Classification of antidysrhythmic drugs. Pharmacol Ther B. 1975;1(1):115–38.
12. Capucci A, Villani GQ, Aschieri D, Rosi A, Piepoli MF. Oral amiodarone increases the efficacy of direct-current cardioversion in restoration of sinus rhythm in patients with chronic atrial fibrillation. Eur Heart J. 2000;21:66–73.
13. Savelieva I, Graydon R, Camm AJ. Pharmacological cardioversion of atrial fibrillation with vernakalant: evidence in support of the ESC Guidelines. Europace. 2014;16:162–73.
14. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016;18(11):1609–78.
15. Camm AJ, Savelieva I. Some patients with paroxysmal atrial fibrillation should carry flecainide or propafenone to self treat. BMJ. 2007;334:637.
16. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. J Am Coll Cardiol. 2001;37:542–7.
17. Khan IA. Oral loading single dose flecainide for pharmacological cardioversion of recent-onset atrial fibrillation. Int J Cardiol. 2003;87:121–8.
18. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, Marchi P, Calzolari M, Solano A, Baroffio R, Gaggioli G. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. N Engl J Med. 2004;351:2384–91.
19. Camm AJ, Savelieva I. Some patients with paroxysmal atrial fibrillation should carry flecainide or propafenone to self treat. BMJ. 2007;334:637.
20. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med. 1991;324:781–8.
21. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014;130(23):e199–267. doi:10.1161/CIR.0000000000000041. Erratum in: Circulation. 2014 Dec 2;130(23):e272–4.
22. Pinski SL, Helguera ME. Antiarrhythmic drug initiation in patients with atrial fibrillation. Prog Cardiovasc Dis. 1999;42(1):75–90.
23. Reiffel JA. Inpatient versus outpatient antiarrhythmic drug initiation: safety and cost-effectiveness issues. Curr Opin Cardiol. 2000;15:7–11.
24. Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF, Belmin J. Antiarrhythmics or maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2012;(5):CD005049.
25. Kühlkamp V, Schirdewan A, Stangl K, Homberg M, Ploch M, Beck OA. Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol. 2000;36:139–46.
26. Plewan A, Lehmann G, Ndrepepa G, Schreieck J, Alt EU, Schömig A, Schmitt C. Maintenance of sinus rhythm after electrical cardioversion of persistent atrial fibrillation: sotalol vs bisoprolol. Eur Heart J. 2001;22:1504–10.
27. Katritsis DG, Panagiotakos DB, Karvouni E, Giazitzoglou E, Korovesis S, Paxinos G, Anagnostopoulos CE, Camm AJ. Comparison of effectiveness of carvedilol versus bisoprolol for maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation. Am J Cardiol. 2003;92:1116–9.
28. Karlson BW, Torstensson I, Abjörn C, Jansson SO, Peterson LE. Disopyramide in the maintenance of sinus rhythm after electroconversion of atrial fibrillation. A placebo-controlled one-year follow-up study. Eur Heart J. 1988;9:284–90.
29. Crijns HJ, Gosselink AT, Lie KI. Propafenone versus disopyramide for maintenance of sinus rhythm after electrical cardiover-

sion of chronic atrial fibrillation: a randomized, double-blind study. PRODIS Study Group. Cardiovasc Drugs Ther. 1996;10:145–52.
30. Chimienti M, Cullen MT Jr, Casadei G. Safety of long-term flecainide and propafenone in the management of patients with symptomatic paroxysmal atrial fibrillation: report from the Flecainide and Propafenone Italian Study Investigators. Am J Cardiol 1996;77:60A-75A.
31. Reimold SC, Maisel WH, Antman EM. Propafenone for the treatment of supraventricular tachycardia and atrial fibrillation: a meta-analysis. Am J Cardiol. 1998;82:66N–71N.
32. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagné P, Nattel S, Thibault B, for the Canadian Trial of Atrial Fibrillation Investigators. Amiodarone to prevent recurrence of atrial fibrillation. N Engl J Med. 2000;342:913–20.
33. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med. 2005;352:1861–72.
34. The AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM Substudy of First Antiarrhythmic Drug. J Am Coll Cardiol. 2003;42:20–9.
35. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function. A Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) Substudy. Circulation. 2001;104:292–6.
36. Singh S, Zoble RG, Yellen L, Brodsky MA, Feld GK, Berk M, et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) Study. Circulation. 2000;102:2385–90.
37. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN, for the Department of Veterans Affairs CHF-STAT Investigators. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT). Circulation. 1998;98:2574–9.
38. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225–37.
39. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH, EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med. 2007;357:987–99.
40. Køber L, Torp-Pedersen C, McMurray JJ, Gøtzsche O, Lévy S, Crijns H, Amlie J, Carlsen J, Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med. 2008;358:2678–87.
41. Hohnloser SH, Connolly SJ, Crijns HJ, Page RL, Seiz W, Torp-Petersen C. Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter. J Cardiovasc Electrophysiol. 2008;19:69–73.
42. Nieuwlaat R, Hohnloser SH, Connolly SJ. Effect of dronedarone in patients with permanent atrial fibrillation during the ATHENA study. Eur Heart J. 2011;32(Suppl):618.
43. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med. 2011;365:2268–76.
44. Camm AJ, Savelieva I. Dronedarone for the treatment of non-permanent atrial fibrillation: National Institute for Health and Clinical Excellence guidance. Heart. 2013;99:1476–80.
45. Ezekowitz MD, Ellenbogen KA, DiMarco JP, Kaszala K, Boddy A, Geba GP, Koren A. A placebo-controlled, double-blind, randomized, multicenter study to assess the effects of dronedarone 400 mg twice daily for 12 weeks on atrial fibrillation burden in subjects with permanent pacemakers. J Interv Card Electrophysiol. 2015;42(2):69–76. doi:10.1007/s10840-014-9966-z.
46. Goehring E., Bohn R, Pezzullo J. and Jones J. Real-world outcomes for dronedarone initiators compared to other antiarrhythmic drugs in the treatment of atrial fibrillation in a large United States population. J Am Coll Cardiol. 2013;61(10_S). doi:10.1016/S0735-1097(13)60269-7.
47. Diemberger I, Massaro G, Reggiani ML, Lorenzetti S, Biffi M, Ziacchi M, Martignani C, Boriani G. Outcomes with dronedarone in atrial fibrillation: what differences between real-world practice and trials? a meta-analysis and meta-regression analysis. Curr Pharm Des. 2016;
48. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Bergmann JF. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2007;(4):CD005049.
49. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. Europace. 2011;13:329–45.
50. Lafuente-Lafuente C, Valembois L, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2015;(3):CD005049.
51. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, et al. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. Lancet. 2012;380:238–46.
52. Camm AJ, Savelieva I. The long and short of antiarrhythmic drug treatment. Lancet. 2012;380:198–200.
53. Ahmed S, Rienstra M, Crijns HJ, Links TP, Wiesfeld AC, Hillege HL, et al. Continuous vs. episodic prophylactic treatment with amiodarone for the prevention of atrial fibrillation: a randomized trial. JAMA. 2008;300:1784–92.
54. Giri S, et al. Oral amiodarone for prevention of atrial fibrillation after open heart surgery, the Atrial Fibrillation Suppression Trial (AFIST): a randomised placebo-controlled trial. Lancet. 2001;357:830–6.
55. Wurdeman RL, Mooss AN, Mohiuddin SM, Lenz TL. Amiodarone vs. sotalol as prophylaxis against atrial fibrillation/flutter after heart surgery: a meta-analysis. Chest. 2002;121:1203–10.
56. Mitchell LB, et al. Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPABEAR: a randomized controlled trial. JAMA. 2005;294:3093–100.
57. Miller S, et al. Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. Heart. 2005;91:618–23.
58. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, Ailawadi G, Kirkwood KA, Perrault LP, Parides MK, Smith RL 2nd, Kern JA, Dussault G, Hackmann AE, Jeffries NO, Miller MA, Taddei-Peters WC, Rose EA, Weisel RD, Williams DL, Mangusan RF, Argenziano M, Moquete EG, O'Sullivan KL, Pellerin M, Shah KJ, Gammie JS, Mayer ML, Voisine P, Gelijns AC, O'Gara PT, Mack MJ, CTSN. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. N Engl J Med. 2016;374(20):1911–21. doi:10.1056/NEJMoa160200 2.
59. Kowey PR, Dorian P, Mitchell LB, Pratt CM, Roy D, Schwartz PJ, Sadowski J, Sobczyk D, Bochenek A, Toft E, Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. Circ Arrhythm Electrophysiol. 2009;2(6):652–9. doi:10.1161/CIRCEP.109.870204.

60. Selzer A, Wray HW. Quinidine syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. Circulation. 1964;30:17–26.
61. Dessertenne F. Ventricular tachycardia with 2 variable opposing foci. Arch Mal Coeur Vaiss. 1966;59(2):263–72.
62. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. Circulation. 1990;82(4):1106–16. Erratum in: Circulation 1991 Feb;83(2):714.
63. MacNeil DJ. The side effect profile of class III antiarrhythmic drugs: focus on d,l-sotalol. Am J Cardiol. 1997;80(8A):90G–8G.
64. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators Survival With Oral d-Sotalol. Lancet. 1996;348(9019):7–12.
65. Kuck KH, Cappato R, Siebels J, Rüppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). Circulation. 2000;102(7):748–54.
66. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med. 2012;367(17):1587–95.
67. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, Sterns LD, Beresh H, Healey JS, Natale A, RAAFT-2 Investigators. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA. 2014;311(7):692–700.
68. Nielsen JC, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Pehrson SM, Englund A, Hartikainen J, Mortensen LS, Hansen PS, MANTRA-PAF Investigators. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. Heart. 2016;
69. Noseworthy PA, et al. Effect of antiarrhythmic drug initiation on readmission after catheter ablation for atrial fibrillation. JACC Clin Electrophysiol. 2015;1:238–44.
70. Roux JF, Zado E, Callans DJ, Garcia F, Lin D, Marchlinski FE, Bala R, Dixit S, Riley M, Russo AM, Hutchinson MD, Cooper J, Verdino R, Patel V, Joy PS, Gerstenfeld EP. Antiarrhythmics after ablation of atrial fibrillation (5A study). Circulation. 2009;120(12):1036–40.
71. Leong-Sit P, Roux JF, Zado E, Callans DJ, Garcia F, Lin D, Marchlinski FE, Bala R, Dixit S, Riley M, Hutchinson MD, Cooper J, Russo AM, Verdino R, Gerstenfeld EP. Antiarrhythmics after ablation of atrial fibrillation (5A Study): six-month follow-up study. Circ Arrhythm Electrophysiol. 2011;4(1):11–4.
72. Darkner S, Chen X, Hansen J, Pehrson S, Johannessen A, Nielsen JB, Svendsen JH. Recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). Eur Heart J. 2014;35(47):3356–64.
73. Kaitani K, Inoue K, Kobori A, Nakazawa Y, Ozawa T, Kurotobi T, Morishima I, Miura F, Watanabe T, Masuda M, Naito M, Fujimoto H, Nishida T, Furukawa Y, Shirayama T, Tanaka M, Okajima K, Yao T, Egami Y, Satomi K, Noda T, Miyamoto K, Haruna T, Kawaji T, Yoshizawa T, Toyota T, Yahata M, Nakai K, Sugiyama H, Higashi Y, Ito M, Horie M, Kusano KF, Shimizu W, Kamakura S, Morimoto T, Kimura T, Shizuta S, EAST-AF Trial Investigators. Efficacy of antiarrhythmic drugs short-term use after catheter ablation for atrial fibrillation (EAST-AF) trial. Eur Heart J. 2016;37(7):610–8.
74. Verrier RL, Kumar K, Nieminen T, Belardinelli L. Mechanisms of ranolazine's dual protection against atrial and ventricular fibrillation. Europace. 2012;15:317–24.
75. Murdock DK, Reiffel JA, Kaliebe JW, Larrain G. The use of ranolazine to facilitate electrical cardioversion in cardioversion-resistant patients: a case series. Pacing Clin Electrophysiol. 2012;35:302–7.
76. De Ferrari GM, Maier LS, Mont L, Schwartz PJ, Simonis G, Leschke M, Gronda E, Boriani G, Darius H, Guillamón Torán L, Savelieva I, Dusi V, Marchionni N, Quintana Rendón M, Schumacher K, Tonini G, Melani L, Giannelli S, Alberto Maggi C, Camm AJ, RAFFAELLO Investigators (see Online Supplementary Appendix for List of Participating Centers and Investigators). Ranolazine in the treatment of atrial fibrillation: results of the dose-ranging RAFFAELLO (Ranolazine in Atrial Fibrillation Following An ELectricaL CardiOversion) study. Heart Rhythm. 2015;12(5):872–8.
77. Murdock DK, Kersten M, Kaliebe J, Larrain G. The use of oral ranolazine to convert new or paroxysmal atrial fibrillation: a review of experience with implications for possible "pill in the pocket" approach to atrial fibrillation. Indian Pacing Electrophysiol J. 2008;9:260–7.
78. Fragakis N, Koskinas KC, Katritsis DG, Pagourelias ED, Zografos T, Geleris P. Comparison of effectiveness of ranolazine plus amiodarone versus amiodarone alone for conversion of recent-onset atrial fibrillation. Am J Cardiol. 2012;110:673–7.
79. Reiffel JA, Camm AJ, Belardinelli L, Zeng D, Karwatowska-Prokopczuk E, Olmsted A, Zareba W, Rosero S, Kowey P, HARMONY Investigators. The HARMONY trial: combined Ranolazine and Dronedarone in the management of paroxysmal atrial fibrillation: mechanistic and therapeutic synergism. Circ Arrhythm Electrophysiol. 2015;8(5):1048–56.
80. Fuller H, Justo F, Nearing BD, Kahlig KM, Rajamani S, Belardinelli L, Verrier RL. Eleclazine, a new selective cardiac late sodium current inhibitor, confers concurrent protection against autonomically induced atrial premature beats, repolarization alternans and heterogeneity, and atrial fibrillation in an intact porcine model. Heart Rhythm. 2016;13(8):1679–86.
81. Justo F, Fuller H, Nearing BD, Rajamani S, Belardinelli L, Verrier RL. Inhibition of the cardiac late sodium current with eleclazine protects against ischemia-induced vulnerability to atrial fibrillation and reduces atrial and ventricular repolarization abnormalities in the absence and presence of concurrent adrenergic stimulation. Heart Rhythm. 2016;13(9):1860–7.
82. Arya A, Silberbauer J, Teichman SL, Milner P, Sulke N, Camm AJ. A preliminary assessment of the effects of ATI-2042 in subjects with paroxysmal fibrillation using implanted pacemaker methodology. Europace. 2009;11(4):458–64.
83. Ezekowitz MD, Nagarakanti R, Lubinski A, Bandman O, Canafax D, Ellis DJ, Milner PG, Ziola M, Thibault B, Hohnloser SH, PASCAL Investigators. A randomized trial of budiodarone in paroxysmal atrial fibrillation. J Interv Card Electrophysiol. 2012;34(1):1–9.
84. Yamamoto W, Hashimoto N, Matsuura J, Machida T, Ogino Y, Kobayashi T, Yamanaka Y, Ishiwata N, Yamashita T, Tanimoto K, Miyoshi S, Fukuda K, Nakaya H, Ogawa S. Effects of the selective KACh channel blocker NTC-801 on atrial fibrillation in a canine model of atrial tachypacing: comparison with class Ic and III drugs. J Cardiovasc Pharmacol. 2014;63(5):421–7.
85. Ford J, Milnes J, El Haou S, Wettwer E, Loose S, Matschke K, Tyl B, Round P, Ravens U. The positive frequency-dependent electrophysiological effects of the IKur inhibitor XEN-D0103 are desirable for the treatment of atrial fibrillation. Heart Rhythm. 2016;13(2):555–64.
86. Podd SJ, Freemantle N, Furniss SS, Sulke N. First clinical trial of specific IKACh blocker shows no reduction in atrial fibrillation burden in patients with paroxysmal atrial fibrillation: pacemaker assessment of BMS 914392 in patients with paroxysmal atrial fibrillation. Europace. 2016;18(3):340–6.
87. Qi XY, Diness JG, Brundel BJ, Zhou XB, Naud P, CT W, Huang H, Harada M, Aflaki M, Dobrev D, Grunnet M, Nattel S. Role of small-conductance calcium-activated potassium channels in atrial electrophysiology and fibrillation in the dog. Circulation. 2014;129(4):430–40.

Anticoagulants for Atrial Fibrillation

9

Keitaro Senoo and Gregory Y.H. Lip

Abstract

Stroke is the major cause of mortality in patients with atrial fibrillation (AF) and oral anticoagulation significantly reduces the risk of stroke/systemic thromboembolism and mortality in AF patients at a high risk. Traditionally, the vitamin K antagonists (VKAs) were the only anticoagulants, but more recently, the non-vitamin K antagonist oral anticoagulants (NOACs) have become available as alternatives to VKAs. Each NOAC has its own features, which could be important considerations for the physicians' decision-making when it comes to drug selection for eligible AF patients. Thus, the physician should select particular NOACs or VKAs with reference to their efficacy and safety, fitting the drug to the patient profile. Use of risk scores such as CHA_2DS_2-VASc, HAS-BLED and SAMe-TT_2R_2 can help decision-making in the selection of appropriate antithrombotic agents and management strategies. Last, patients should be actively involved with their clinician in decision-making about their anticoagulant treatment options.

Keywords

Atrial fibrillation • $CHADS_2$ score • CHA_2DS_2-VASc score • HAS-BLED score • Oral anticoagulation • Vitamin K antagonists • Non-vitamin K antagonist oral anticoagulants • Bleeding • SAMe-TT_2R_2 score • Patient preferences

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, but results in a fivefold increase in stroke risk. Strokes associated with AF are associated with a greater mortality and morbidity, with more disability, less independence and lower likelihood of being discharged to one's home [1, 2].

K. Senoo, M.D.
Institute of Cardiovascular Sciences, City Hospital, University of Birmingham, Birmingham, UK
e-mail: swcqg251@yahoo.co.jp

G.Y.H. Lip, M.D. (✉)
Institute of Cardiovascular Sciences, City Hospital, University of Birmingham, Birmingham, UK

Department of Clinical Medicine, Aalborg Thrombosis Research Unit, Aalborg University, Aalborg, Denmark
e-mail: gregory.lip@gmail.com

Thus stroke prevention is central to the management of AF.

Traditionally, the vitamin K antagonists (VKA, e.g. warfarin) were the only anticoagulants widely used for the stroke prevention in AF. However, several practical issues are evident with warfarin therapy, such as narrow therapeutic range and need for frequent monitoring. Thus, the non-vitamin K antagonist oral anticoagulants (NOACs) have been developed, which include direct thrombin inhibitor (e.g. dabigatran) and factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban), designed to target the different levels of the coagulation cascade.

Several randomized trials have established the value of oral anticoagulants (OACs) for preventing stroke in patients with nonvalvular AF [3]. Indeed, adjusted dose warfarin reduces stroke by 64% and all-cause mortality by 26% compared to control or placebo. In contrast, aspirin resulted in a non-significant 19% reduction in stroke risk compared to control, with no significant impact on mortality [3].

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_9

Despite the strong evidence of OACs for stroke prevention, a systematic review [4], found the suboptimal use of OACs (defined as <70% of eligible patients receiving OAC) particularly among patients at a high risk. Overestimation of the bleeding risk by physicians often leads to under treatment with OAC, particularly amongst elderly patients [5, 6].

Assessing Stroke and Bleeding Risks in Atrial Fibrillation

Individual assessment of stroke and bleeding risk can help decision making when antithrombotic therapy is used. Of the various risk stratification schemes, the commonest ones in use are the $CHADS_2$ and CHA_2DS_2-VASc scores for stroke risk, and the HAS-BLED score for assessing bleeding risk (Table 9.1).

The $CHADS_2$ Score

The $CHADS_2$ score was derived from the stroke risk factors identified in the AF Investigators [7] and SPAF risk schemes [8], and is therefore based on the non-VKA arms of the historical trial cohorts [9]. These trials only randomized <10% of patients screened, and many common stroke risk factors were not recorded nor consistently defined. Nonetheless, the $CHADS_2$ score was intended to help identify 'high risk' patients for OAC but the use of VKA had limited relationship to stroke risk strata and many high risk patients remained suboptimally treated [10].

Whilst the $CHADS_2$ score is commonly used as a risk score for stroke prevention, several limitations have been highlighted [11, 12]. Like most clinical risk scores, the $CHADS_2$ score has modest predictive value for 'high risk' patients [13]. The pooled analysis indicates that both the classic and revised views of stratification offer limited predictive value for 'high risk' patients [12].

Second, several common risk factors, for example, age 65–74, female sex and vascular disease, are not included in the $CHADS_2$ score [14, 15]. Thirty to fifty percent of AF patients have a $CHADS_2$ score of 0–1, showing that a large number of AF patients have no clear recommendation for anticoagulation based on these criteria. For instance, patients with a $CHADS_2$ score of 0 can have a stroke rate as high as 3.2% per year (which is not 'low risk') and those with a score of 1 can have a stroke rate of 8% per year [16]. Thus, stroke risk assessments need to evolve to be able to identify the 'truly low risk' patients who do not need antithrombotic therapy [11, 17].

Table 9.1 Scores for stroke risk stratification

Stroke risk scores	Risk score
$CHADS_2$	
CHF	1
Hypertension	1
Age ≥ 75	1
Diabetes	1
Stroke or TIA	2
CHA_2DS_2-VASc	
CHF	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/TE	2
Vascular disease	1
Age 65–74	1
Sex category (female)	1

CHF congestive heart failure; *TIA* transient ischemic attack; *TE* thromboembolism; *$CHADS_2$ score* Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and previous stroke/TIA (2 points); *CHA_2DS_2-VASc score* Congestive heart failure, Hypertension (Systolic blood pressure > 160 mmHg), Age ≥ 75 years (2 points), Diabetes mellitus, previous stroke/TIA/TE (2 points), Vascular disease (Prior myocardial infarction, peripheral artery disease, and/or aortic plaque), Age 65–74 years, and female gender

The CHA_2DS_2-VASc Score

To overcome some of the limitations of the $CHADS_2$ score, the CHA_2DS_2-VASc score was proposed, which incorporated additional 'non-$CHADS_2$' stroke risk modifiers, such as age 65–74, vascular disease and female sex [18, 19].

In the Euro Heart Survey, the CHA_2DS_2-VASc score was compared with seven other stroke risk stratification schemas in 1084 AF patients and demonstrated reasonable predictive ability for high-risk patients but was good at identifying low-risk patients [20]. The Danish nationwide cohort study [16] showed patients with a $CHADS_2$ score = 0 were not all 'low risk', with 1-year event rates ranging from 0.84% (CHA_2DS_2-VASc score = 0) to 3.2% (CHA_2DS_2-VASc score = 3). The C statistics of the Cox regression model were significantly improved from 0.632 (95% confidence interval 0.619–0.646) to 0.663 (0.650–0.676) when the CHA_2DS_2-VASc score was used for stroke risk categorization instead of the $CHADS_2$ score. The Belgrade AF study conducted a registry-based, observational cohort study of 345 patients initially diagnosed with low risk AF. In the multivariable analysis, only the CHA_2DS_2-VASc score of 0 was significantly related to the absence of stroke (odds ratio 5.1, 95% CI: 1.5–16.8, P = 0.008). Only the CHA_2DS_2-VASc score had a significant prediction ability for the absence of stroke (c-statistic 0.72 [0.61–0.84], P = 0.031) [21]. Thus, the CHA_2DS_2-VASc score was best in identifying truly low risk patients who did not need any antithrombotic therapy, although the C statistic of CHA_2DS_2-VASc score varies, depending on the cohort used.

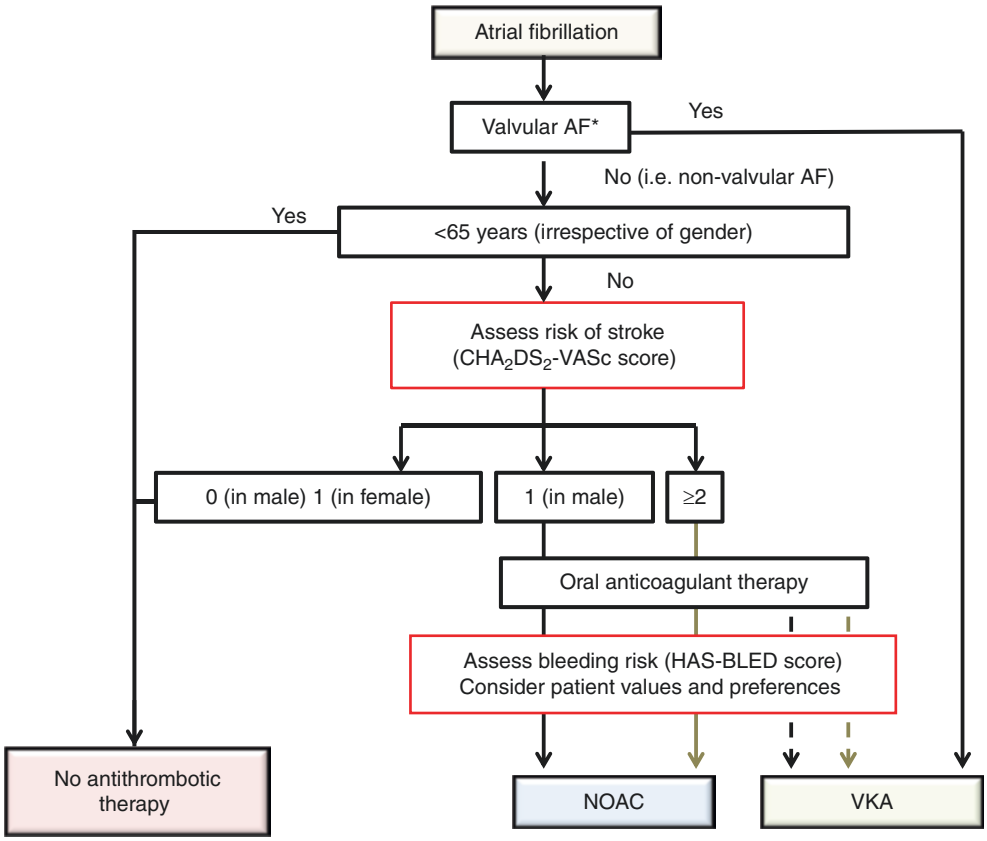


Fig. 9.1 Approach to stroke prevention in atrial fibrillation. Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered. AF = atrial fibrillation, CHA_2DS_2-VASc = see Table 9.1, HAS-BLED = see Table 9.2, NOAC = non-vitamin K antagonist oral anticoagulant, VKA = vitamin K antagonist. * (*asterisk*) includes rheumatic valvular disease and prosthetic valves

Thus, the European Society of Cardiology (ESC) guidelines now recommend the use of the CHA_2DS_2-VASc score for stroke risk stratification [22]. In the ESC guidelines, the first decision step is to identify those patients with a CHA_2DS_2-VASc score of 0 (in males) and 1 (in females) who may be considered for no antithrombotic treatment [21, 23, 24]. Subsequent to this step, all other AF patients with ≥1 stroke risk factors (that is CHA_2DS_2-VASc score = 1 in males, or score ≥ 2 in all) should be considered for OACs (Fig. 9.1). The CHA_2DS_2-VASc score is also the recommended stroke risk stratification score in guidelines from the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS), Asia Pacific Heart Rhythm Society (APHRS) and National Institute for Health and Care Excellence (NICE) [25–27].

The HAS-BLED Score

Many risk stratification schemes for bleeding have been derived for and validated in AF populations; $HEMORR_2HAGES$ (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke) [28], ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) [29], HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol) [30] and ORBIT (Outcomes Registry for Better Informed Treatment) scores [31] (Table 9.2).

Among these, the most commonly used HAS-BLED score was first proposed in 2010, having been derived and validated in the Euro Heart survey population [30]. The HAS-BLED score represents each of the following common bleeding risk factors and assigns 1 point for each: hypertension (uncontrolled systolic blood pressure > 160 mmHg), abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios [INRs], elderly, and concomitant drugs and/or alcohol excess. A HAS-BLED scores ≥3 indicates a high risk of bleeding, for which caution and regular review of patients are recommended.

The predictive values of HAS-BLED/ATRIA/$HEMORR_2HAGES$ were compared in a post hoc analysis of data from the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) trial. The HAS-BLED score demonstrated better discriminatory performance for the outcome of clinically relevant bleeding, reflected by significant AUC differences when compared with ATRIA ($p = 0.002$),

Table 9.2 Scores for bleeding risk stratification

Bleeding risk score	Risk score
HAS-BLED	
Hypertension (uncontrolled)	1
Abnormal renal or liver function	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile INRs	1
Elderly (eg. age>65, extreme frailty, etc)	1
Drugs (concomitant aspirin or NSAID) or excess alcohol	1 or 2
HEMORR$_2$HAGES	
Hepatic or renal disease	1
Ethanol abuse	1
Malignancy	1
Older age	1
Reduced platelet count or function	1
Rebleeding risk	2
Hypertension	1
Anemia	1
Genetic factors	1
Excessive fall risk	1
Stroke	1
ATRIA	
Anemia	3
Severe renal disease	3
Age ≥ 75 years	2
Prior bleeding	1
Hypertension	1
ORBIT	
Older age	1
Reduced hemoglobin/Hct/anemia	2
Bleeding history	2
Insufficient kidney function	1
Treatment with antiplatelets	1

INR international normalized ratio; *HAS-BLED score* Hypertension, Abnormal renal or liver function, Stroke, Bleeding history, Labile INRs, Elderly (age > 65 years), Drugs/alcohol concomitantly; *HEMORR$_2$HAGES score* Hepatic or renal disease, Ethanol abuse, Malignancy, Older age (age > 75 years), Reduced platelet count or function, Rebleeding risk (history of past bleeding) (2 points), Hypertension (uncontrolled), Anemia (hemoglobin <13 g/dL in men and <12 g/dL in women), Genetic factors (CYP2C9 variant), Excessive fall risk, and Stroke; *ATRIA score* = Anemia (hemoglobin <13 g/dL in men and <12 g/dL in women) (3 points), Severe renal disease (glomerular filtration rate < 30 mL/min or dialysis dependent) (3points), Age ≥ 75 years (2 points), Prior bleeding (1 point) and Hypertension (1 point); *ORBIT score* Older age (≥74 years), reduced hemoglobin/Hct/Anemia [(hemoglobin <13 g/dL in men and <12 g/dL in women) or (hematocrit <40% for males and <36% for females) (2 points)], Bleeding history (2 points), Insufficient kidney function (glomerular filtration rate < 60 mL/min/1.73 m^2), Treatment with antiplatelets

HEMORR$_2$HAGES (p = 0.003) and, a new bleeding prediction score, ORBIT score (p = 0.001) [32, 33].

Based on the Swedish Hospital Discharge Register, the risk of ischemic stroke without anticoagulant treatment is higher than the risk of intracranial bleeding with anticoagulant treatment, the net clinical benefit is positive in favour of anticoagulation for AF patients with ≥1 additional stroke risk factors. Of note, aspirin did not have any positive net clinical benefit at any $CHADS_2$ or CHA_2DS_2-VASc score strata [34].

Oral Anticoagulants

Vitamin K Antagonists (VKA)

Four proteins (factor II, VII, IX, X) play key roles in the blood coagulation cascade require vitamin K for their production. Warfarin inhibits the action of vitamin K dependent coagulation factors, limiting the production of these four anticoagulation proteins [35, 36].

VKAs such as warfarin have been the standard care of oral anticoagulation for several decades. As mentioned above, dose adjusted warfarin was associated with a 64% relative risk reduction for stroke compared with placebo and a 39% relative risk reduction in stroke compared with antiplatelet drugs [3]. Warfarin is significantly better than dual antiplatelet (DAPT) therapy for the stroke prevention, without a significant increased bleeding risk [37].

However, many people who have been diagnosed with AF are not receiving guideline recommended pharmacotherapy. Untreated and undertreated patients are considered to be a major source of preventable strokes. Possible reasons for underuse of warfarin include the following [36]: (a) the need for regular monitoring of the anticoagulant response to warfarin (by measuring INR), which may be seen as an inconvenience to both patients and health professionals; (b) the difficulty in managing INR in some patients (medicine interactions, contraindications and dietary restrictions); (c) patients' reluctance to take warfarin, which may require patient education; (d) fear of bleeding, which often influences a physicians' decision making (particularly, Asians are prone to bleeding when treated with warfarin, and Asian physicians tend to keep it in a lower range [e.g. INR 1.6–2.6] for elderly patients despite limited evidence).

When using warfarin, attention to the quality of anticoagulation control is needed, as reflected by the average time in therapeutic range (TTR). Indeed, well-managed warfarin with a high TTR is associated with low rates of stroke and bleeding [36, 38]. High quality anticoagulation control with warfarin is associated with better efficacy and safety [39], and hence effective stroke prevention in several guidelines with oral anticoagulants refers to well-controlled warfarin (e.g. TTR ≥70% [36]) or one of the NOACs [22].

The use of point-of-care testing (PoCT) for the measurement of INR values should be considered as an option for warfarin management, particularly in the community setting.

Such testing could be conducted at a medical practice or could involve a collaborative shared-care arrangement between patients' medical practitioners and other health professionals with whom patients have regular contact.

Non-vitamin K Antagonist Oral Anticoagulants (NOAC)

The Non-vitamin K antagonist oral anticoagulants (NOACs), that is, oral direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), have recently emerged as alternatives to warfarin to prevent stroke in AF patients. NOACs have a rapid onset and offset, and have a predictable effect with fewer drug-drug interactions (Table 9.3). Moreover, NOACs are used in fixed doses without need for monitoring of anticoagulation intensity. The value of NOACs for stroke prevention in AF has been demonstrated in multiple large Phase 3 clinical trials, which randomized patients to NOAC therapy versus dose-adjusted VKA therapy for the prevention of stroke in patients with nonvalvular AF.

The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) [40] trial was a randomized, open-label, phase III trial of stroke or systemic embolism prevention in patients with nonvalvular AF. A total of 18,113 patients were randomized to two doses of dabigatran, 110 or 150 mg twice daily (bid), or to dose-adjusted warfarin (INR 2.0–3.0). In this trial, dabigatran 150 mg bid was associated with a lower incidence of stroke and thromboembolism compared with warfarin (1.11% vs. 1.71% per year, $P < 0.001$ for superiority) but was similar in the incidence of major bleeding (3.32% vs. 3.57% per year, $P = 0.31$), whereas dabigatran 110 mg bid was associated with a similar incidence of stroke and thromboembolism (1.54% vs. 1.71% per year, $P < 0.001$ for non-inferiority, $P = 0.30$ for superiority) and a lower incidence of major bleeding (2.87% vs. 3.57% per year, $P = 0.003$). Intracranial bleeding occurred less frequently in the dabigatran groups (dabigatran 150 mg and 110 mg vs. warfarin: 0.30% and 0.23% vs. 0.76% per year, respectively).

The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) [41] trial was a randomized, double-blind, double-dummy trial of stroke or systemic embolism prevention in patients with nonvalvular AF. A total of 14,264 patients were randomized to either rivaroxaban 20 mg once daily (od) (15 mg od if creatinine clearance was 30–49 mL/min) or dose-adjusted warfarin (INR 2.0–3.0). ROCKET-AF showed that rivaroxaban was non-inferior to warfarin in the prevention of stroke or systemic embolism (2.12% vs. 2.42% per year, $P < 0.001$ for non-inferiority, $P = 0.12$ for superiority), with no difference in the risk of major and non-major clinically relevant bleeding (14.9% vs. 14.5% per year, $P = 0.44$). Intracranial hemorrhage occurred less frequently in rivaroxaban (0.49% vs. 0.74% per year; $P = 0.019$).

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) [42] trial was a randomized double-blind, double-dummy, phase III trial of stroke or systemic embolism prevention in patients with nonvalvular AF. A total of 18,201 patients were randomized to either apixaban 5 mg bid (reduce to 2.5 mg if patients with ≥2 of the following criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL), or to dose-adjusted warfarin (INR 2.0–3.0). ARISTOTLE showed apixaban was superior to warfarin in the prevention of stroke or systemic embolism (1.27% vs. 1.60%, per year; $P < 0.001$ for non-inferiority, $P = 0.01$ for superiority), and it resulted in less bleeding (2.13% vs. 3.09% per year, $P < 0.001$) and lower mortality (3.52% vs. 3.94% per year, $P = 0.047$). Intracranial hemorrhage occurred less frequently in apixaban (0.33% vs. 0.80% per year, $P < 0.001$).

The ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) [43] trial was a randomized, double-blind, double-dummy, phase III trial of stroke or systemic embolism prevention in patients with nonvalvular AF. A total of 21,105 patients were randomized to edoxaban 60 or 30 mg od, or to dose-adjusted warfarin (INR 2.0–3.0). The dose was reduced to 30 mg with the following

Table 9.3 Pharmacological characteristics of oral anticoagulants

	Warfarin [25, 26]	Dabigatran [31]	Rivaroxaban [32]	Apixaban [33]	Edoxaban [34]
Mechanism	Vitamin K antagonist	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Oral bioavailability	79–100%	6.5%	80–100%	50%	62%
Half-life (h)	20–60	12–14	8–11	12	10–14
Renal clearance	92%	80%	33% kidney, 66% liver	25%	50%
Regimen	Flexible	Twice[a]	Once[a]	Twice[a]	Once[a]
Interaction	Numerous	P-gp	3A4/P-gp	3A4/P-gp	P-gp

[a]Depend on indicate

criteria: CrCl 30–50 mL/min, a body weight <60 kg, or the concomitant use of verapamil or quinidine.

Both doses of edoxaban were non-inferior to warfarin for the prevention of stroke or systemic embolism (edoxaban 60 mg and edoxaban 30 mg vs. warfarin 1.18% and 1.61% vs. 1.50% per year, respectively) and were associated with lower rates of bleeding (2.75% and 1.61% vs. 3.43% per year, respectively) and cardiovascular death (2.74% and 2.71% vs. 3.17% per year, respectively). Intracranial hemorrhages occurred less frequently in edoxaban group (0.39% and 0.26% vs. 0.85% per year, respectively).

Ruff et al. performed a meta-analysis (71,683 participants) using the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 trials. NOACs had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of NOACs was consistent across a wide range of patients [44].

Management of Bleeding

Major bleeding was associated with substantially increased risk of death, ischemic stroke, or myocardial infarction, especially following intracranial haemorrhage [45]. Hence, the importance of avoiding bleeding in anticoagulated patients, but the management of active bleeding with oral anticoagulation is still an ongoing clinical challenge.

In patients receiving warfarin, management of bleeding using a number of therapies is fairly established, including intravenous vitamin K, fresh frozen plasma (FFP), activated and inactivated pro-thrombin complex concentrates (PCCs), and recombinant activated factor VII (rFVIIa), to prevent hemorrhage expansion, limit tissue damage, and facilitate surgical intervention as needed. Whilst Vitamin K could be a specific antidote for a VKA, it has a slow onset of action (average 9–12 h), and would not suffice for emergency treatment, and thus, non-specific supportive measures are needed.

Current recommendations for patients taking NOACs are mostly limited to supportive care (including volume resuscitation, hemodynamic support, and primary intervention) [22]. To ameliorate bleeding associated with NOACs, physicians have used PCC or rFVIIa. In healthy volunteers, administration of PCC completely reversed rivaroxaban-induced prolongation of the PT, but had no effect on dabigatran-induced prolongation of coagulation tests, in particular of thrombin time and ecarin clotting time (ECT) [46]. Recombinant factor VIIa was associated with reduced blood loss, improvement of coagulation variables and decreased need for transfusions [47], but one analysis found older patients treated with rFVIIa had almost three times the risk of arterial thrombosis than did healthy controls [48]. The use of other pro-coagulants such as antifibrinolytics (e.g. tranexamic acid or aminocaproic acid) or desmopressin can be considered, although there are almost no clinical data of their effectiveness in NOAC-associated bleeding.

A specific antibody based antidote to dabigatran has shown great promise, and has regulatory approval in USA and EU for use in dabigatran-associated bleeding or where urgent surgery is needed in a patient anticoagulated with dabigatran [49]. Andexanet alfa, a modified recombinant protein, dose-dependently reversed the inhibition of factor Xa by direct factor Xa inhibitors and corrected the prolongation of ex vivo clotting times by such inhibitors [50]. Andexanet alfa has the potential to be used as an antidote for a broad range of factor Xa inhibitors but more data on its safety and efficacy are expected.

Finally, dabigatran can be removed from the blood by haemodialysis [51–53], and in cases of excess ingestion, activated charcoal can minimize absorption. Given the moderate half-life of the NOACs, the initial non-specific supportive measures may suffice.

Choosing Between VKA or NOAC?

Each NOAC has unique features, which could be important considerations for the physicians' decision-making when it comes to drugs selection for eligible nonvalvular AF patients. Thus, the physician should properly select each NOAC or VKA with reference to their efficacy and safety, fitting the drug to the patient profile.

There are no head-head comparisons of these four NOACs, but indirect comparisons have been published giving some insight into the comparisons of each other in terms of efficacy and safety [54, 55]. Of note, indirect comparisons have major limitations, such as the assumption that all the drugs and trials are homogeneous, but in reality there are important differences in patient profile among those trials (e.g., mean $CHADS_2$ score and TTR) [56, 57]. Given the drug characteristics and trial outcomes, we can fit a particular NOAC to the patient profile for stroke prevention in nonvalvular AF [58]. Using prescribing label or guideline adherent treatment is also associated with better efficacy and safety outcomes [59]. Indeed, patients with end-stage renal disease [ESRD; e.g. CrCl < 30 mL/min/1.73 m^2] are excluded from the clinical trials.

In a newly diagnosed non-anticoagulated AF patient, some healthcare settings still require a 'trial of warfarin' for (say) 6 months to see the TTR, before a NOAC is allowed to be prescribed. This may put patients at risk of stroke given that TTRs in inception cohorts tend to be suboptimal [60], leading to an excess of strokes in the early period following the introduction of warfarin [61]. Rather than expose to inadequate thromboprophylaxis with a 'trial of warfarin', the SAMe-TT_2R_2 score

Table 9.4 The SAMe-TT_2R_2 score

Acronym	Definitions	Points
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history[a]	1
T	Treatment (interacting Rx, e.g. amiodarone for rhythm control)	1
T	Tabacco use (within 2 years)	2
R	Race (non Caucasian)	2
	Maximum points	8

[a]Two or more of the following: hypertension, diabetes, myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease

[62] (Table 9.4) may help decision-making. Patients with a SAMe-TT_2R_2 score 0–2 are likely to do well on warfarin by achieving a high TTRs. In contrast, a SAMe-TT_2R_2 score of >2 is associated with a poor TTR and thus, such patients may require more careful review or counseling [63] or be best treated with a NOACs. The SAMe-TT_2R_2 score has now been validated in various independent cohorts [64–67], and could be considered in patient management pathways.

It is important to stress that NOACs have a relatively short half-life whereby the anticoagulant effect wears off 12–24 h after the last intake, and therefore strict adherence and compliance by patients is vital for stroke prevention. Thus, patients are less likely to be protected from stroke when treatment of NOAC, which has a short half-life, is interrupted. Although medication adherence in clinical trials is minimized by careful monitoring of compliance during follow-up, patients taking warfarin in real-life clinical practice are less likely to be in a therapeutic range than those in controlled studies [68]. Hence, physicians have to involve patients in discussions about treatment options and elicit their preferences [67, 69–71], and consequently physicians can get the opportunity to educate patients about AF and the risks/benefits of treatment.

For example, Shore et al., studied a national cohort of 5376 patients with NVAF, initiated on dabigatran. Adherence to dabigatran was calculated as proportion of days covered (PDC) and association between PDC and outcomes was assessed. Among them, 28% of patients in our cohort had poor adherence. After multivariable adjustment, lower adherence was associated with increased risk for combined all-cause mortality and stroke (HR 1.13, 95% CI 1.07–1.19 per 10% decrease in PDC) [72]. Nationwide Danish registries (n = 2960 patients) were used to identify newly diagnosed AF patients taking dabigatran. More than 75% of patients were showed >80% adherence to medication regimes during the first year. Patients with higher morbidity, including a higher risk of stroke or bleeding, revealed better adherence. This improvement may be attributable to more regular contact with the healthcare system [73].

Major clinical trials of antithrombotic therapy and subsequent meta-analyses have excluded patients with any type of prosthetic heart valves, those with mitral stenosis, and those with decompensated valvular heart disease who were likely to require valve replacement in the near future. Therefore, Vitamin K antagonist should be prescribed for these patients, not NOACs.

The prevalence of AF in patients with chronic renal failure (CRF) and ESRD is very high and also in this population AF is associated with an increased risk of stroke [74]. Warfarin use in CRF and haemodialysis (HD) patients has been associated with an increased risk of bleeding compared with patients with normal renal function [75]. Moreover, historical studies suggest that warfarin increases the incidence of both ischemic and haemorrhagic strokes in HD patients [76, 77]. Thus, a clear benefit/risk ratio against warfarin in patients with CRF or ESRD and AF has not been firmly demonstrated. Although NOACs are now available, patients with severe CRF or ESRD were excluded from the trials that have established their efficacy and safety and therefore, warfarin should be used instead of NOACs.

Patient Values and Preferences

Patients' preferences for OAC therapy should be an integral part of the treatment decision-making process [70], as advocated by current clinical guidelines [22].

To enable patients to make informed choices about whether or not to initiate OAC and to allow them to choose between the available OAC drugs requires the patient to be appropriately educated about their own individual risk of stroke (hence the need for OAC) and their risk of major bleeding associated with the different OACs. The responsibility for educating AF patients and allowing them to voice their preferences for OAC treatment lies with the treating clinician [71].

A recent study by La Haye et al. [78] used an iPad to present patients with their individual risk of stroke (using CHA_2DS_2-VASc score) and bleeding with treatment (using a variety of different formats) and elicited their preferences for antithrombotic therapy. This study confirms previous research [70] which reports that patients are more concerned about the risk of stroke than the risk of bleeding; patients were prepared to suffer 4.4 major bleeding in order to prevent one stroke [78].

Conclusion

Stroke is the major cause of mortality in patients with AF and oral anticoagulation can reduce the risk of stroke in patients at a high risk. Decisions regarding appropriate stroke prevention involve individual assessment of stroke and bleeding risk associated with VKA or NOACs.

As there is no need for routine coagulation monitoring with the NOACs, some concern has been expressed about patient adherence. Therefore, health care professionals should ensure that patients understand why they are taking oral anticoagulants for atrial fibrillation and the expected benefits. Use of risk scores such as CHA_2DS_2-VASc, HAS-BLED and SAMe-TT_2R_2 scores can help in the selection of appropriate antithrombotic agents and management strategies. Clearly, patients must be actively involved with their clinician in decision-making about their anticoagulant treatment options.

Conflict of Interest Keitaro Senoo: Nothing to disclose.

Gregory Y.H. Lip: Scientific Documents Committee, European Heart Rhythm Association (EHRA). Reviewer for various guidelines and position statements from ESC, EHRA, NICE etc. Steering Committees/trials: Includes steering committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc. Consultant for Bayer/Jensen J&J, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo.

References

1. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. Stroke. 1996;27:1765–9.
2. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996;27:1760–4.
3. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–67.
4. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010;123:638–645.e4.
5. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. Age Ageing. 2011;40:675–83.
6. Lip GY, Zarifis J, Watson RD, Beevers DG. Physician variation in the management of patients with atrial fibrillation. Heart. 1996;75:200–5.
7. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154:1449–57.
8. SPiAF Investigators. Risk factors for thromboembolism during aspirin therapy in patients with atrial fibrillation: the stroke prevention in atrial fibrillation study. J Stroke Cerebrovasc Dis. 1995;5:147–57.
9. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–70.
10. Nieuwlaat R, Capucci A, Lip GY, Olsson SB, Prins MH, Nieman FH, Lopez-Sendon J, Vardas PE, Aliot E, Santini M, Crijns HJ, Euro Heart Survey Investigatiors. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. Eur Heart J. 2006;27:3018–26.
11. Karthikeyan G, Eikelboom JW. The CHADS2 score for stroke risk stratification in atrial fibrillation—friend or foe? Thromb Haemost. 2010;104:45–8.
12. Keogh C, Wallace E, Dillon C, Dimitrov BD, Fahey T. Validation of the CHADS2 clinical prediction rule to predict ischaemic stroke. A systematic review and meta-analysis. Thromb Haemost. 2011;106:528–38.
13. Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE, ATRIA Study Group. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2008;51:810–5.
14. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271:840–4.
15. Kerr CR, Humphries K. Gender-related differences in atrial fibrillation. J Am Coll Cardiol. 2005;46:1307–8.
16. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0–1: a nationwide cohort study. Thromb Haemost. 2012;107:1172–9.
17. Lip GY. Stroke in atrial fibrillation: epidemiology and thromboprophylaxis. J Thromb Haemost. 2011;9(Suppl 1):344–51.
18. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33:1500–10.
19. Olesen JB, Lip GY, Lane DA, Kober L, Hansen ML, Karasoy D, Hansen CM, Gislason GH, Torp-Pedersen C. Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. Am J Med. 2012;125:826.e13–23.
20. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263–72.
21. Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Prostran MS, Lip GY. Reliable identification of "truly low" thromboembolic risk in patients initially diagnosed with "lone" atrial fibrillation: the Belgrade atrial fibrillation study. Circ Arrhythm Electrophysiol. 2012;5:319–26.
22. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, ESC Committeee for Practice Guidelines-CPG, Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Europace. 2012;14:1385–413.
23. Taillandier S, Olesen JB, Clementy N, Lagrenade I, Babuty D, Lip GY, Fauchier L. Prognosis in patients with atrial fibrillation and CHA2DS2-VASc Score = 0 in a community-based cohort study. J Cardiovasc Electrophysiol. 2012;23:708–13.
24. Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost. 2011;9:39–48.
25. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1–76.

26. Ogawa S, Kazutaka A, Tse HF, et al. The APHRS's 2013 statement on antithrombotic therapy of patients with nonvalvular atrial fibrillation. J Arrhythm. 2013;29:190–200.
27. National Institute for Health and Clinical Excellence (NICE). NICE CG(180), Atrial Fibrillation(Update): The management of atrial fibrillation. 2014. http://guidance.nice.org.uk/CG180.
28. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006;151:713–9.
29. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011;58:395–401.
30. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138:1093–100.
31. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. Eur Heart J. 2015;36:3258–64. doi:10.1093/eurheartj/ehv476
32. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. J Am Coll Cardiol. 2012;60:861–7.
33. Senoo K, Proietti M, Lane DA, Lip GY. Evaluation of the HAS-BLED, ATRIA and ORBIT bleeding risk scores in atrial fibrillation patients on warfarin. Am J Med. 2016;129:600–7. 10.1016/j.amjmed.2015.10.001
34. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E, BAFTA Investigators, Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007;370:493–503.
35. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI, European Society of Cardiology Working Group on Thrombosis Task Force on Anticoagulants in Heart D. General mechanisms of coagulation and targets of anticoagulants (Section I). Position paper of the ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013;109:569–79.
36. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013;110:1087–107.
37. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367:1903–12.
38. Gallego P, Roldan V, Marin F, Romera M, Valdes M, Vicente V, Lip GY. Cessation of oral anticoagulation in relation to mortality and the risk of thrombotic events in patients with atrial fibrillation. Thromb Haemost. 2013;110:1189–98.
39. Sjogren V, Grzymala-Lubanski B, Renlund H, Friberg L, Lip GY, Svensson PJ, Sjalander A. Safety and efficacy of well managed warfarin. A report from the Swedish quality register Auricula. Thromb Haemost. 2015;113:1370–7.
40. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
41. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
42. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
43. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
44. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955–62.
45. Held C, Hylek EM, Alexander JH, Hanna M, Lopes RD, Wojdyla DM, Thomas L, Al-Khalidi H, Alings M, Xavier D, Ansell J, Goto S, Ruzyllo W, Rosenqvist M, Verheugt FW, Zhu J, Granger CB, Wallentin L. Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. Eur Heart J. 2015;36:1264–72.
46. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011;124:1573–9.
47. Warkentin TE, Margetts P, Connolly SJ, Lamy A, Ricci C, Eikelboom JW. Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. Blood. 2012;119:2172–4.
48. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010;363:1791–800.
49. Pollack CV Jr, Levy JH, Eikelboom J, Weitz JI, Sellke FW, Huisman MV, Steiner T, Kamphuisen P, Bernstein RA. Dabigatran-related coagulopathy: when can we assume the effect has "worn off"? Am J Emerg Med. 2014;32:1433–4.
50. Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, Luan P, Hutchaleelaha A, Inagaki M, Conley PB, Phillips DR, Sinha U. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med. 2013;19:446–51.
51. Chang DN, Dager WE, Chin AI. Removal of dabigatran by hemodialysis. Am J Kidney Dis. 2013;61:487–9.
52. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet. 2010;49:259–68.

53. Khadzhynov D, Wagner F, Formella S, Wiegert E, Moschetti V, Slowinski T, Neumayer HH, Liesenfeld KH, Lehr T, Hartter S, Friedman J, Peters H, Clemens A. Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. Thromb Haemost. 2013;109:596–605.
54. Verdecchia P, Angeli F, Lip GY, Reboldi G. Edoxaban in the evolving scenario of non vitamin K antagonist oral anticoagulants imputed placebo analysis and multiple treatment comparisons. PLoS One. 2014;9:e100478.
55. Skjoth F, Larsen TB, Rasmussen LH, Lip GY. Efficacy and safety of edoxaban in comparison with dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation. An indirect comparison analysis. Thromb Haemost. 2014;111:981–8.
56. Skjoth F, Larsen TB, Rasmussen LH. Indirect comparison studies—are they useful? Insights from the novel oral anticoagulants for stroke prevention in atrial fibrillation. Thromb Haemost. 2012;108:405–6.
57. Harenberg J, Marx S, Wehling M. Head-to-head or indirect comparisons of the novel oral anticoagulants in atrial fibrillation: what's next? Thromb Haemost. 2012;108:407–9.
58. Senoo K, Lip GY. Comparative efficacy and safety of the non-vitamin k antagonist oral anticoagulants for patients with nonvalvular atrial fibrillation. Semin Thromb Hemost. 2015;41:146–53.
59. Lip GY, Clemens A, Noack H, Ferreira J, Connolly SJ, Yusuf S. Patient outcomes using the European label for dabigatran. A post-hoc analysis from the RE-LY database. Thromb Haemost. 2014;111:933–42.
60. Molteni M, Cimminiello C. Warfarin and atrial fibrillation: from ideal to real the warfarin affaire. Thromb J. 2014;12:5.
61. Azoulay L, Dell'Aniello S, Simon TA, Renoux C, Suissa S. Initiation of warfarin in patients with atrial fibrillation: early effects on ischaemic strokes. Eur Heart J. 2014;35:1881–7.
62. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. Chest. 2013;144:1555–63.
63. Clarkesmith DE, Pattison HM, Lip GY, Lane DA. Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. PLoS One. 2013;8:e74037.
64. Gallego P, Roldan V, Marin F, Galvez J, Valdes M, Vicente V, Lip GY. SAMe-TT2R2 score, time in therapeutic range, and outcomes in anticoagulated patients with atrial fibrillation. Am J Med. 2014;127:1083–8.
65. Abumuaileq RR, Abu-Assi E, Raposeiras-Roubin S, Lopez-Lopez A, Redondo-Dieguez A, Alvarez-Iglesias D, Rodriguez-Manero M, Pena-Gil C, Gonzalez-Juanatey JR. Evaluation of SAMe-TT2R2 risk score for predicting the quality of anticoagulation control in a real-world cohort of patients with non-valvular atrial fibrillation on vitamin-K antagonists. Europace. 2015;17:711–7.
66. Poli D, Antonucci E, Testa S, Lip GY. A prospective validation of the SAME-TT2R 2 score: how to identify atrial fibrillation patients who will have good anticoagulation control on warfarin. Intern Emerg Med. 2014;9:443–7.
67. Ruiz-Ortiz M, Bertomeu V, Cequier A, Marin F, Anguita M. Validation of the SAMe-TT2R2 score in a nationwide population of nonvalvular atrial fibrillation patients on vitamin K antagonists. Thromb Haemost. 2015;114:695–701.
68. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. Med Care. 2002;40:794–811.
69. Zolfaghari S, Harenberg J, Froelich L, Wehling M, Weiss C. Development of a tool to identify patients' preference for vitamin K antagonist or direct oral anticoagulant therapy. Semin Thromb Hemost. 2014;40:121–8.
70. Lane DA, Barker RV, Lip GY. Best practice for atrial fibrillation patient education. Curr Pharm Des. 2015;21:533–43.
71. Lane DA, Lip GY. Patient's values and preferences for stroke prevention in atrial fibrillation: balancing stroke and bleeding risk with oral anticoagulation. Thromb Haemost. 2014;111(3):381.
72. Shore S, Carey EP, Turakhia MP, Jackevicius CA, Cunningham F, Pilote L, Bradley SM, Maddox TM, Grunwald GK, Baron AE, Rumsfeld JS, Varosy PD, Schneider PM, Marzec LN, Ho PM. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the veterans health administration. Am Heart J. 2014;167:810–7.
73. Gorst-Rasmussen A, Skjoth F, Larsen TB, Rasmussen LH, Lip GY, Lane DA. Dabigatran adherence in atrial fibrillation patients during the first year after diagnosis: a nationwide cohort study. J Thromb Haemost. 2015;13:495–504.
74. Genovesi S, Pogliani D, Faini A, Valsecchi MG, Riva A, Stefani F, Acquistapace I, Stella A, Bonforte G, DeVecchi A, DeCristofaro V, Buccianti G, Vincenti A. Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients. Am J Kidney Dis. 2005;46:897–902.
75. Sanchez-Perales C, Vazquez E, Garcia-Cortes MJ, Borrego J, Polaina M, Gutierrez CP, Lozano C, Liebana A. Ischaemic stroke in incident dialysis patients. Nephrol Dial Transplant. 2010;25:3343–8.
76. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol. 2009;20:2223–33.
77. Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, Kerr PG, Young EW, Robinson BM. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int. 2010;77:1098–106.
78. Lahaye S, Regpala S, Lacombe S, Sharma M, Gibbens S, Ball D, Francis K. Evaluation of patients' attitudes towards stroke prevention and bleeding risk in atrial fibrillation. Thromb Haemost. 2014;111:465–73.

Cardiac Pacemakers

10

Jose F. Huizar and Kenneth A. Ellenbogen

Abstract

Pacemakers have revolutionized treatment options for many patients with bradycardia. Due to advances in technology, pacemakers have evolved and so have the indications for pacemaker implantation. Patients' needs are different and the appropriate pacemaker and pacing mode should be chosen accordingly. We expect the number of patients receiving permanent pacemakers will continue to increase as life-expectancy continues to increase. Pacemaker indications are multiple, yet it is as important to understand those clinical scenarios when a pacemaker has no benefit or can even cause harm.

Pacemaker behavior depends on programmed pacing mode rather than the pacing components. Pacing nomenclature is key to understand the pacing mode and pacemaker behavior. Thus, health care providers should have a basic understanding of the pacemaker components, pacing nomenclature, pacing modes, indication, follow up and electrocardiographic features of pacemakers. Device malfunction can be recognized with subsequent proper troubleshooting if one understands normal pacemaker behavior.

Keywords

Pacemaker • Pacing nomenclature • Pacing modes • Pacemaker indications • Cardiac resynchronization therapy • Biventricular pacemaker • Electrocardiogram • Outpatient follow up • Pacemaker troubleshooting

Introduction

As the need for pacemakers has increased, pacemaker technology has continued to evolve in complexity since their inception over 60 years ago. Pacemakers have not only become more efficient with longer battery longevity, but have also incorporated features to assist the treatment of arrhythmias and heart failure, and are capable of identifying lead or pulse generator failure. Complex pacemaker features have made ECG interpretation quite challenging, yet it is important to understand their basic operations of pacemakers to differentiate between normal and anomalous pacemaker function. In this chapter, we

J.F. Huizar, M.D. (✉)
Cardiology Division, Pauley Heart Center, Virginia Commonwealth University, Post Office Box 980053, Richmond, VA 23298-0053, USA

Arrhythmia and Device Clinic, Hunter Holmes McGuire VA Medical Center, 1201 Broad Rock Blvd., 4th Floor, Room 4A-100, Richmond, VA 23249, USA
e-mail: jose.huizar2@va.gov; jfhuizar@gmail.com

K.A. Ellenbogen, M.D.
Cardiology Division, Pauley Heart Center, Virginia Commonwealth University, Post Office Box 980053, Richmond, VA 23298-0053, USA
e-mail: kellenbogen@vcuhealth.org; ken.ellenbogen@gmail.com

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_10

review basic pacemaker components, principles of pacemaker nomenclature, pacing modes, pacemaker indications, electrocardiographic features and basic pacemaker troubleshooting.

Pacemaker Components

A traditional implantable pacemaker requires a pulse generator and one, two or three pacing leads, all of which must be in proper condition to allow appropriate pacemaker function. While a left or right delto-pectoral incision is required to implant the pulse generator and leads, most leads (except epicardial) are inserted using a transvenous access (cephalic/axillary/subclavian veins) through the same incision to reach the desired cardiac chamber. The pulse generator is positioned in the subcutaneous tissue over the deltopectoral region.

The pulse generator consists of several components: a battery, electronic circuitry and the header with proper adaptors to connect corresponding leads. The pulse generator is responsible for delivering pacing stimuli through electrodes to properly initiate myocardial excitation and then contraction in the stimulated cardiac chamber.

The number and position of these leads depends on the pacing indication and the cardiac chambers wished to stimulate (Fig. 10.1). The simplest pacemakers are single-chamber, which can be either atrial or ventricular pacemakers and require implantation of a single-lead in the respective chamber. However, their function is limited to the implanted chamber, which can limit cardiac function in the presence of AV dissociation. A dual-chamber pacemaker requires two leads, an atrial and ventricular lead commonly implanted in the right atrial (RA) appendage and right ventricular (RV) septum, respectively, allowing pacing in both chambers if AV synchrony is needed.

Finally, biventricular pacemakers provide cardiac resynchronization therapy (CRT), requiring an RA, RV and left ventricular (LV) leads as it is intended to trigger each ventricular contraction by pacing RV and LV chambers after each P wave or atrial pacing. In contrast to RA and RV leads, the LV lead is implanted in the epicardium of the LV though the coronary sinus into a posterior or lateral cardiac vein (branch off the coronary sinus). Occasionally, transvenous LV lead implantation is not possible due to anatomical limitations, in which case, cardiothoracic surgery (for true epicardial placement) is a frequent alternative. Biventricular pacemakers are implanted in patients with heart failure in order to improve LV dyssynchrony (uncoordinated contraction of LV segments) commonly seen in patients with an underlying LBBB and reduced LV ejection fraction (<35%).

Pacing Nomenclature

Pacing nomenclature has increased in complexity over the last decades due to the increased numbers of new indications and new pacing algorithms. The most recent example is the introduction of biventricular pacemakers less than 20 years ago. Thus, a combined effort from the Mode Code Committee of the North American Society of Pacing and Electrophysiology in cooperation with the British Pacing and Electrophysiology Group standardized the nomenclature used in all pacemakers (Table 10.1). The current nomenclature includes a five-letter code that describes the overall pacemaker function, also referred as "pacing mode" [1].

The first letter represents the chamber(s) in which pacemaker stimulation occurs: "A" refers to atrial pacing, "V" denotes ventricular pacing and "D" indicates both atrial and ventricular pacing. The second letter reflects to the chamber(s) able to sense cardiac signals: "A" signifies the ability to sense atrial signals, "V" denotes the ability to sense ventricular signals, "D" indicates ability to sense both atrial and ventricular signals, and "O" represents lack of sensing at all (asynchronous mode). The third letter indicates the pacemaker response to sensed cardiac events, where "I" indicates that atrial or ventricular pacing will be inhibited in the presence of atrial or ventricular signals, respectively; "T" reflects ventricular pacing will be triggered by the presence of an atrial signal in order to maintain atrial-ventricular synchrony; "D" denotes both "inhibition" and "trigger or tracking" mode of response, and "O" represents lack of any response to sensed events. A typical example of a dual response to sensed events can be seen when an intrinsic P wave (atrial event) is sensed by the atrial channel therefore inhibiting atrial pacing, yet it will trigger ventricular pacing if no sensed QRS (ventricular event) is noted, referred as P-synchronous pacing. The fourth letter "R" or "O" indicates whether the pacemaker is able to control the rate based on an activity sensor referred as "sensor-rate modulation or rate-modulating pacing" is enabled (R) or not (O). Finally, the fifth letter represents whether multisite pacing is present in the atria "A", ventricle "V", both atria and ventricle "D" or not present at all denoted with an "O". This fifth letter has become relevant with the launch of biventricular devices.

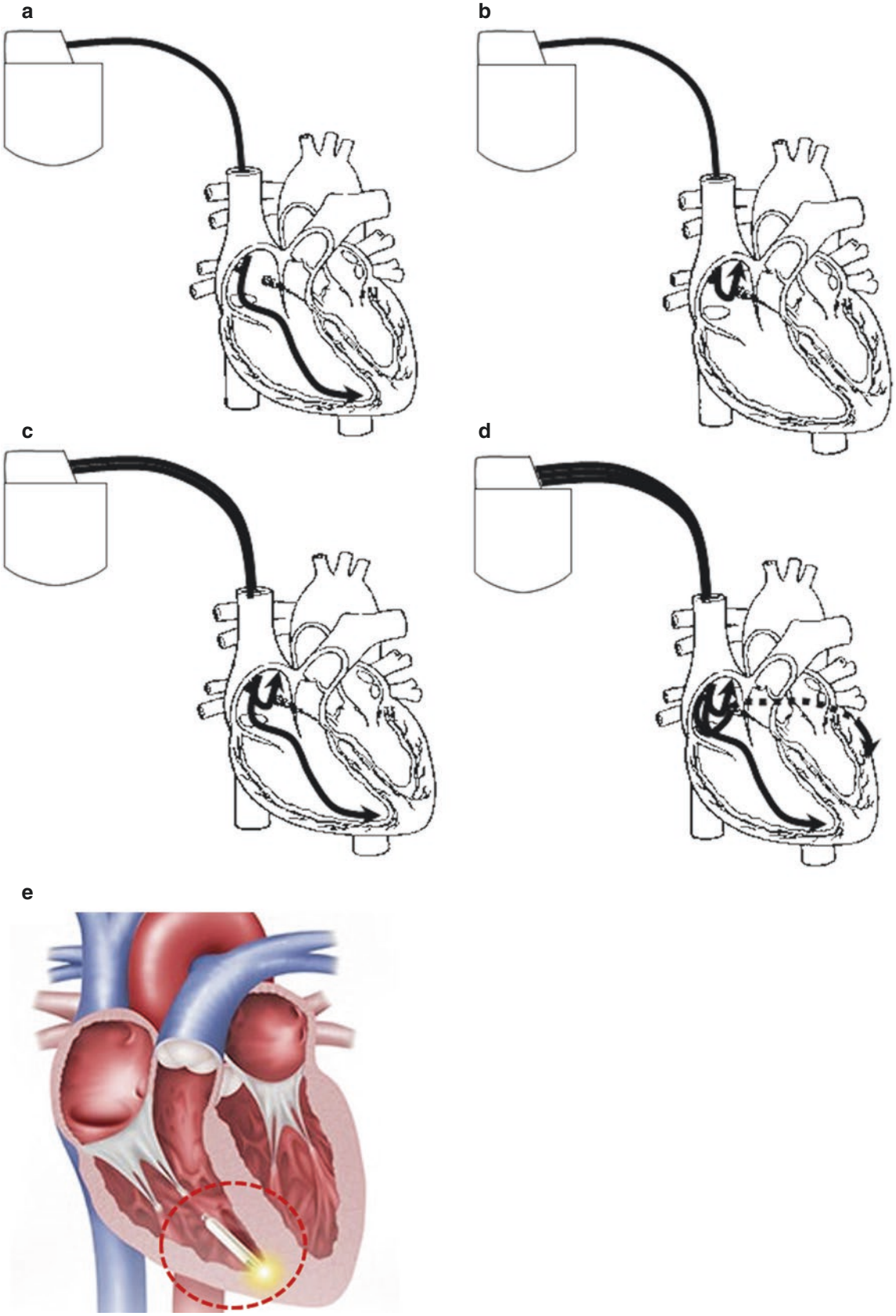


Fig. 10.1 Schematic of commonly used pacemaker systems and newly developed leadless pacemakers. (**a**) Single-chamber ventricular pacemaker; (**b**) Single-chamber atrial pacemaker; (**c**) Dual-chamber pacemaker; (**d**) Triple-chamber (biventricular) pacemaker (Permission granted by Mayo Clinic Proceedings); (**e**) Nanostim leadless pacemaker (St. Jude Medical, Inc., Sylmar, CA). Small pen-size device which includes battery, electronic circuitry and pacing electrodes

Table 10.1 Revised NASPE/BPEG generic code for bradycardia, adaptive-rate, and multisite pacing [1]

Position				
I: Chamber(s) paced	II: Chamber(s) sensed	III: Response to sensing	IV: Rate modulation	V:Multisite pacing
O = None	O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	T = Triggered	R = Rate modulation	A = Atrium
V = Ventricle	V = Ventricle	I = Inhibited		V = Ventricle
D = Dual (A + V)	D = Dual (A + V)	D = Dual (T + I)		D = Dual (A + V)

BPEG British Pacing and Electrophysiology Group, *NASPE* North American Society of Pacing and Electrophysiology. Modified from Bernstein et al. [1]

Pacing Modes

Over the past years, pacing modes have advanced as the clinical needs have increased and consequences of chronic pacing have become clearer. The availability to program a specific pacing mode is contingent to the number of implanted pacing leads. The most frequent pacing modes (Figs. 10.2 and 10.3) including their indications, advantages and disadvantages are summarized in Table 10.2.

Single or Dual-Chamber Asynchronous Pacing (AOO, VOO, DOO)

These are the simplest pacing modes since there is absence of sensing or rate-response allowing only to program a lower rate limit (LRL). Atrial asynchronous mode (AOO) will only pace the atrial channel regardless of the underlying atrial or ventricular rhythm (due to the lack of sensing). Similar to AOO, Ventricular asynchronous mode (VOO) will pace ventricle at LRL despite the presence of intrinsic atrial or ventricular rhythm (Fig. 10.2a). Finally, dual-chamber asynchronous mode (DOO) will pace both atria and ventricle at LRL with a programmable atrio-ventricular interval (AVI), regardless of intrinsic rhythm (P wave or QRS). These pacing modes are commonly used briefly in pacemaker-dependent pacemakers to prevent inappropriate pacing inhibition during procedures associated with electrocautery or other noise generating devices (Table 10.2).

AAI(R) and VVI(R) Pacing Modes

These are referred as single-chamber (atrial or ventricular) inhibited pacing modes (Fig. 10.2b, c). AAI can be programmed in a single-lead atrial pacemaker or a dual-chamber pacemaker. AAI mode is only able to pace the atria (A, first letter), sense the atria (A, second letter) and inhibit atrial pacing (I, third letter) in response to a P wave (Fig. 10.2b). VVI can be programmed in a single-lead ventricular pacemaker or a dual-chamber pacemaker, allowing to pace the ventricle (V, first letter), sense the ventricle (V, second letter) and inhibit ventricular pacing (I, third letter) in response to a QRS signal (Fig. 10.2c). Percutaneous temporary pacing wires are often programmed to VVI to provide "back-up" pacing.

Both, AAI and VVI pacing modes incorporate sensing on the atrial or ventricular channel, atrial or ventricular pacing at programmed LRL if intrinsic rhythm is below LRL, while inhibiting atrial or ventricular pacing if the underlying rhythm is faster than LRL in its respective chamber. A fourth letter "R" is present in either AAI or VVI if rate-modulation is enabled, which will allow either pacing to occur at faster rates than programmed LRL only when sensor-indicated rate instructs pacemaker to do so. These sensors are designed to track with patient activity and may be based upon detection of respiratory rate via changes in thoracic impedance or motion using an accelerometer.

AAI pacing mode is indicated in pure symptomatic atrial bradyarrhythmias with intact AV nodal and His-Purkinje conduction. Yet, pure AAI mode is rarely used due to the inability to pace ventricle in the event of future AV nodal disease that could result in AV block and asystole. VVI pacing mode is commonly used in patients with: (1) single-chamber implantable defibrillators that usually lack pacing indications, (2) chronic atrial fibrillation or atrial tachyarrhythmias, and (3) mode switch to prevent inappropriate tracking during paroxysmal episodes of atrial fibrillation or flutter.

DDD Pacing Mode

DDD pacing mode can be described as AV sequential (D) pacing, dual chamber sensing (D) with inhibition and P-synchronous pacing (D). This pacing mode is the most commonly used in dual-chamber devices (DDD or DDDR) and biventricular pacemakers (DDDOV or DDDRV).

In DDD mode the pacemaker is capable of atrial and ventricular pacing and sensing with dual response (inhibited and triggered pacing) to an intrinsic atrial or ventricular sensed events (Fig. 10.2d). Both, atrial and ventricular (AV sequen-

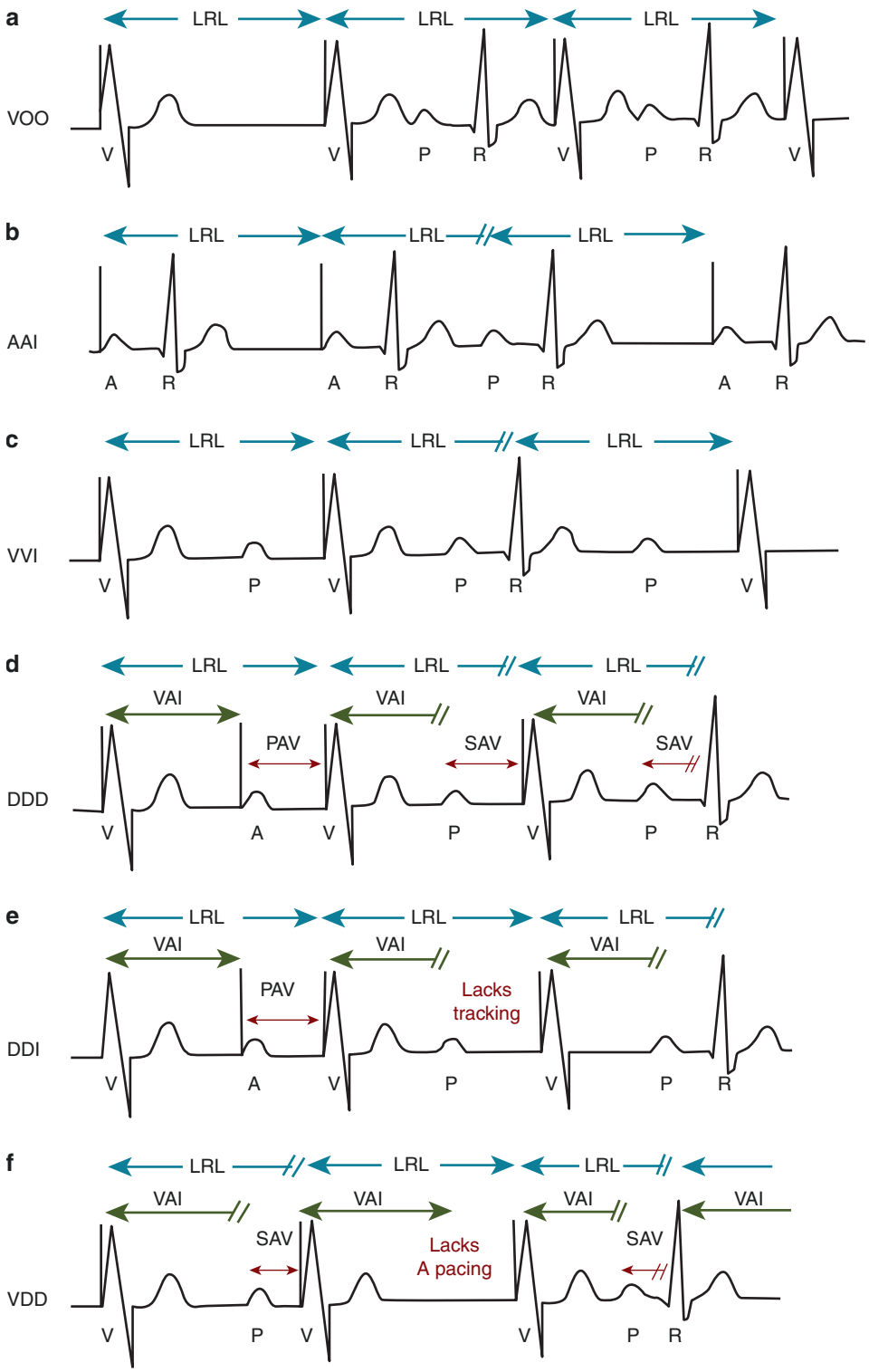


Fig. 10.2 Most frequent pacing modes. See text for details. *LRL* lower rate limit; *V* ventricular paced event; *R* intrinsic ventricular sensed event (QRS); *A* atrial paced event; *P* intrinsic atrial event (P wave); *SAV* sensed AV delay, which refers to programmed ventricular pacing after an intrinsic P wave; *PAV* paced AV delay, refers to programmed ventricular pacing after atrial pacing; *VAI* ventriculo-atrial interval, which refers to a period after a ventricular event when atrial pacing will occur only if this timing is completed (Modified from: Sakena S, Camm AJ, eds. Electrophysiological Disorders of the Heart, 2nd Ed. Philadelphia, PA: Elsevier Saunders, 2012: 441–456)

tial) pacing will only occur at the programmed AV delay or interval (AVI) if the intrinsic atrial and ventricular rates are below the LRL. If the intrinsic sinus rate is slower than LRL, the atrium will be paced at LRL while *inhibiting* ventricular pacing if intrinsic AV conduction (QRS event) is sensed within a predetermined AVI. If the sinus or atrial rate is faster than the LRL but no intrinsic AV conduction is present (no QRS) after the programmed AV delay, the pacemaker *inhibits* atrial pacing but *triggers* ventricular pacing (P-synchronous pacing) (Fig. 10.2d). However, tracking the intrinsic atrial rhythm will only occur up to a programmable maximum tracking rate (MTR), which will prevent pacemaker from

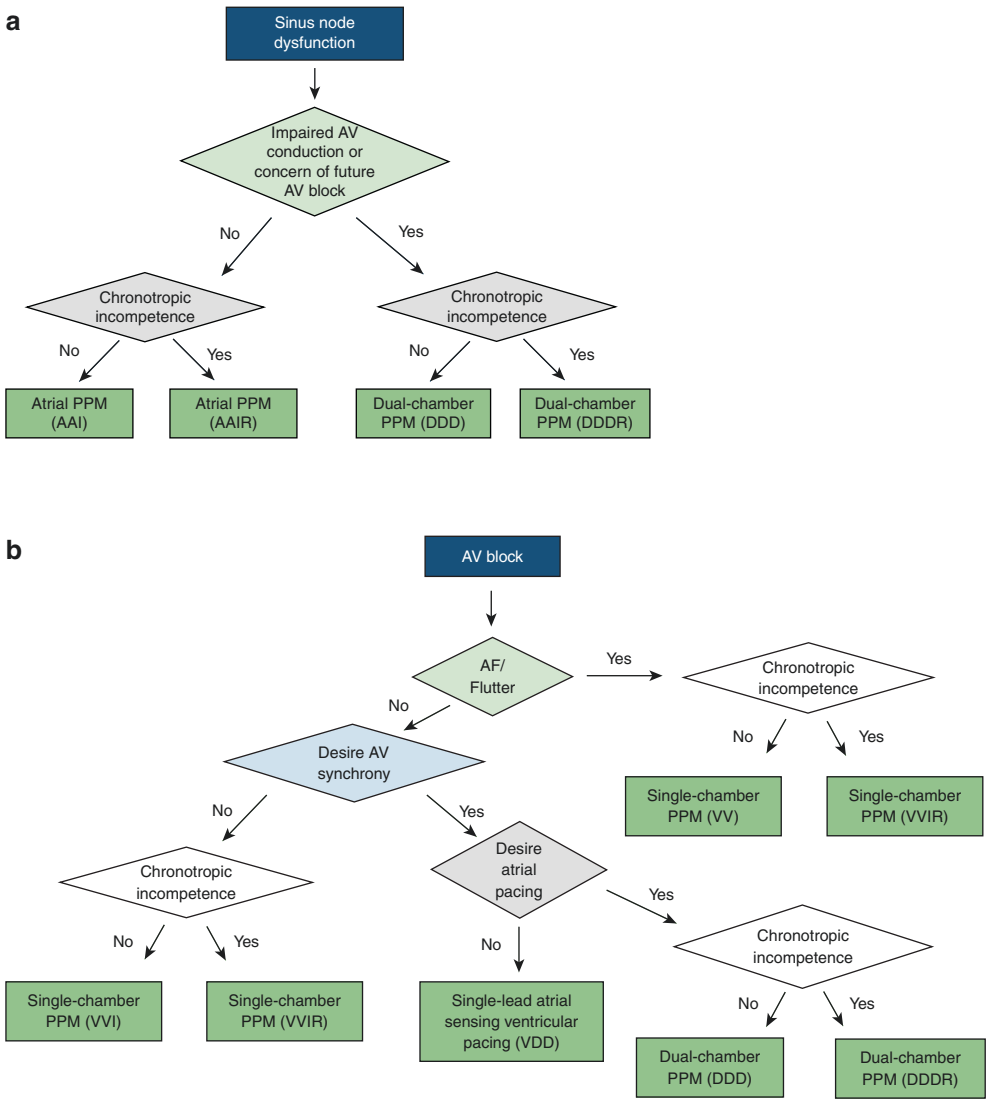


Fig. 10.3 Recommended pacemaker and pacing mode based on indications for (**a**) sinus node dysfunction and (**b**) AV block. Modified from 2012 ACCF/AHA/HRS Focused Update Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities [3]

tracking atrial dysrhythmias. Lastly, pacing in both the atrium and ventricle will be inhibited if the sinus rate is faster than LRL and intrinsic AV conduction is shorter than the programmed AVI. Similar to AAI and VVI pacing modes, the DDDR pacing mode represents the ability of the pacemaker to respond to activity with "rate-modulation", allowing pacing at faster rates than programmed LRL only when the sensor-indicated rate instructs the pacemaker to do so.

DDI Pacing Mode

DDI is similar to DDD mode without the ability to track atrial events (lacks P-synchronous pacing). Thus, it can be described as AV sequential pacing (D) with dual chamber sensing (D) and pacing inhibition (I) without P-synchronous pacing. Thus, ventricular pacing rate is never greater than the programmed LRL regardless of the atrial rate (Fig. 10.2e), while AV sequential pacing will occur only if no intrinsic AV conduction (QRS) is present after the programmed AV interval is expired. Thus, DDI pacing mode is commonly used for mode switching (Table 10.2), which means in the presence of an atrial tachyarrhythmias (atrial fibrillation (AF) or flutter) the pacing mode will automatically switch from a tracking pacing mode (DDD) to a non-tracking mode (DDI) to prevent rapid and irregular ventricular pacing. Rate modulation can also be enabled (DDIR) to increase the pacing rate based on the activity sensor in those patients with chronotropic incompetence while in AF with a slow ventricular rate.

VDI Pacing Mode

VDI pacing mode can be described as ventricular pacing only (V) with both atrial and ventricular sensing (D) and inhibition of ventricular pacing (I) in the presence of intrin-

Table 10.2 Indications, advantages and disadvantages of the most commonly used pacing mode

Pacing mode	Indication/advantages	Disadvantages
Asynchronous pacing (AOO, VOO, DOO)	Pacemaker dependent patients exposed to noise (e.g. electrocautery during surgery). Avoids oversensing and asystole	Pacing regardless of intrinsic events. Potential risk for arrhythmia induction
Single chamber inhibited pacing AAI(R), VVI(R)	AAI—sick sinus syndrome with intact AV node; preserves AV synchrony VVI—atrial fibrillation with slow VR and single-lead ICDs Both modes require a single lead and increase battery longevity	AAI lacks ventricular pacing in the event of intermittent AV block VVI is associated with AV dyssynchrony (manifest as pacemaker syndrome) and has higher incidence of atrial arrhythmias [9]
DDD, DDD(R)V (CRT)	Preserves AV synchrony (less pacemaker syndrome) Low incidence of atrial arrhythmias and improved hemodynamics	Requires at least a two-chamber lead system and has a lesser battery longevity
DDI(R)	Functions as two different pacemakers (AAI and VVI). Used as mode switch to avoid tracking atrial tachyarrhythmias	Same as DDD. Possible AV dyssynchrony and pacemaker syndrome (does not track atrial sensed events)
VDI(R)	Alternative mode switch to DDI (lacks atrial pacing), since it is unable to track sensed atrial events above LRL	Similar to VVI, as it is associated with AV dyssynchrony and potential atrial arrhythmias
VDD	Appropriate sinus node function with AV node disease; dual-chamber with high atrial pacing threshold to minimize battery depletion	Lack of atrial pacing Potential AV dyssynchrony at sinus rates below lower rate limit

Modified from Huizar JF, Kaszala K, Ellenbogen KA. Cardiac Pacing Modes and Terminology. In: Sakena S, Camm AJ, eds. Electrophysiological Disorders of the Heart, 2nd Ed. Philadelphia, PA: Elsevier Saunders, 2012: 441–456

sic QRS without the ability P-synchronous pacing (cannot track P waves). Thus, it lacks atrial pacing and AV sequential pacing, frequently resulting in AV dyssynchrony (ventricular pacing at programmed LRL) regardless of the intrinsic atrial rate. Thus, this is an alternative pacing mode in patients with chronic atrial fibrillation or flutter and it is available as a mode switch feature in some pacemakers (Table 10.2). Similar to other pacing modes, rate modulation can also be enabled (VDIR) to allow increase in pacing rate during activity.

VDD Pacing Mode

VDD pacing mode can be described as ventricular pacing only (V), while sensing both atria and ventricle (D) and able to inhibit ventricular pacing in the presence of intrinsic QRS and trigger or track intrinsic atrial rhythm (P-synchronous pacing) (Fig. 10.2f). However, it is different from DDD since it is unable to pace the atria which could result in AV dyssynchrony if atrial rate is below LRL. Nowadays, VDD pacing mode is used in single-pass ventricular leads (ventricular leads that have additional atrial sensing pole electrodes) which are unable to pace atria, yet they allow P-synchronous pacing (maintaining AV synchrony) (Table 10.2). Rate modulation in this pacing mode is not recommended since it will likely result in AV dyssynchrony due to ventricular pacing at sensor rates without the ability to pace the atria. VDD mode although rare, can also be used in cardiac resynchronization therapy [2].

Pacing Indications

There are many indications and recommendations for pacing, yet not all patients with bradycardia meet criteria, require, or benefit from pacemaker implant. In general, pacemaker implantation recommendations are predominantly based upon symptoms. Frequently, ambulatory heart rhythm monitoring (e.g. Holter) is needed to correlate symptoms with bradycardia. Current ACCF/AHA/HRS pacemaker guidelines [3] classify indications based on the benefit versus risk in four different recommendations: (1) class I: pacemaker "is recommended" as it is known to be useful and effective, (2) class IIa: pacemaker implant "is reasonable" since there is some evidence of benefit, (3) class IIb: pacemaker "may be considered" since its usefulness and benefit is less well established, and finally (4) class III: pacemaker "is not useful/effective or may be harmful". These recommendations are based on the level of evidence in three different categories: "A" data derives from multiple randomized clinical trials or meta-analysis, "B" recommendation originates from a single randomized trial or non-randomized studies, and "C" recommendation comes from consensus opinion of experts, case studies or standard of care. Thus, pacemaker recommendations can be complex with multiple variants. For easier understanding, Tables 10.3 and 10.4 lists the most common class I and III pacemaker recommendations, describing when a pacemaker should be strongly considered or when it may cause harm, respectively.

The most frequent pacemaker indications (Table 10.4) [3] are due to sinus node dysfunction, including sinus bradycardia, sino-atrial block, sinus arrest and sinus pauses that commonly occur after episodes of sustained tachycardia (e.g. atrial fibrillation), referred as tachy-brady syndrome. In these

Table 10.3 Class I pacemaker recommendation—pacemaker is indicated (benefit >>> risk) [3]

Diagnosis	Other features to meet criteria for pacemaker implant	Level of evidence
Sinus node dysfunction (SND)	– SND with symptomatic bradycardia or pauses	C
	– Symptomatic chronotropic incompetence	C
Mobitz II and third degree AV block	– Symptoms or arrhythmias	C
	– No symptoms with asystole >3 s	C
	– Escape rhythm <40 bpm below AVN	C
Bifascicular block	– Mobitz II AVB and Intermittent third degree AVB	B
	– Alternating bundle branch block	C
AV block after acute phase of AMI	– Persistent second degree AVB in His with alternating BBB or third degree AVB within or below His-Purkinje	B
	– Persistent and symptomatic second or third degree AVB	C
	– Transient Mobitz II or third degree infranodal AVB or BBB	B
Hypersensitive carotid sinus syndrome and neurogenic syncope	– Recurrent syncope due to spontaneously carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole >3 s	C

Note: *AVB* atrio-ventricular block, *BBB* bundle branch block

Table 10.4 Class III pacemaker recommendation—pacemaker is NOT useful or may be harmful (risk > benefit) [3]

Diagnosis	Other features to meet criteria for pacemaker implant	Level of evidence
Sinus node dysfunction	– Asymptomatic sinus node dysfunction	C
AV node dysfunction	– Asymptomatic first degree AVB	C
	– Asymptomatic Mobitz I AVB not at level of Intra or infra-His	C
	– AVB expected to resolve (drugs, hypoxia-sleep apnea, Lyme)	C
Bifascicular block	– Fascicular block without AVB or symptoms	B
	– Fascicular block with 1st degree AVB without symptoms	B
AV block after acute phase of AMI	– Transient AVB in the absence of infra-nodal disease	B
	– Transient AVB in the presence of isolated LAFB	B
	– New BBB or fascicular block in the absence of AVB	B
	– Persistent asymptomatic 1st degree AVB and BBB or fascicular block	B
Hypersensitive carotid sinus syndrome and neurogenic syncope	– Hypersensitive cardio-inhibitory response to carotid sinus stimulation without symptoms or vague symptoms	C
	– Situational vasovagal syncope in which avoiding trigger is effective	C

Note: *AVB* atrio-ventricular block, *BBB* bundle branch block

clinical scenarios, some clinicians will implant a single atrial-chamber pacemaker (AAI pacing mode) as long as there is no evidence of AV nodal disease (Figs. 10.1b and 10.2b). However, in the United States these patients often receive a dual-chamber pacemaker due to uncertainty about the development of AV nodal disease in the future in which case a single atrial-lead pacemaker would not prevent asystole due to AV block (Fig. 10.3).

A single ventricular-chamber pacemaker (VVI pacing mode) is commonly seen in patients without the need for pacing (implantable defibrillators) and/or when AV synchrony is not possible, such as in permanent atrial fibrillation and/or flutter (Fig. 10.1a). Leadless pacemakers are entering clinical practice and function as VVI pacemakers. Their housing, which can fit inside a pen-cap, serves as the pulse generator and pacing electrode (Fig. 10.1e).

Dual-chamber pacemaker (DDD pacing mode) is advantageous and commonly required in patients in sinus rhythm or with paroxysmal atrial arrhythmias with symptomatic AV block or His-Purkinje disease at increased risk of complete AV block to maintain AV synchrony. Fig. 10.3 summarizes recommended pacemaker and pacing mode indication in patients with AV block [3]. In addition, special circumstances include patients with autonomic dysfunction syndrome, which include those with neurocardiogenic syncope or carotid sinus hypersensitivity who may benefit from dual-chamber pacemakers (Table 10.3) [3]. Dual-chamber pacemakers are less frequently associated with *pacemaker syndrome*, which refers to the presence of symptoms such as fatigue, palpitations, general malaise and/or fullness in the neck or throat during ventricular pacing which is predominantly related to AV dissociation and AV dyssynchrony.

Table 10.5 Biventricular pacemaker (cardiac resynchronization therapy, CRT) recommendations and level of evidence [3]

Class I—biventricular pacemaker is indicated (benefit >>> risk)	Level of evidence
LVEF ≤35%, sinus rhythm and LBBB with QRS ≥150 ms and NYHA class II despite medical therapy	B
LVEF ≤35%, sinus rhythm and LBBB with QRS ≥150 ms and NYHA class III or ambulatory IV despite medical therapy	A
Class IIa—biventricular pacemaker is resonable (benefit >>risk)	
LVEF ≤35%, sinus rhythm and LBBB with QRS 120–150 ms and NYHA class II, III or ambulatory IV NYHA despite medical therapy	B
LVEF ≤35%, sinus rhythm and non-LBBB pattern with QRS ≥150 ms and class III or ambulatory IV NYHA despite medical therapy	A
Atrial fibrillation with LVEF ≤35% despite medical therapy if patient requires ventricular pacing or AV nodal ablation with near 100% pacing	B
LVEF ≤35% despite medical therapy if it is anticipated that patient requires >40% ventricular pacing	C
Class IIb—biventricular pacemaker may be considered (benefit > risk)	
Ischemic cardiomyopathy with LVEF ≤30% and LBBB with QRS ≥150 ms and NYHA class I despite medical therapy	C
LVEF ≤35%, non-LBBB pattern with QRS duration 120–150 ms and NYHA class III or ambulatory class IV despite medical therapy	B
LVEF ≤35%, non-LBBB pattern with QRS ≥150 ms and NYHA class II despite medical therapy	B
Class III—biventricular pacemaker is NOT indicated or maybe harmful (benefit < risk)	
NYHA class I or II and non-LBBB with QRS ≤150 ms	B
Limited functional capacity and survival less than 1 year	C

Finally, biventricular pacing or cardiac resynchronization therapy (CRT) was developed to improve LV mechanics in patients with LV dyssynchrony in patients with heart failure. CRT is strongly recommended (class I) in patients with LVEF ≤35%, LBBB with QRS duration ≥150 ms and class II, III, or ambulatory IV despite medical therapy. Other recommendations for biventricular pacemakers are detailed in Table 10.5, including clinical scenarios in which CRT is not beneficial or even harmful (Class III) [3].

Pacemaker Outpatient Follow-Up

As pacemaker technology has evolved, so has the follow up of this devices. Follow up is not as frequent as required in the past, not only due to the significant reliability of the devices, but most importantly due to the addition of remote home monitoring. Pacemakers should be followed on a regular schedule to monitor clinical status, as well as integrity of the system (pulse generator and leads) and optimize device function and battery longevity. In general, pacemakers are usually followed 2–4 weeks immediately after implant to assess wound healing and exclude lead dislodgement, since the risk of this complication is highest the first 3 months after implant. A 3-month follow up after device implant is frequently performed not only to rule out lead dislodgment, but most importantly because lead parameters are unlikely to change after that point, making it important to minimize pacing output and optimize battery longevity. Long term pacemaker follow up is based on pacemaker performance, patient's clinical needs and underlying indication for pacemaker and interim problems. In many patients without any significant underlying complex medical problems the pacemaker can be assessed every 6–12 months either in person or remotely. It is not infrequent that pacemaker patients only need a yearly evaluation, particularly with remote home monitoring. Most devices can have battery status, pacing and sensing thresholds, underlying rhythm and lead impedances monitored with remote home monitoring. Only unique circumstances, such as pacemaker/battery or lead recalls, malfunctions and near end-of-life battery status require more frequent 1–3 month follow up.

Electrocardiogram Characteristics Based on Pacing Lead Location

The pacing stimulus is frequently recognized as a pacing spike that initiates a P wave or QRS on ECG. In the past, unipolar leads (pulse generator functions as anode) were frequently implanted, making the identification of pacing spikes quite easy. In contrast, bipolar leads generate smaller pacing spikes.

The P wave and QRS morphologies are generated by the location of the atrial and ventricular pacing leads, respectively. Thus, the ECG can help us determine the location of leads since the P wave and QRS axis is opposite the site of stimulation (Table 10.6). For instance, if the activation vector has an inferior-posterior, leftward and apical direction (QRS positive in the inferior leads-II, III, aVF, negative in V_1 and aVR and positive in I, and $V_{5–6}$; Fig. 10.4), we can infer that ventricular electrode is located in the superior-basal region (near tricuspid valve) of the RV septum.

P Wave Morphology

The atrial electrode is usually placed in the right atrial (RA) appendage, situated in the superior-anterior free wall of the RA. Thus, the atrial activation vector travels away from this region, demonstrating an infero-posterior, leftward axis since LA depolarizes after RA (P wave is positive in inferior leads and lead I and aVL, while negative in V_1 and aVR) (Table 10.6). Of note, pacing leads positioned near the posterior-superior

Table 10.6 ECG characteristics of P wave and QRS axis and morphology based on lead location

Lead position	Axis	Duration	Lead I	Leads III, aVF	Leads V_{1-2}	Leads V_{5-6}
Atrial—P wave						
RA appendage	Sup → Inf, Ant → Post, R → L	=	+	+ or ±	−	±
Superior Crista terminalis	Sup → Inf, Ant → Post, R → L	=	+	+	±	+ or ±
Inferior Crista terminalis	Inf → Sup, Ant → Post, R → L	=	+	−	±	+ or ±
Superior RA septum	Sup → Inf, R = L	↓↓↓	±	+	±	+
Ventricular—QRS complex						
RV apex	Inf → Sup, Ant → Post, R → L, Apex → Base	↑↑↑	+	−	LBBB qS	−
RV outflow tract	Sup → Inf, Ant → Post, R → L, Base → Apex	↑↑	±	+	LBBB qS	+
RV Parahisian region	Sup → Inf, Ant → Post, R → L, Base → Apex	↑	+	+	LBBB qS	+
Posterior-lateral region of LV base	Sup → Inf, Post → Ant, L → R, Base → Apex	↑↑↑↑	−	− or ±	RBBB rsR'	+ or ±
Biventricular (RV apex and sup-posterior region of LV base)	Sup → Inf, R → L, Apex = Base	↑↑	− or qR	+	rS	− or ±

Inf = inferior, Sup = superior, Post = posterior, Base = near annular valve, L = left, R = right, ± = biphasic, LBBB = left bundle branch block pattern, RBBB = right bundle branch block pattern, number of arrows represent the increase in P wave or QRS duration compared to baseline values

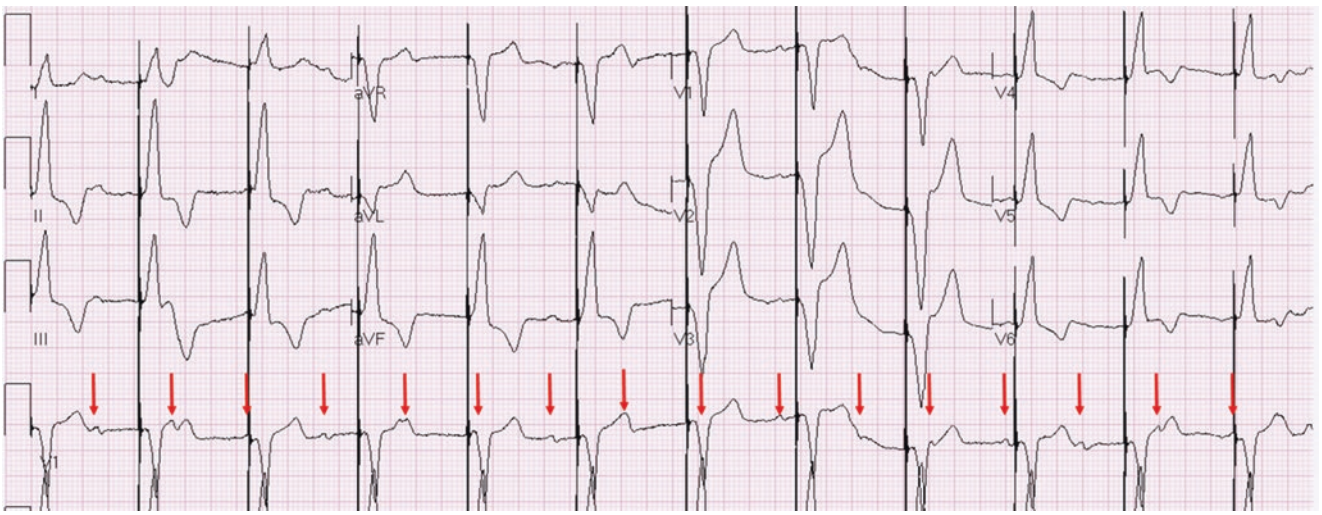


Fig. 10.4 Sinus tachycardia (*arrows* denote P wave) and ventricular paced rhythm (AV dyssynchrony) due to complete AV block and a pacemaker programmed a VVI pacing mode. RV pacing from the superior base of the RV septum resulting in an inferior, leftward and apical activation vector. Permission obtain from: Uribe W, eds. Electrocardiografia Clinica: De lo Basico a lo Complejo (Chapter 33). Distribuna Editorial. Bogota, Colombia, 2015: 463–477

aspect of the RA may cause unwanted right phrenic nerve stimulation. In general, the P wave duration is very similar as long as RA lead is placed in the superior-lateral aspect of the RA, causing a sequential RA and LA activation. P wave axis, duration and morphology based on the most frequent RA lead positions is summarized in Table 10.6 and represented in Fig. 10.5. However, atrial lead position can be challenging if P wave amplitude is small (due to atrial fibrosis) often seen in patients with heart failure.

Morphology of QRS Complex

The RV lead in a dual-chamber pacemaker is commonly placed in the septal region of the RV apex since it is considered the most stable position with the lowest probability of RV perforation. Alternatively, the RV lead can be positioned in the septal region of the RV base (near the tricuspid valve) near the outflow tract or parahisian region, due to its proximity to the normal His-Purkinje conduction

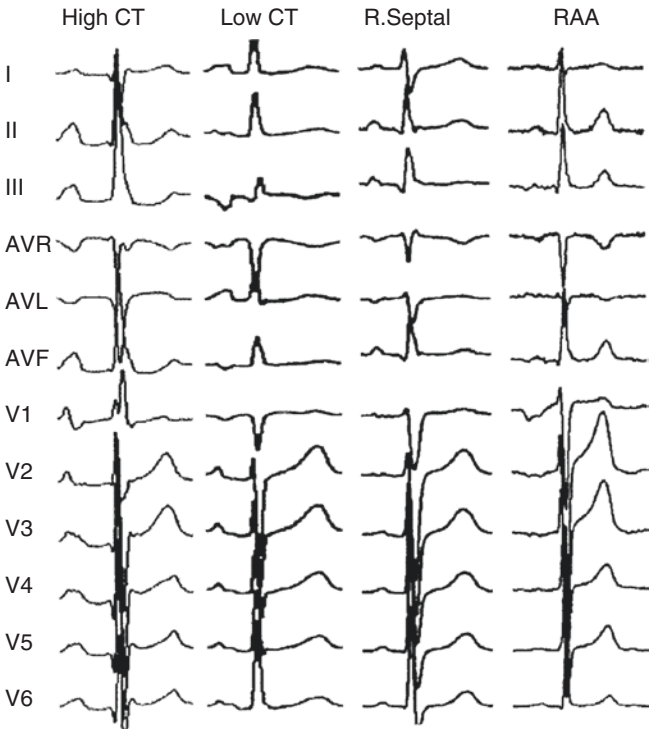


Fig. 10.5 P wave morphology, axis and duration based on the most frequent RA lead positions. *High CT* Superior crista terminalis, *Low CT* Inferior crista terminalis, *R. Septal* Right septal region, *RAA* right atrial appendage. Modified from Kistler PM, et al. J Am Coll Cardiol. 2006 Sep 5;48(5):1010–7

system causing a narrower QRS complex and a lesser degree of LV dyssynchrony (compared to RV apical pacing) even though its clinical benefit is not clear [4, 5]. In each one of the different RV lead positions, QRS demonstrate a distinct morphology summarized in Table 10.6 and represented in Fig. 10.6 A–F. In general, the QRS complex from RV pacing should reveal a LBBB pattern in ECG regardless of the exact location of the RV lead. This is an important concept since a RBBB pattern in a dual-chamber pacemaker should raise the possibility of RV septal perforation or an improper lead placement in the LV cavity through an inter-atrial or inter-ventricular septal defect, which could potentially result in clot formation and systemic embolic events.

Occasionally, QRS morphology and duration after the ventricular pacing spike may be noted to be slightly wide or even normal despite having a dual-chamber pacemaker with an RV lead positioned in the RV apex. This can be noted in patients where the intrinsic PR interval is close to the programmed AV delay in a DDD pacing mode or right bundle branch block (RBBB), thus ventricular pacing tracking a P wave occurs a few milliseconds after intrinsic AV conduction and His bundle activation, causing fusion between the QRS morphology of an intrinsic AV conducted beat and RV apical pacing (Fig. 10.7).

Over the past few years, placing the RV lead directly into the His-bundle position has been possible with direct recoding the His-bundle from the pacing electrode reproducing a narrow QRS that can be undistinguishable from the intrinsic QRS complex identified only by the preceding pacing spike (Fig. 10.8). A recent retrospective study [6] with His-bundle pacing suggests that His-bundle pacing may lead to improved clinical outcomes. In this study, His-bundle pacing was associated with a greater than 40% reduction in heart failure hospitalization compared to patients with a pacing lead in the RV apex.

Even though, pacing lead location can be predicted primarily based on QRS axis and morphology during pacing, extensive cardiac fibrosis, such as with myocardial infarction and infiltrative myocardial diseases can give significant variations of the QRS axis and morphology that may limit localization of pacing lead.

Biventricular Pacemakers

While RA and RV leads are implanted inside the cavity (endocardium) of the respective chambers, the LV lead is usually implanted in the epicardium though the coronary sinus into a lateral, posterolateral or anterolateral cardiac vein. Thus, the position of the LV lead is limited by the cardiac venous anatomy. Occasionally, LV lead implantation requires surgery for epicardial lead implantation due to anatomical restriction of the cardiac venous system.

Regardless of implantation, LV epicardial pacing usually has a longer QRS duration (>160 ms) due to the relative increased distance from the endocardial His-Purkinje network, while QRS morphology is similar to a RBBB pattern in lead V_1 (anterior lead) since ventricular activation is from LV free wall (posterior origin) towards RV (anterior) (Fig. 10.6-F). The QRS morphology of pure LV pacing in the most frequent locations is summarized in (Table 10.6). LV endocardial lead placement (via transseptal approach) has been used sporadically in patients where delivery through the coronary sinus has failed [7]. This technique carries a higher risk and require full anticoagulation to prevent embolic events.

Biventricular pacemakers should demonstrate a pacing spike that triggers each QRS complex as it is intended to improve LV dyssynchrony of each LV contraction. Depolarization of the entire left ventricle occur faster when compared to RV pacing alone, due to a fusion of the ventricular activation wavefront initiated from the RV and LV pacing electrodes and that results in a narrower QRS duration (Fig. 10.9).

QRS morphology of a biventricular paced complex can be recognized by careful inspection of the 12-lead ECG (Table 10.6). It is characterized by: (1) shorter QRS duration when compared to intrinsic LBBB during intrinsic AV conduction, (2) small R wave in V_1 that demonstrate a posterior to anterior vector due to activation of the LV free wall

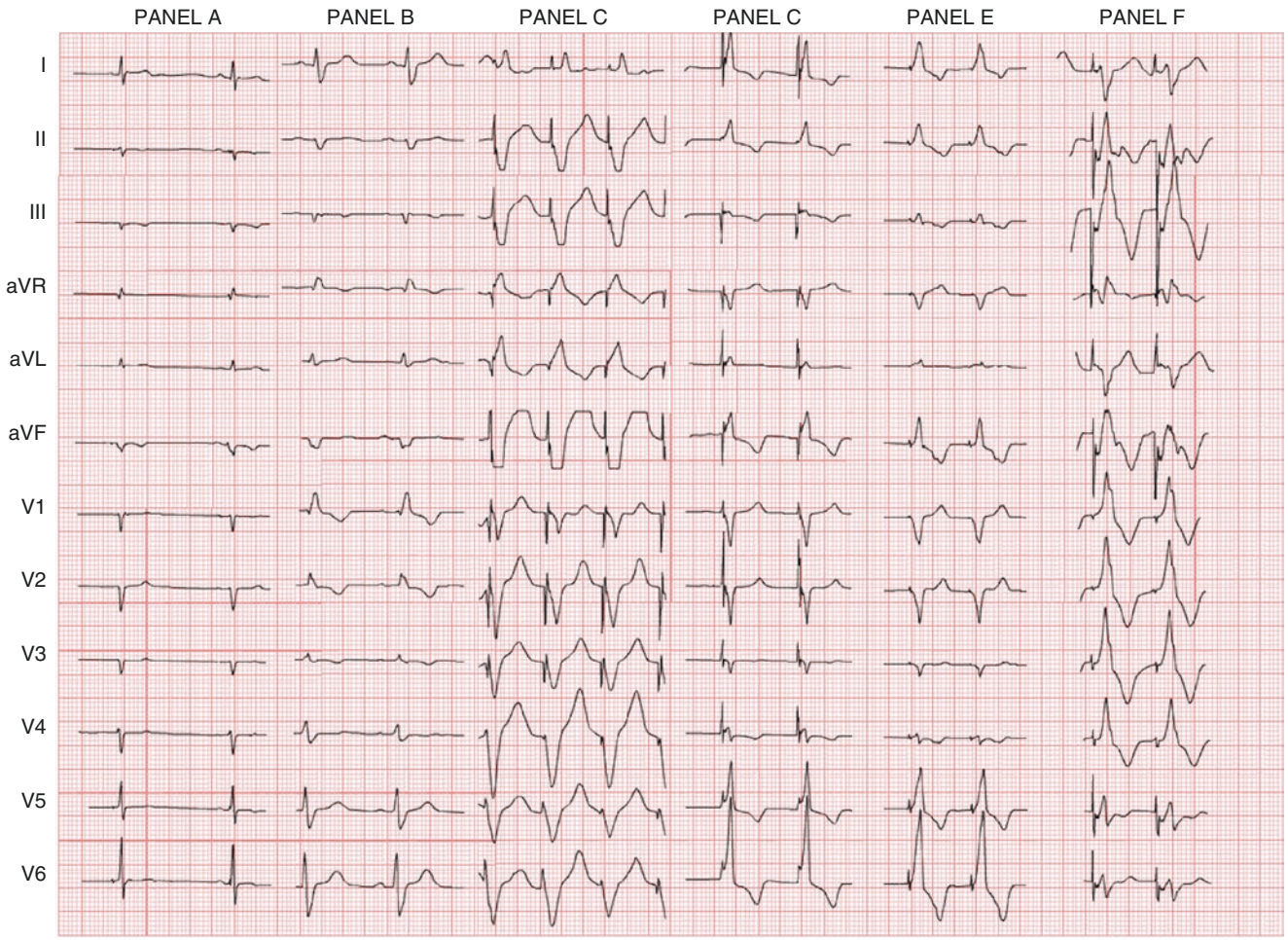


Fig. 10.6 Samples of distinct QRS morphologies and axis based on different RV pacing locations. Panel *A*, intrinsic normal QRS; Panel *B*, Sinus rhythm with RBBB and Left anterior fascicular block; Panel *C*, RV apical pacing; Panel *D*, RV parahisian and His bundle pacing, Panel *E*, Parahisian RV pacing alone (without His capture); Panel *F*, Left ventricular pacing from a superior and basal region of the posterolateral LV wall. Permission obtain from: Uribe W, eds. Electrocardiografia Clinica: De lo Basico a lo Complejo (Chapter 33). Distribuna Editorial. Bogota, Colombia, 2015: 463–477

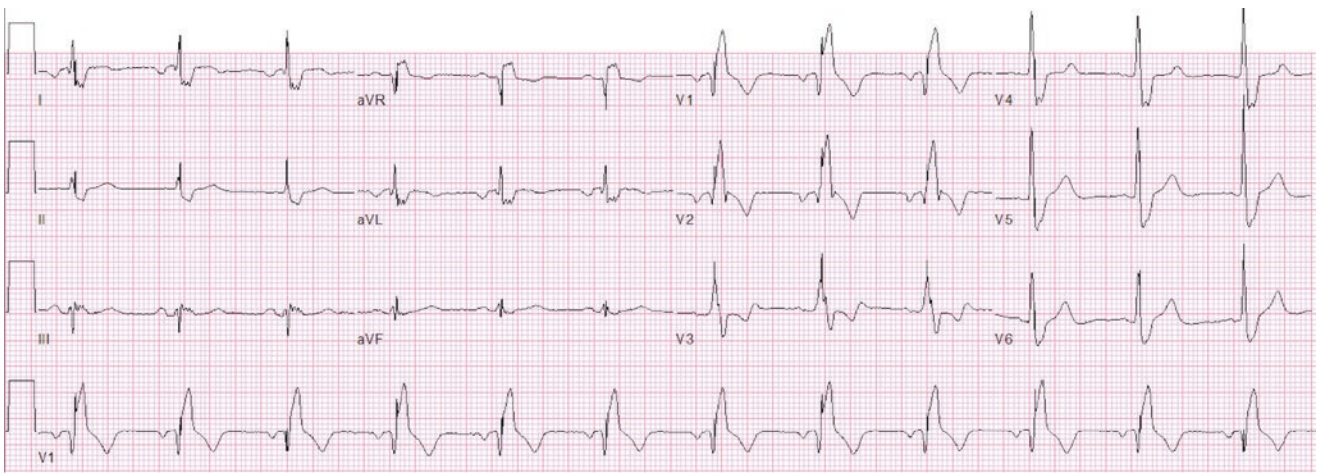


Fig. 10.7 ECG demonstrates sinus rhythm with a right bundle branch block and a pacing spike 40 ms after initiation of QRS (Q wave in V1). We can be certain that this is a dual-chamber pacemaker since it is tracking P waves (P-synchronous), likely programmed to a DDD pacing mode. Even though, pacing spike appears to be inappropriate, this is appropriate device function since the RV lead is unable to sense early in the QRS due to the delay in RV apical activation caused by the RBBB, triggering ventricular pacing (150 ms after AV interval expires) without much contribution in QRS morphology

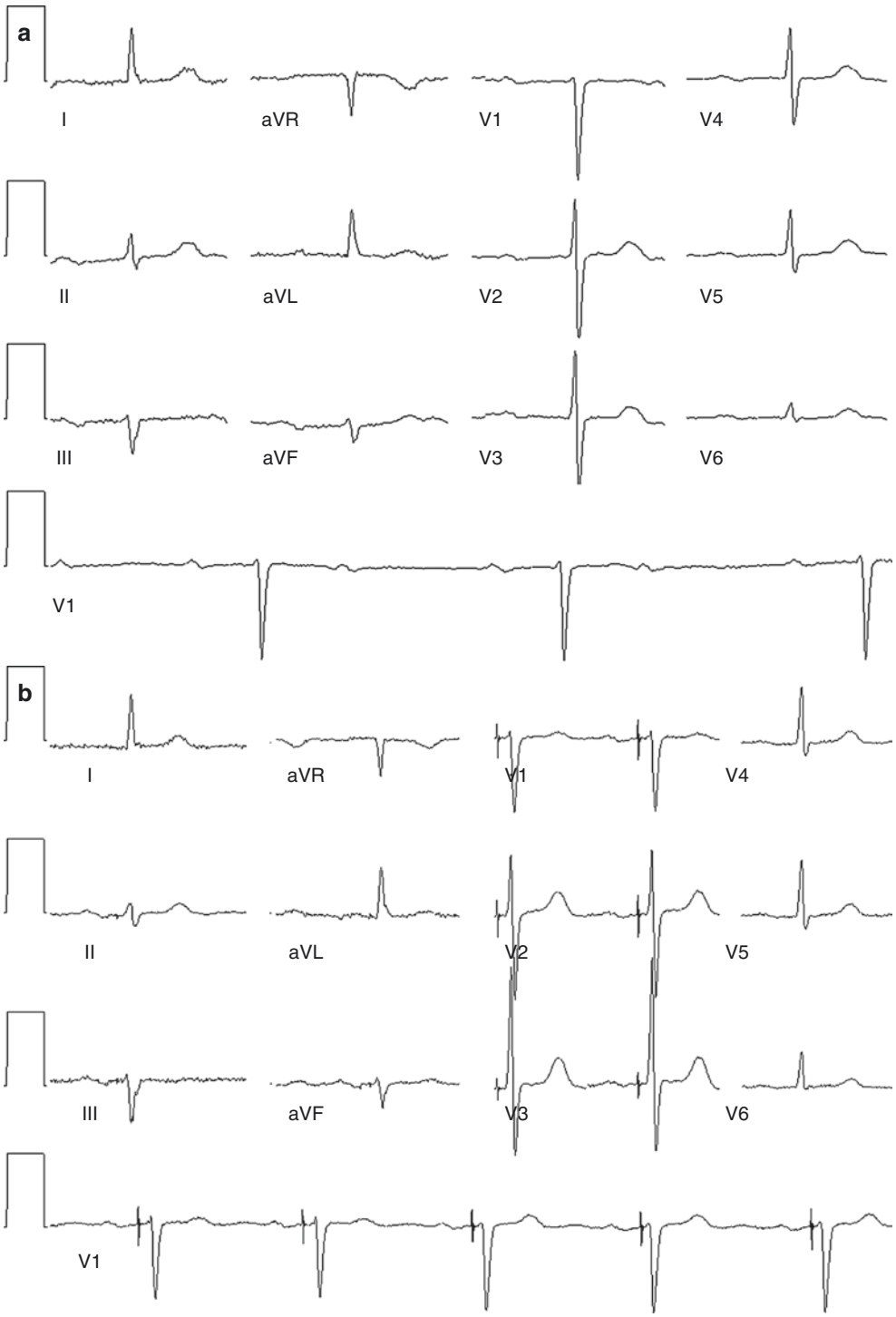


Fig. 10.8 His bundle pacing. Panel (**a**) shows a patient with bradycardia due to 2:1 AV block with a narrow QRS. Panel (**b**) demonstrates same patient after pacemaker implant with a P-synchronous pacing where the ventricular pacing lead is implanted in the His bundle. Therefore, pacing spike initiates a narrow QRS similar to the native one before implant

towards the RV, and (3) small Q wave in I and aVL that represents initial vector going away from LV free wall due to a left to right LV activation. The latter two ECG features can be accentuated if the LV is paced slightly ahead of the RV, which is possible due to a programmable LV–RV timing available in all new biventricular pacemakers. A different timing between LV and RV pacing, frequently recognized by the presence of two distinct pacing spikes at the beginning of the QRS, is commonly used to optimize QRS duration and resynchronization of the LV (Fig. 10.9).

Occasionally, a pacing spike can be recognized or noted immediately after an intrinsic QRS complex of a PVC or normal AV conduction, which can be mistaken as a malfunction of the pacemaker. However, this is not uncommon in biventricular pacemakers as it represents a feature called "biventricular trigger" intended to force pacing in the LV in

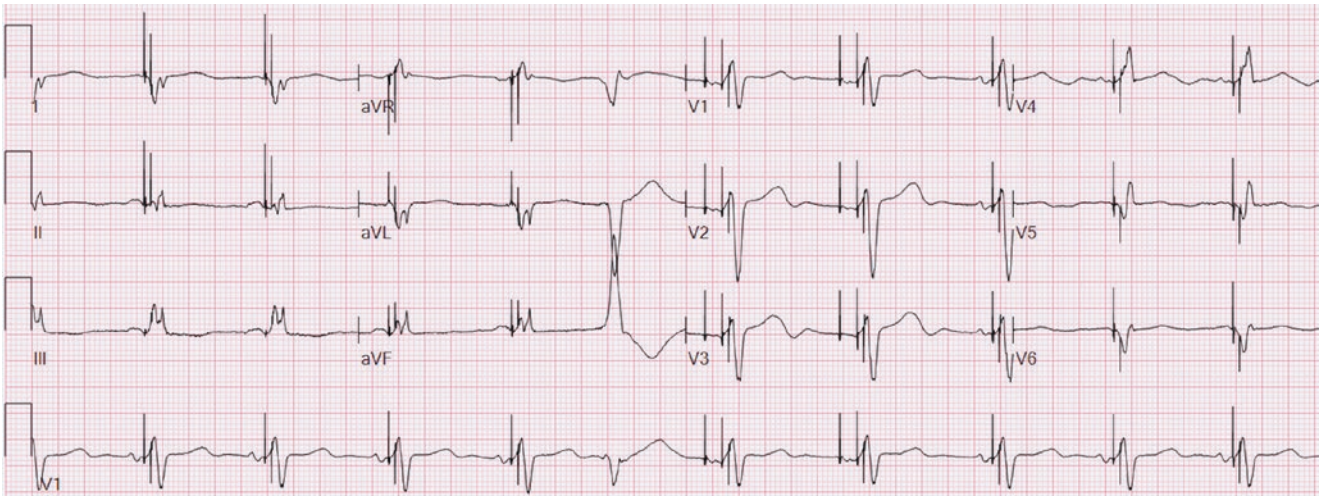


Fig. 10.9 Biventricular pacemaker. Typical QRS morphology in a CRT device with an rS pattern in V1 and Q wave in lead I triggered by ventricular pacing stimulus after tracking an intrinsic P wave (P-synchronous). Note the presence of two stimuli at the beginning of the QRS ($V_{4–6}$) due to a programmed LV offset of −30 ms. LV offset results in pacing of the RV and LV at slightly different times in order to optimize QRS duration and LV resynchronization

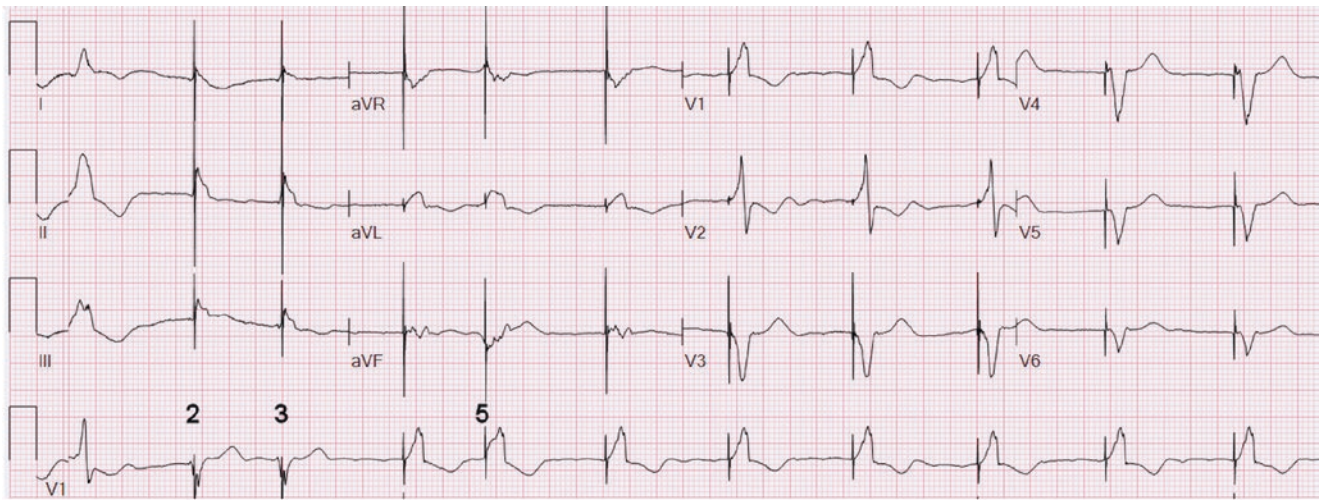


Fig. 10.10 Biventricular trigger. Right side of ECG tracing demonstrates atrial fibrillation with biventricular pacing since pacing stimulus clearly precedes and initiate QRS complex. Beats 2, 3 and 5 exhibit a pacing stimulus immediately after initiation of QRS complex consistent with biventricular trigger, intended to force LV pacing in an attempt to resynchronize either intrinsic beats (beats 2 and 3) and/or ventricular ectopic beats (beat 5)

special circumstances where biventricular pacing is compromised, such as with PVCs or during atrial fibrillation with a rapid ventricular response (Fig. 10.10).

Other ECG Changes Related to Pacing Stimulation

Patients undergoing pacing often exhibit abnormal repolarization. T wave frequently demonstrate non-specific abnormalities or even T wave inversion even if ventricular pacing is absent. This is speculated to represent abnormal repolarization in response to a change in ventricular propagation during ventricular pacing. Interestingly, these T wave abnormalities can persist even without ventricular pacing (during intrinsic AV conduction) in subjects exposed to long-term ventricular pacing and this is referred as "T wave memory" (Fig. 10.11). This is thought to be due to memory of abnormal repolarization due to chronic ventricular pacing [8]. T wave memory may take weeks to months for the T waves to fully normalize.

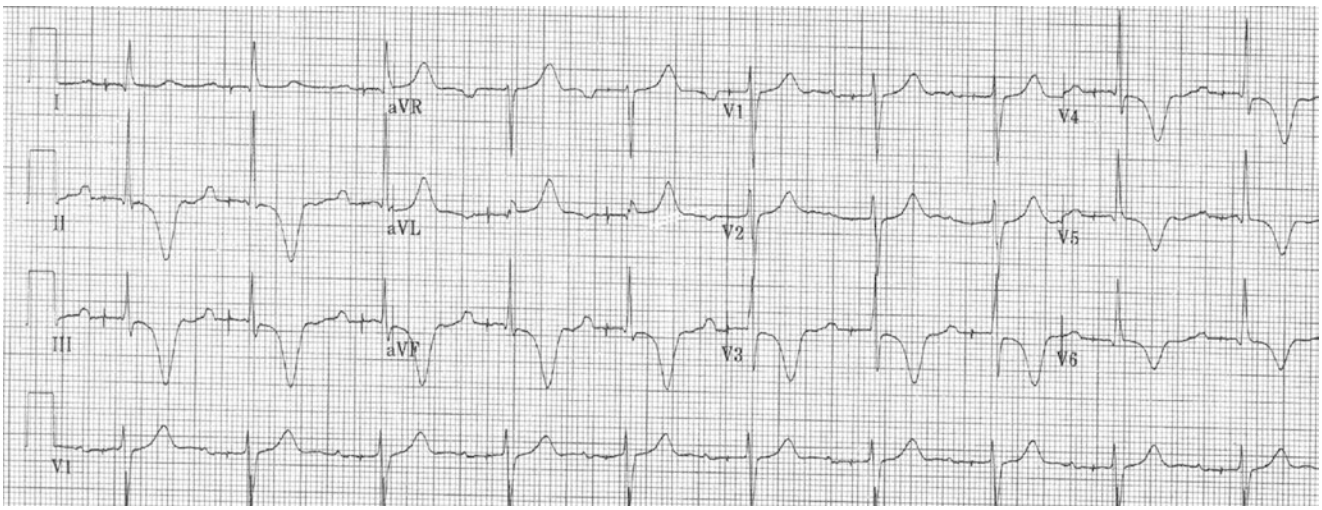


Fig. 10.11 ECG demonstrates sinus rhythm with a P-synchronous ventricular pacing spike (DDD pacing mode) that fails to capture. Intrinsic narrow QRS with diffuse T wave inversion "T wave memory" present after intrinsic AV conduction with a prolong PR (first degree AV block). This occurs after a long period of ventricular pacing and it may take weeks to months for the T waves to fully normalize

Troubleshooting

Due to the complexity of the pacemakers, interpretation of a malfunction requires a deep understanding of the programmed pacing mode and pacemaker features, which can frequently lead to a misinterpretation of pacemaker function. Overall, pacemaker malfunction can be divided into pacing or sensing abnormalities.

Pacing abnormalities refers to malfunction in pacing function such as, change in pacing impedance and/or threshold that can result in lack of capture upon pacing. This can be caused by abnormal battery depletion, lead dislodgment, pacing lead fracture or insulation breach, inappropriate lead-to-header connection (loose set-screw), and change in lead-myocardial tissue interface (fibrosis/infarct, electrolyte changes, antiarrhythmics) [8].

Sensing anomalies can be categorized into two groups: "oversensing" or "undersensing". Oversensing refers to the sensing of inappropriate signals, resulting in lack of pacing where the device would be expected to pace. This commonly occurs due to sensing of cardiac signals such as T wave, R wave far-field or P-wave far field oversensing by the opposite chamber or pacing artifact commonly referred as crosstalk. Oversensing can also be due to sensing of non-cardiac signals including: (1) external noise/artifact such as myopotentials or electromagnetic interference, or (2) pacemaker component failure such as lead fracture or loose-set screw [8].

Undersensing refers to the lack of appropriate sensing of existing cardiac signals, which can be suspected by the presence of pacing spikes with or without capture when the device is not expected to pace. This can occur due to lead dislodgement, lead fracture or change in lead-myocardial tissue interface [8].

If pacemaker or lead malfunction is suspected, clinical history, 12-lead ECG, chest-X ray and a detailed device interrogation are required to assess the presence and potential consequences of such pacemaker malfunction. Thus, it is important to inquire about symptoms such as dizziness, palpitations, exercise intolerance and/or syncope. Device interrogation, on the other hand, will assist to understand battery status, presence of noise detection, integrity of the pacing leads (sensing, impedance and threshold) and potential sensing or pacing issues. In addition, direct device manipulation and/or isometric exercises of the ipsilateral upper limb during device interrogation can help us unmask abnormal sensing/noise or lead parameters. Chest-X ray (postero-anterior and lateral projections) and/or fluoroscopy can assist to assess lead position, gross integrity of the lead as well as proper lead connection to the header of pacemaker.

Summary

Pacemakers have and will continue to increase in complexity as the field of cardiovascular medicine advances. New components and pacemaker features have added new indications and flexibility to treat different cardiac illnesses. Although rare, the addition of new pacemaker components and features increase the probability of failure of any of the new components. It is for that reason that providers involved in the care of patients with an implantable cardiac device should be aware of different components, indications, basic function of these devices including pacing modes, and be aware of

potential pacemaker malfunction that should be referred to proper specialist.

References

1. Bernstein AD, Daubert JC, Fletcher RD, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group. Pacing Clin Electrophysiol. 2002;25(2):260–4.
2. Bernheim A, Ammann P, Sticherling C, et al. Right atrial pacing impairs cardiac function during resynchronization therapy: acute effects of DDD pacing compared to VDD pacing. J Am Coll Cardiol. 2005;45(9):1482–7.
3. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61(3):e6–75.
4. Stambler BS, Ellenbogen K, Zhang X, et al. Right ventricular outflow versus apical pacing in pacemaker patients with congestive heart failure and atrial fibrillation. J Cardiovasc Electrophysiol. 2003;14(11):1180–6.
5. Occhetta E, Quirino G, Baduena L, et al. Right ventricular septal pacing: safety and efficacy in a long term follow up. World J Cardiol. 2015;7(8):490–8.
6. Sharma PS, Dandamudi G, Naperkowski A, et al. Permanent His-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. Heart Rhythm. 2015;12(2):305–12.
7. Domenichini G, Diab I, Campbell NG, et al. A highly effective technique for transseptal endocardial left ventricular lead placement for delivery of cardiac resynchronization therapy. Heart Rhythm. 2015;12(5):943–9.
8. Ellenbogen KA. Clinical cardiac pacing, defibrillation, and resynchronization therapy. 3rd ed. Philadelphia: Saunders/Elsevier; 2007.
9. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation. 2003;107(23):2932–7.

Implantable and Wearable Defibrillator Therapy

11

Samir Saba and N.A. Mark Estes

Abstract

Based on the results of multiple prospective randomized trials, the implantable cardioverter defibrillator (ICD) has become the dominant strategy for primary and secondary prevention of sudden cardiac death. When used in conjunction with cardiac resynchronization therapy for patients with impaired left ventricular function, left bundle-branch block, and heart failure, ICDs have resulted in decreased heart failure hospitalizations and prolonged survival. These improved outcomes are also accompanied by reverse remodeling based on echo parameters. More recently, a totally subcutaneous implantable cardioverter defibrillator has been developed. While it eliminates the transvenous lead, it has no bradycardia or antitachycardia pacing. The role of the wearable cardiac defibrillator in prevention of sudden cardiac death in high-risk populations remains less clearly defined due to the absence of appropriate designed prospective randomized trials.

Keywords

Sudden death • Cardiac arrest • Ventricular tachycardia • Ventricular fibrillation • Implantable cardioverter defibrillator • Wearable cardioverter defibrillator • Subcutaneous cardioverter defibrillator • Defibrillator

Definition and Epidemiology of Sudden Cardiac Death

By definition, sudden cardiac death (SCD) is unexpected cardiovascular collapse without pulse or signs of circulation in the absence of non-cardiac causes of death. Death occurring within 1 h of the onset of symptoms is also considered to be SCD. Cardiac arrest represents the most common cause of death in industrialized countries [1–4]. Currently it accounts for >50% of all deaths from cardiovascular disease worldwide [1–4]. In the United States, SCD results in >250,000–300,000 deaths annually. Because SCD happens outside of the hospital setting most commonly and is often not witnessed, SCD can be assumed when unexpected death or unwitnessed death occurs [1–4]. The term sudden cardiac arrest is often used to designate non-fatal SCD, where cardiopulmonary resuscitation is applied promptly and circulation is restored [1–4].

Prompt defibrillation for termination of VF or VT is the cornerstone of therapy to save patients' lives, before end-organ damage, primarily brain damage, occurs [1–4]. Because out-of-hospital cardiac arrests are often unwitnessed, and because prompt defibrillation is usually delayed by barriers to access to medical personnel, survival of out-of-hospital SCD victims remains poor [1–4]. Survival declines by >10% per minute for patients in ventricular fibrillation

S. Saba, M.D., F.A.C.C., F.H.R.S. (✉)
Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
e-mail: sabas@upmc.edu

N.A. Mark Estes, MD, FACC, FAHA, FHRS, FESC
New England Arrhythmia Center, Tufts-New England Medical Center, Boston, MA, USA

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_11

[1–4]. This underscores the critical importance of early and definitive intervention with defibrillation. The implantable cardioverter and wearable cardioverter defibrillator have emerged as devices to deliver therapy to victims of cardiac arrest within several seconds and thereby prevent SCD and improve clinical outcomes of survivors. Recently there has been a decrease in the incidence of cardiac arrest from ventricular fibrillation [1–4]. While the factors accounting for this remain undefined, they are likely to include improvements in prevention of cardiovascular disease and community approaches to resuscitation and care after out-of hospital cardiac arrest [1–4].

Because most individuals experiencing SCD currently are not identifiable as being at high risk, community-based public access to defibrillation programs have emerged using the automated external cardioverter defibrillator to provide definitive therapy with defibrillation within minutes of the onset of a cardiac arrest [1–4]. Prompt access to cardiopulmonary resuscitation, defibrillation, and advanced medical care as part of the "Chain of Survival" has been demonstrated to improve neurological and functional outcomes for cardiac arrest victims [1–4]. While the recent decline in the incidence of SCD parallels the decline in the decrease in cardiovascular mortality, the burden of SCD remains substantial [1–4]. On average, <10% of those receiving community-based resuscitation are discharged from the hospital neurologically intact [1–4].

Mechanisms of SCD

The mechanisms of SCD are variable but most commonly are arrhythmic in origin. Ventricular fibrillation is the mechanism underlying most sudden cardiac arrest episodes [1–4]. Less commonly other cardiac tachycardias, bradycardias, or pulseless electric activity can result in lack of cardiac mechanical activity with absence of circulation [1–4]. Cardiac arrest typically arises in an individual with an underlying cardiovascular condition that serves as the appropriate anatomic or electrophysiological substrate without an identifiable trigger [1–4]. However, there is commonly a trigger such as ischemia in the setting of appropriate anatomic or electrophysiological substrate. Currently the paradigm for the pathophysiology of SCD is that an abnormal myocardial substrate is a requisite with transient factors that trigger the cardiac arrest. In most instances a clinical trigger cannot be identified [1–4].

Risk Stratification for SCD

Risk factors for SCD include advanced age, male sex, cigarette smoking, hypertension, diabetes mellitus, hypercholesterolemia, obesity, and a family history of coronary artery disease [1–4]. These risk factors for SCD are also predictors of coronary heart disease-related death and all-cause mortality [1–4]. Impaired left ventricular function as well as multiple other genetic, anatomic, and electrophysiological risk factors for sudden death have been identified [1–4]. These risk factors are temporally dynamic and vary by anatomic and electrophysiological substrate, age, sex, and race. Although risk stratification is useful to identify populations of individuals at risk for SCD, current techniques to identify high-risk individuals lack sufficient predictive value to have clinical utility because of the relatively low event rates or absolute risk [1–4].

Survivors of SCD constitute a small group of patients at significantly high risk of recurring fatal arrests, in whom protection with defibrillator therapy (Fig. 11.1) improves survival [5–7]. Patients with stable, depressed myocardial function from ischemic heart disease or other conditions are also at increased risk of ventricular arrhythmia [5–7]. In this group of patients, predictors of benefit from defibrillation therapy have depended on the presence of severely depressed myocardial function as measured by a left ventricular ejection fraction ≤35% [8, 9]. Although, measures of electrical instability such as T wave alternans or autonomic tone have

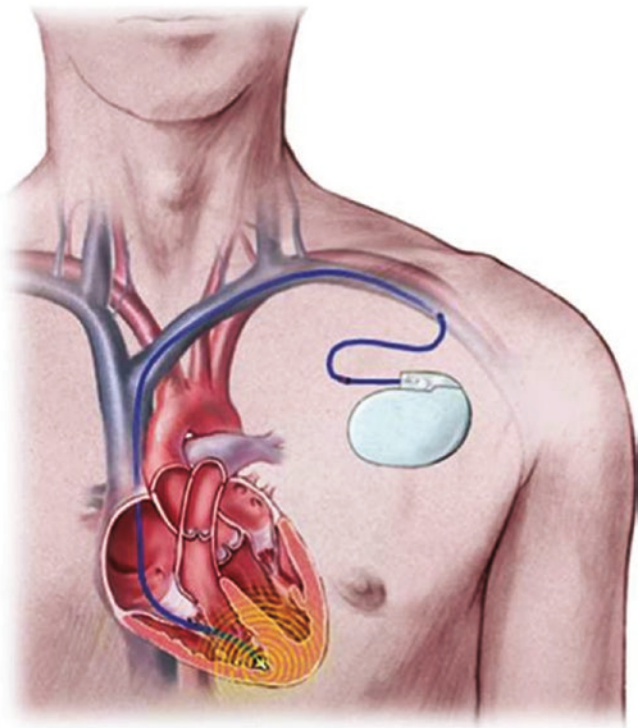


Fig. 11.1 This figure shows a schematic of an implantable cardioverter defibrillator (ICD), which is a small electronic device implanted in the shoulder area under the skin, or deeper, under the Pectoralis major muscle, and is connected to the heart by a lead that goes through the venous system and is positioned in the right ventricle. The defibrillator can sense the rhythm of the heart and is designed to life-threatening arrhythmias. Transvenous defibrillators can also pace the heart

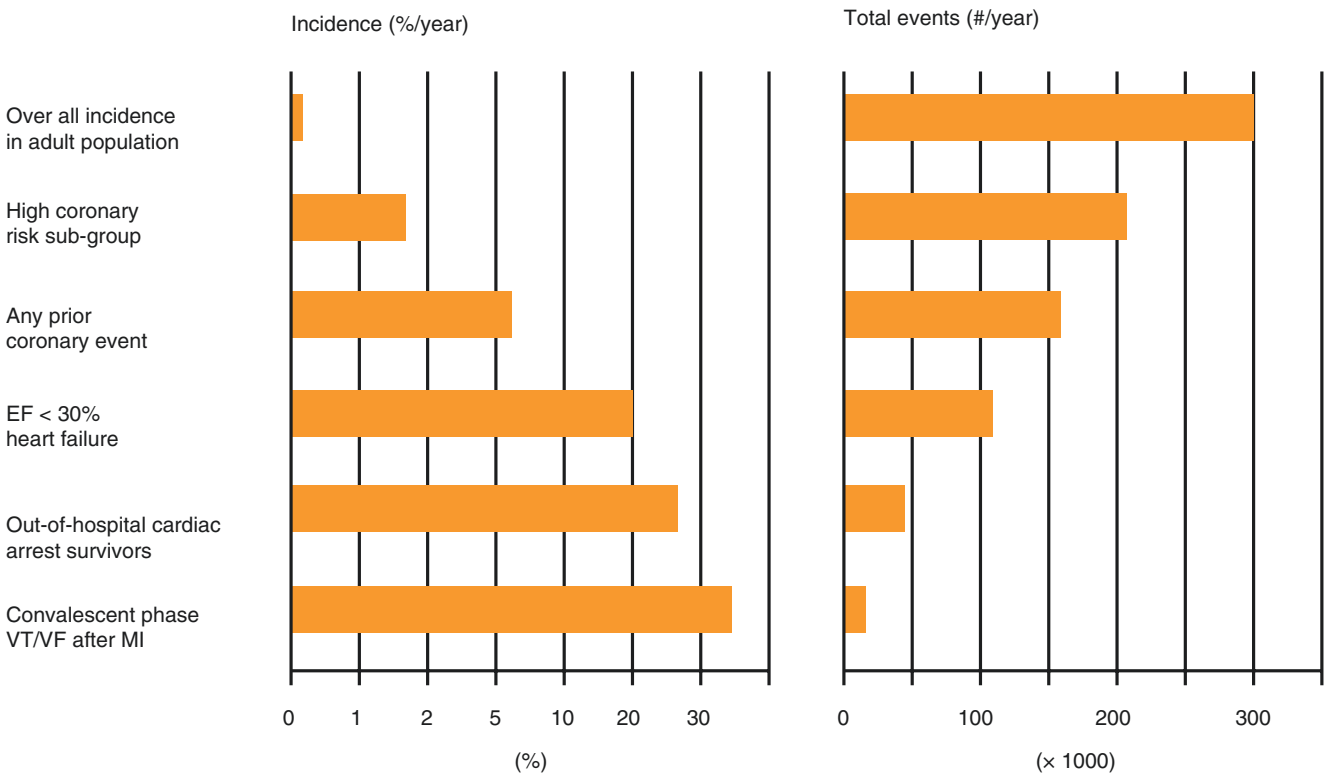


Fig. 11.2 This figure shows the incidence (*left panel*) and the total number of events (*right panel*) of sudden cardiac death (SCD) in the general adult population and other populations at risk. Although the incidence of SCD is lowest in the general population, the actual number of SCD events is highest in that group. Adapted from Myerburg RJ. Circulation 1992;85(suppl I):I2–I10

been proposed as markers of a higher risk substrate with varying degrees of accuracy, to date, only the measure of left ventricular ejection fraction determines eligibility for defibrillator therapy [8–13]. Despite this knowledge, the majority of SCD occur in the general population, not in patients with prior aborted events or with cardiomyopathy (Fig. 11.2). Medical research therefore continues to focus on identifying predictors of these fatal events upstream of their occurrence or of the development of severe myocardial dysfunction. Promising prediction tools may include advanced cardiac imaging such as cardiac magnetic resonance imaging which can characterize tissue and visualize scar burden as well as individualized genetic testing for risk assessment. Whether these tools will eventually be incorporated into the clinical management of patients at risk of SCD remains controversial.

Defibrillators, a Historical Perspective

Based on the recognition that prompt defibrillation of SCD victims who have a 'shockable' rhythm is an essential component of resuscitative measures, there has been an emphasis on prompt recognition and definitive treatment of a cardiac arrest with CPR and defibrillation [14]. Because many barriers prevent timely defibrillation such as with unwitnessed or remote access arrests, the concept of a device that can monitor continuously the heart rhythm of high risk patients and that can automatically deliver defibrillation therapy (Fig. 11.3) became very attractive. In 1975, the first prototype of an implantable defibrillator was developed and inserted in a dog via thoracotomy [15, 16]. The first implantable defibrillator consisted of a very large 'shock box' capable only of delivering a high energy electrical impulse through patched sutured to the epicardium. After that original development, implantable defibrillators improved steadily, becoming smaller and smarter. Improved defibrillator models were able to deliver synchronized shocks for VT and biphasic as opposed to monophasic shock waveforms with higher defibrillation success. They were also able to provide back-up pacing through an endovascular lead system and acquired other functionality including the ability to deliver atrioventricular synchronous pacing, tiered-therapy with anti-tachycardia pacing, and rhythm discrimination among many other newer features. More recently at the beginning of the new millennium, defibrillators capable of pacing synchronously the right and left ventricles were developed and became important tools in the management of

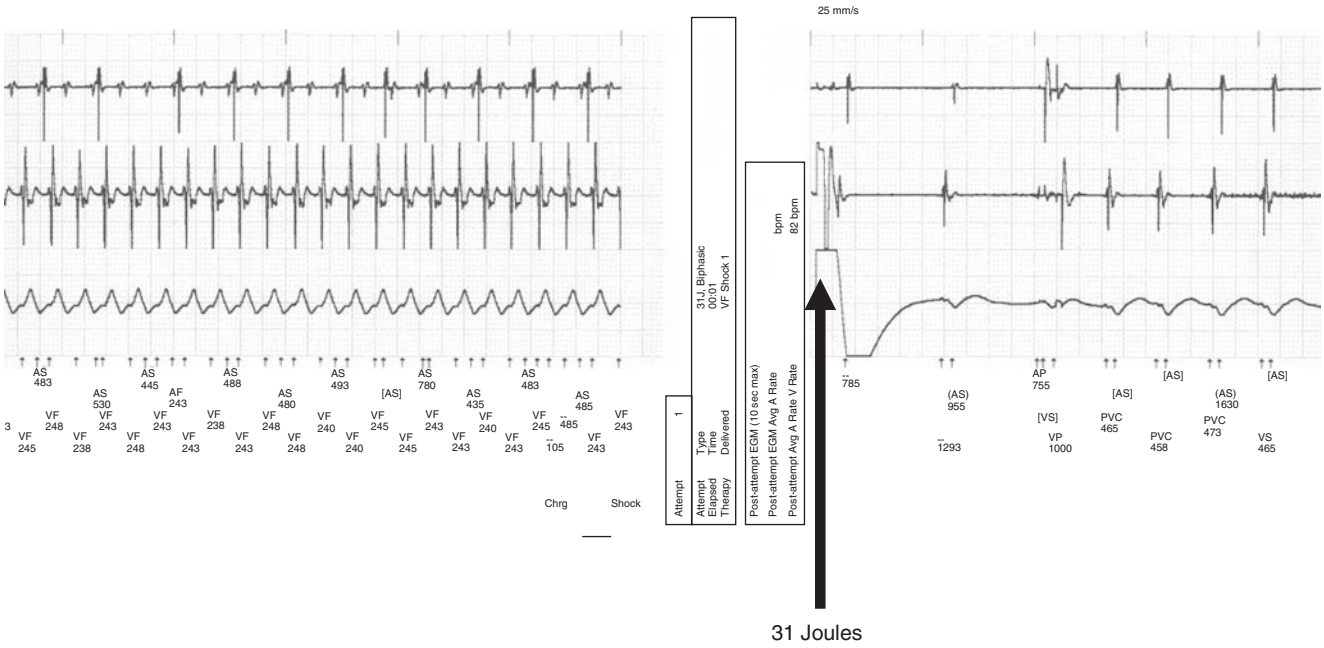


Fig. 11.3 This figure shows a tracing obtained from an implantable cardioverter defibrillator (ICD). From top to bottom, the tracings represent the bipolar atrial signal, the bipolar ventricular signal, the far-field 'shock' electrogram, and the marker channel. The left part of the panel shows a monomorphic ventricular tachyarrhythmia with atrioventricular dissociation at a rate of 250 beats per min. A 31 J shock delivered by the ICD terminates the tachyarrhythmia

heart failure patients. Most recently, a totally subcutaneous defibrillator was developed and obtained Food and Drug Administration approval for implantation in the United States [17].

Strategies for SCD Prevention

Primary prevention of SCD with risk stratification and intervention in those individuals with established cardiovascular disease placing them at high risk for SCD is the essential strategy to improve outcomes [1–4]. Pharmacological interventions in patients with impaired left ventricular function from coronary disease or cardiomyopathy including beta-blockers, angiotensin-converting enzyme inhibitors, and statins have failed to reduce the risk of sudden cardiac arrest. Suppression of spontaneous ventricular arrhythmias with antiarrhythmic agents has been shown to have a neutral or negative effect on mortality in prospective randomized trials [1–4]. By contrast, use of the ICD has been demonstrated to reduce sudden death and improve total mortality in selected patient populations, including those with impaired ventricular function and those with ischemic or nonischemic cardiomyopathy [18–28]. Multiple clinical trials randomizing several thousand patients have demonstrated that the ICD prevents sudden death and significantly reduces overall mortality among patients with left ventricular dysfunction due to dilated nonischemic cardiomyopathy or ischemic heart disease (Table 11.1) [18–28]. Secondary prevention refers to clinical intervention in patients who have survived a prior cardiac arrest or sustained ventricular tachycardia [5–7]. In these patients, the ICD has proven superior to antiarrhythmic drug therapy for prolonging survival [5–7]. It should be noted that these recommendations for ICD therapy apply only to patients who are receiving optimal medical therapy and have a reasonable expectation of survival with good functional status for >1 year [4].

Primary Prevention of Sudden Cardiac Death: Ischemic Cardiomyopathy

Despite the beneficial effects of medications such as β-blockers and angiotensin converting enzyme inhibitors in survivors of myocardial infarctions (MI) who suffer from severe cardiomyopathy, these patients remain at long term significant risk of SCD, primarily from lethal ventricular arrhythmias. Many trials have examined the role of ICD therapy in survivors of MI, with mixed results which are driven primarily by the type of patients enrolled in these trials and the timing of ICD therapy with respect to the coronary event or revascularization [18–22].

The Coronary Artery Bypass Graft Patch Trial (CABG-Patch) examined the impact of ICD therapy on mortality in 900 patients who were randomized at the time of elective coronary artery bypass grafting to receive or not receive ICD

Table 11.1[a] Randomized trials of defibrillator therapy for the primary and secondary prevention of sudden cardiac death

Trial reference	Year	Patients (n)	LVEF	Additional study features	Hazard ratio[a]	95% CI	P value
Primary prevention							
MADIT I [19]	1996	196	<35%	NSVT and EP+	0.46	(0.26–0.82)	$P = 0.009$
MADIT II [21]	2002	1232	<30%	Prior MI	0.69	(0.51–0.93)	$P = 0.016$
MUSTT [20]	2000	1397	<40%	Prior MI, NSVT, inducible VT	0.77	(0.62–0.94)	$P = 0.005$
SCD-HeFT [22]	2006	1676	<35%	Prior MI or NICM	0.77	(0.62–0.96)	$P = 0.007$
DEFINITE [27]	2004	485	<35%	NICM, PVCs or NSVT	0.65	(0.40–1.06)	$P = 0.08$
CABG-Patch [18]	1997	900	<36%	+SAECG and CABG	1.07	(0.81–1.42)	$P = 0.63$
DINAMIT [23]	2004	674	<35%	6–40 days post-MI and impaired HRV	1.08	(0.76–1.55)	$P = 0.66$
IRIS [24]	2009	898	405 <30 days post-MI HR >90 or NSVT	1.04	(0.81–1.35)	$P = 0.78$	IRIS
Secondary prevention							
AVID [7]	1997	1016	Prior cardiac arrest	NA	0.62	(0.43–0.82)	NS
CASH [5]	2000	191	Prior cardiac arrest	NA	0.766		One-sided $P = 0.081$
CIDS [6]	2000	659	Prior cardiac arrest, syncope	NA	0.82	(0.06–1.1)	NS

AVID antiarrhythmics versus implantable defibrillators, *CABG* coronary artery bypass graft surgery, *CABG-Patch* coronary artery bypass graft-patch, *CASH* Cardiac Arrest Study Hamburg, *CI* confidence interval, *CIDS* Canadian Implantable Defibrillator Study, *DEFINITE* Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation, *DINAMIT* Defibrillator in Acute Myocardial Infarction Trial, *EP* electrophysiological study, *LVD* left ventricular dysfunction, *LVEF* left ventricular ejection fraction, *MADIT I* Multicenter Automatic Defibrillator Implantation Trial I, *MADIT II* Multicenter Automatic Defibrillator Implantation Trial II, *MI* myocardial infarction, *MUSTT* Multicenter Unsustained Tachycardia Trail, *N* number of patients, *NICM* nonischemic cardiomyopathy, *NS* not statistically significant, *NSVT* nonsustained ventricular tachycardia, *PVCs* premature ventricular complexes, *SAECG* signal-averaged electrocardiogram, *SCD-HeFT* Sudden Cardiac Death in Heart Failure Trial, and + positive

[a]Adapted from ref. 4 with permission

therapy [18]. Eligible patients had to have an ejection fraction of 35% or less and an abnormal signal average electrocardiogram, indicating a higher risk of ventricular arrhythmias. At a mean follow-up of 32 months, CABD-Patch showed no difference in all-cause mortality by treatment arm. The negative results of this trial were attributed by most to the effect of revascularization on reducing event rates in both arms of the trial as well as to the poor performance of signal-average electrocardiogram as a risk-stratification tool.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT), published in 1996, was the first clinical trial to show a benefit for ICD therapy in reducing all-cause mortality in a primary prevention setting [19]. MADIT enrolled patients with prior remote myocardial infarction, depressed left ventricular function (EF ≤ 35%), history of asymptomatic non-sustained VT, and inducible sustained VT during invasive electrophysiological (EP) testing, that could not be suppressed by the use of anti-arrhythmic medications (mainly procainamide) [19]. A total of 196 patients were randomized to ICD therapy or anti-arrhythmic drugs (mainly Amiodarone). After a mean follow-up of 27 months, there was a significant reduction in total mortality in the ICD compared to the control arm driven by a significant reduction in arrhythmic death [19].

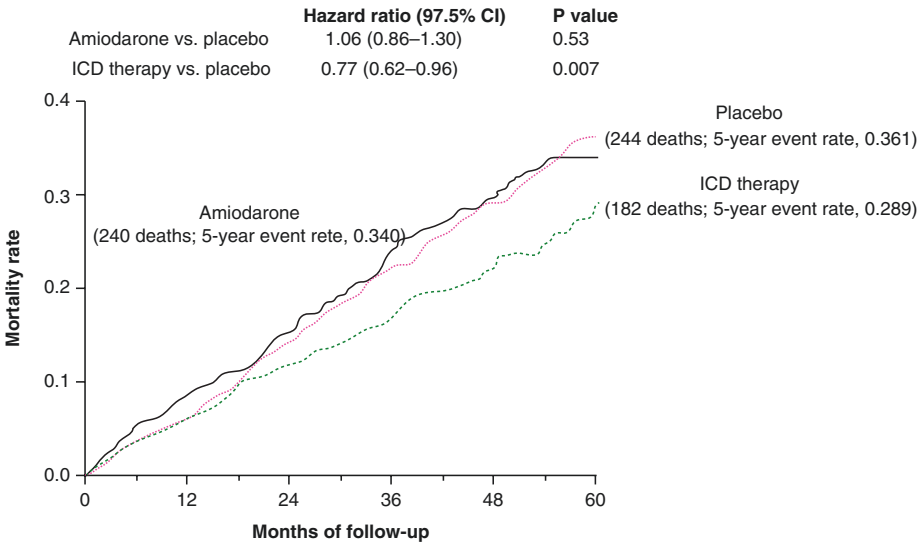
The Multicenter Unsustained Tachycardia Trial (MUSTT) compared two strategies of management in patients with ischemic cardiomyopathy (EF ≤ 40%) who has inducible VT or ventricular fibrillation during invasive electrophysiological testing: (1) EP-guided anti-arrhythmic drug therapy with class 1 or 3 Vaughn Williams anti-arrhythmic drugs, followed by ICD therapy if the pharmacological intervention failed to suppress arrhythmia inducibility versus (2) standard medical therapy primarily with β-blockers [20]. A total of 704 eligible patients were randomized of whom 351 patients were assigned to the EP-guided anti-arrhythmic drug arm. Of those, 161 patients ended-up receiving ICD therapy [20]. At a median follow-up duration of 39 months, MUSTT

showed no difference in total mortality by strategy of treatment but a significant reduction all-cause death in ICD recipients compared to patients with no ICD (5-year mortality of 24% versus 55%, P < 0.001). Based on the results of MADIT and MUSTT, implanting a prophylactic ICD in patients with prior myocardial infarction, non-sustained VT, and an EF ≤ 40%, who are inducible into sustained ventricular arrhythmia during invasive EP testing is a class I indication for ICD therapy.

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) randomized 1232 ischemic cardiomyopathy patients with ventricular dysfunction (≤30%) and heart failure symptoms (New York Heart Association classes I, II, or III) to receive ICD therapy versus standard medical therapy [21]. At a mean follow-up of 20 months, ICD therapy reduced the relative risk of death by 31% (14.2% versus 19.8%, $P = 0.016$) compared to the control. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is the largest primary prevention trial examining the impact of ICD therapy on all-cause mortality [22]. This trial enrolled both ischemic and non-ischemic cardiomyopathy patients with severely reduced myocardial function (EF ≤ 35%) and class II or III symptoms of heart failure, according to the New York Heart Association classification. SCD-HeFT randomized 2521 patients to 1 of 3 study arms: (1) Standard medical therapy, (2) anti-arrhythmic therapy with Amiodarone, and (3) ICD therapy. At a mean follow-up of 45.5 months, ICD therapy reduced all-cause death by 23% (ICD 22% versus Amiodarone 28% and placebo 29%, $P = 0.007$, Fig. 11.4). SCD-HeFT confirmed the MADIT II results for ischemic cardiomyopathy patients who currently have a class I indication for prophylactic ICD implantation according to published guidelines in the presence of severe cardiomyopathy and heart failure symptoms (EF ≤ 35% and class II or III heart failure symptoms or EF ≤ 30% in the presence of class I heart failure symptoms) [22].

A number of randomized trials were designed to answer questions regarding the appropriate timing of ICD implantation after acute myocardial infarction, given the known high risk of SCD early after these events [23]. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) tested the hypothesis that implanting a prophylactic ICD within 6–40 days of an acute myocardial infarction reduces all-cause mortality [23]. Eligible patients (n = 674) who had decreased left ventricular function (EF ≤ 35%) and reduced heart rate variability, high risk marker for ventricular arrhythmias were randomized to ICD versus standard medical therapy. Patients who had recent coronary revascularization were excluded from this study, given the results of CABG-Patch. At a mean follow-up of 30 months, DINAMIT showed no difference between study groups in overall survival but a 58% reduction in the risk of arrhythmic death with ICD therapy ($P = 0.009$). DINAMIT was therefore a negative trial where the reduced arrhythmic death did not translate into reduced total mortality because of an unexplained excess of non-arrhythmic deaths in the ICD arm presumably related to recurrent ischemia or myocardial infarctions after the index event, thus leading to death that could not be mitigated by ICD therapy [23].

The Immediate Risk-Stratification Improves Survival (IRIS) Trial also examined the question of timing of ICD implantation after myocardial infarction and had a compa-



No. at risk						
Amiodarone	845	772	715	484	280	97
Placebo	847	797	724	505	304	89
ICD therapy	829	778	733	501	304	103

Fig. 11.4 This figure shows the primary outcome of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial which demonstrated a total mortality benefit from the use of defibrillator therapy for primary prevention in heart failure patients with left ventricular ejection fraction ≤35% due to ischemic or non-ischemic etiology. Adapted from Bardy GH et al. N Engl J Med 2005; 352:225–237

rable design to DINAMIT [24]. IRIS randomized 898 survivors of myocardial infarction to ICD or standard medical therapy within 5–31 days of the index event. Patients qualified for enrollment if they had (1) EF ≤ 40% and (2) a heart rate >90 beats per minute or non-sustained VT on the first available electrocardiogram or Holter monitor recorded after myocardial infarction. Similarly to DINAMIT, IRIS failed to demonstrate a survival benefit with the ICD (P = 0.78) at a mean follow-up of 37 months. Here again, ICD therapy reduced the risk of SCD (P = 0.049) but was associated with a higher risk of non-sudden cardiac deaths (P = 0.001). Based on the results of DINAMIT and IRIS, implanting a prophylactic ICD within 40 days of acute myocardial infarction is contraindicated according to the published guidelines [7, 8].

Primary Prevention of Sudden Cardiac Death: Non-ischemic Cardiomyopathy

Despite demonstrating a survival benefit for primary ICD therapy in ischemic cardiomyopathy patients, reproducing these results in non-ischemic cardiomyopathy patients remained elusive for a number of years, until the results of the SCD-HeFT trial became available. Several smaller randomized controlled trials examined this clinical question [25, 26]. The Amiodarone versus Implantable Defibrillator Trial (AMIOVIRT) randomized 103 patients with non-ischemic cardiomyopathy (EF ≤ 35%), asymptomatic non-sustained VT, and New York Heart Association heart failure classes I, II, or III to ICD therapy (often with amiodarone) versus amiodarone alone [25]. AMIOVIRT was stopped prematurely for reasons of futility with 3-year survival rates of 87% and 88% in the ICD and amiodarone arms, respectively (P = 0.8).

Similarly, the Cardiomyopathy Trial (CAT) [26] randomized 104 patients with recently (within 9 months) diagnosed non-ischemic cardiomyopathy (EF ≤ 30%) to ICD versus standard medical therapy. Like AMIOVIRT, CAT also showed no difference in all-cause mortality between the two study groups (4-year survival rates of 86% and 80% in the ICD and control arms, respectively, P = 0.554). The negative results of AMIOVIRT and CAT were blamed on them being underpowered to show a mortality difference, a fact that was further exacerbated by the lower than expected observed event rates.

The larger Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) was designed to mitigate these issues. It randomized 458 non-ischemic cardiomyopathy patients (EF < 36%) with heart failure symptoms (New York Heart Association heart failure classes I, II, or III), and with ambient arrhythmia defined as frequent premature ventricular contractions (at least ten premature beats) or runs of non-sustained VT (at least one run of non-sustained VT lasting 3–15 beats at a rate >120 beats per minute) on a 24-h Holter monitor or telemetry to ICD versus standard medical therapy [27]. DEFINITE demonstrated a 50% relative reduction in all-cause mortality with this ICD, but this did not reach statistical significance (P = 0.08). The risk of sudden cardiac death was however significantly reduced with ICD therapy (80% relative reduction, P = 0.006). Like AMIOVIRT and CAT before it, DEFINITE also fell victim of lower than anticipated event rates. As previously mentioned, SCD-HeFT the largest primary prevention ICD trial, enrolled cardiomyopathy patients of non-ischemic etiology and demonstrated a significant reduction in total mortality with ICD therapy. When only non-ischemic cardiomyopathy patients were considered, ICD therapy demonstrated a 27% relative reduction in all-cause mortality compared to the control arm of the study (P = 0.06). As a result of SCD-HeFT, non-ischemic cardiomyopathy patients with EF ≤ 35% and New York Heart Association heart failure classes II and III have a class 1 indication for prophylactic ICD therapy according to published guidelines [8–13].

Secondary Prevention of Sudden Cardiac Death

Several large prospective trials have demonstrated the superiority of the (implantable cardioverter-defibrillator) ICD over antiarrhythmic therapy in secondary prevention of SCD [5–7]. On the basis of this evidence, a cardiac arrest in the absence of a reversible cause is now a class I indication for ICD therapy [8–13]. The Cardiac Arrest Study Hamburg (CASH) was a prospective, randomized, controlled trial that examined the outcome of survivors of cardiac arrests due to ventricular arrhythmias after treatment with ICD therapy versus anti-arrhythmia drugs [5]. Initially, the study had four arms (ICD therapy, β-blockers, amiodarone, and propafenone), but the propafenone arm was discontinued prematurely after an interim analysis had shown higher mortality in patients treated with this medication. In the remaining 288 patients assigned to the other three treatment arms, CASH demonstrated at a mean follow-up duration of 57 months a 23% reduction in the primary endpoint of all-cause mortality with ICD therapy compared to treatment with β-blockers or amiodarone. This difference failed however to reach statistical significance.

Similarly, the Canadian Implantable defibrillator Study (CIDS) trial examined the effect of ICD therapy on mortality in survivors of cardiac arrest [6]. It randomized 659 patients to ICD therapy versus amiodarone. At a mean follow-up time of 3 years, ICD therapy decreased the endpoint of total mortality by 20%, and arrhythmic mortality by 33%, but both reductions failed to reach statistical significance. The

Antiarrhythmic versus Implantable Defibrillator (AVID) trial was the largest of the ICD trials for secondary prevention of SCD [7]. It randomized 1013 patients to ICD therapy versus class III antiarrhythmic medications, primarily amiodarone. Eligible patients had to be resuscitated from near-fatal VF or shocked out of hemodynamically destabilizing VT. They also had to have a left ventricular ejection fraction of less than 40%. AVID demonstrated the superiority of ICD therapy over antiarrhythmic drugs for reducing all-cause mortality, with a 7% absolute reduction at 1 year and 11% at 3 years. Based on the results of AVID, ICD therapy became indicated in survivors of cardiac arrests outside of the context of reversible causes, according to published guidelines and receives coverage.

Defibrillator Therapy for the Management of Heart Failure

Cardiac resynchronization therapy (CRT) has emerged over the past 15 years as an important tool for the management of heart failure patients. The simultaneous or near simultaneous pacing of the right and left ventricles has been shown to have symptomatic, echocardiographic, as well as mortality benefits in heart failure patients with ventricular conduction abnormalities, which are depicted by a wide QRS complex (>120 ms) on the surface electrocardiogram (Table 11.2). Although CRT can be delivered through a pacemaker, more often than not it is provided by a defibrillator.

The Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE ICD II) was a randomized, double-blind, parallel-controlled clinical trial of CRT in NYHA class II heart failure patients on optimal medical therapy with a left ventricular (LV) ejection fraction ≤35%, a QRS ≥130 ms, and a class I indication for an ICD [28]. One hundred and eighty-six patients were randomized: 101 to the control group (ICD activated, CRT off) and 85 to the CRT group (ICD activated, CRT on). End points included peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, NYHA class, quality of life, 6-min walk distance, LV volumes and ejection fraction, and composite clinical response. Compared with the control group at 6 months, no significant improvement was noted in peak $\dot{V}O_2$, yet there were significant improvements in ventricular remodeling indexes, specifically LV diastolic and systolic volumes ($P = 0.04$ and $P = 0.01$, respectively), and LV ejection fraction ($P = 0.02$). CRT patients showed statistically significant improvement in $\dot{V}E/\dot{V}CO_2$ ($P = 0.01$), NYHA class ($P = 0.05$), and clinical composite response ($P = 0.01$). In the MIRACLE ICD II Study patients with mild heart failure symptoms on optimal medical therapy with a wide QRS complex and an ICD indication, CRT did not alter exercise capacity but did result in significant improvement in cardiac structure and function and composite clinical response over 6 months [28].

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, randomized 1520 patients with advanced symptoms of heart failure (New York Heart Association classes III and IV), low EF (≤35%), and wide QRS complex on surface electrocardiogram (>120 ms) to one of three management strategies: (1) optimal pharmacological therapy alone; (2) optimal pharmacological therapy with CRT using a pacemaker

Table 11.2 Cardiac resychronization therapy trials

Study Year Reference	Design	Patients (n)	NYHA	LVEF (%) Inclusion (mean)	Primary endpoint	Secondary endpoint	Results significantly favor intervention group
COMPANION 2004 [29]	CRT-D/ CRT-P/ ICD	617/595/308	III, IV	≤35% 22%	Total mortality or hospitalization	Cardiac mortality	+
MIRACLE ICD II 2004 [28]	CRT-D/ ICD	85/101	II	≤35% 25%	Peak VO_2	NYHA QOL, 6-min walk, LVV, LVEF, CCR	+
REVERSE 2008 [32]	CRT-P/ ICD	419/191	I, II	≤35% 25%	CCR	LVESVi	+
MADIT-CRT 2009 [30]	CRT-D/ ICD	1089/731	I, II	≤30% 25%	Total mortality or HF hospitalization	LVESV LVEDV LVEF	+
MADIT RAFT 2010 [31]	CRT-D/ ICD	869/904	II, III	≤30% 24%	Total mortality or HF hospitalization	Cardiac death HF hospitalization	+

device; and (3) optimal pharmacological therapy with CRT using a defibrillator [29]. COMPANION demonstrated a significant reduction in the primary endpoint of death or heart failure hospitalization with CRT using either a pacemaker or a defibrillator compared to optimal pharmacologic therapy alone.

The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) examined the role of CRT in patients with mild to moderate heart failure symptoms (New York Heart Association HF classes I and II). MADIT-CRT randomized 1820 patients with low EF (≤30%) and a wide QRS complex (>130 ms) to defibrillator therapy alone versus defibrillator therapy in conjunction with CRT [30]. Although the overall mortality in MADIT-CRT was similar between the two study arms, there was a CRT 34% reduction in the primary endpoint of death or HF hospitalization ($P = 0.001$) with CRT as well as evidence of reverse remodeling by echocardiographic imaging.

In the RAFT Trial patients with New York Heart Association (NYHA) class II or III heart failure, a left ventricular ejection fraction of 30% or less, and an intrinsic QRS duration of 120 ms or more or a paced QRS duration of 200 ms or more to were randomized receive either an ICD alone or an ICD plus CRT [31]. The primary outcome was death from any cause or hospitalization for heart failure. 1798 patients were followed for a mean of 40 months. The primary outcome occurred in 297 of 894 patients (33.2%) in the ICD–CRT group and 364 of 904 patients (40.3%) in the ICD group (hazard ratio in the ICD–CRT group, 0.75; 95% confidence interval [CI], 0.64–0.87; P < 0.001). In the ICD–CRT group, 186 patients died, as compared with 236 in the ICD group (hazard ratio, 0.75; 95% CI, 0.62–0.91; $P = 0.003$), and 174 patients were hospitalized for heart failure, as compared with 236 in the ICD group (hazard ratio, 0.68; 95% CI, 0.56–0.83; P < 0.001). However, at 30 days after device implantation, adverse events had occurred in 124 patients in the ICD–CRT group, as compared with 58 in the ICD group (P < 0.001). The RAFT Trial demonstrated that among patients with NYHA class II or III heart failure, a wide QRS complex, and left ventricular systolic dysfunction, the addition of CRT to an ICD reduced rates of death and hospitalization for heart failure.

Similarly, the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial randomized 610 patients with mild heart failure symptoms (New York Heart Association classes I and II), low ejection fraction (≤40%) and wide QRS complex (>120 ms) to CRT therapy (CRT-ON) versus control (CRT-OFF) [32]. Although the primary endpoint of composite heart failure score was not significantly improved with CRT therapy, patients in the CRT-ON group had significant incremental improvement in their echocardiographic endpoints of left ventricular end-systolic and end-diastolic volumes as well as their ejection fraction at 1 year post randomization. Their time to first heart failure hospitalization was also significantly better than the CRT-OFF group.

Trials that examined the role of CRT-defibrillators in improving outcomes in heart failure patient with a narrow QRS complex on surface electrocardiogram (<130 ms) have all failed demonstrate any benefit in this patient population [33]. The Cardiac-Resynchronization Therapy in Heart Failure with Narrow QRS Complexes (RethinQ) trial randomized 172 patients with narrow QRS complex but evidence of ventricular mechanical dyssynchrony to CRT versus control and followed them for 6 months. RethinQ failed to show any benefit of CRT in this patient population on the primary endpoint of reduction in oxygen consumption.

Following RethinQ, the much larger Echo-CRT trial randomized 809 patients with advanced heart failure (New York Heart Association classes III and IV), narrow QRS (<130 ms) in the presence of left ventricular mechanical dyssynchrony, and low EF (≤35%) to CRT-ON versus CRT-OFF and followed them to the primary endpoint of death or heart failure hospitalization [34]. The trial was terminated prematurely for futility, revealing upon further analysis an increased risk of all-cause mortality in the CRT-ON arm. Based on these results, CRT defibrillator implantation is contraindicated in patients with narrow QRS on surface electrocardiogram [8, 9].

The Subcutaneous Defibrillator (S-ICD)

Given concerns about acute complications of transvenous defibrillator implantation which include pneumothorax, hemothorax, and cardiac tamponade, and longer term problems such as bacteremia, endocarditis, or vascular occlusions which often necessitate explanting the defibrillator system with its indwelling leads, a technically challenging and high risk procedure, the SICD (Boston Scientific Inc., St. Paul, Minnesota) was developed to mitigate many of these problems. The system consists of the actual device which is connected to a single lead [35–37]. The device is implanted in the left axillary area whereas the defibrillation lead coil is placed along the sternum, both subcutaneously (Fig. 11.5). An 80 J shock is delivered between the device and the coil to terminate a life-threatening ventricular arrhythmia. Sensing of arrhythmia events can be along one of three possible vectors (A–B, A–C, or B–C, Fig. 11.5) and is automatically chosen by a device algorithm at the time of implantation, based on a favorable R wave to T wave amplitude ratio. In one study, rhythm discrimination in the SICD was equivalent if not better than in other transvenous defibrillator systems [38].

Although the SICD lacks basic functions that transvenous systems have such as backup pacing (except for 30 s following shock delivery) and anti-tachycardia pacing for arrhythmia termination, it also presents important advantages. First, it can be implanted without the need for fluoroscopy, thus leading to less radiation exposure to patients and operators as well as more flexibility as to the physical setting where it is implanted. Second, the SICD presents a solution to the problem of limited venous access often encountered in patients with cardiovascular problems, who frequently have other comorbidities such as renal failure which further complicate matters. This solution can replace in some patients the need to insert epicardial patches through a thoracotomy. Third, in the event of infection, the likelihood of bacteremia or endocarditis is significantly reduced with the SICD, since all the hardware is outside of the heart and vasculature and explanting the hardware is a less invasive procedure limited to the subcutaneous space. Lastly, although not validated by other research, one study suggests a lower risk of myocardial injury from shock delivery with the SICD compared to the transvenous defibrillator ICD [39].

The early experience with the SICD demonstrates a high rate of termination of induced ventricular fibrillation at the time of device implantation and therefore appears to be safe and effective [40]. More recent reports from the US experience confirm the safety of the SICD at longer follow-up [41, 42].

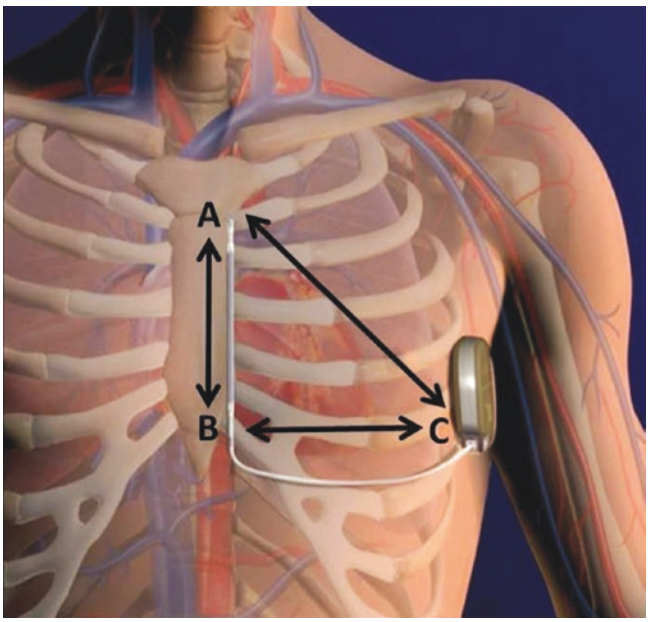


Fig. 11.5 This figure shows the configuration of the SICD. The device is placed under the skin in the left axillary area and is connected to a shocking lead, the coil of which lies under the skin along the sternum. The sensing of cardiac rhythm is through one of the three possible configurations (A–B, A–C, or B–C). The shock is delivered between the device and the coil

The Wearable Defibrillator (LifeVest)

The wearable defibrillator or LifeVest (Zoll Inc., Pittsburgh, Pennsylvania) (Fig. 11.6) is a wearable vest that has sensing electrodes that can detect arrhythmias and can treat them using electrical pads that are in contact with the skin [43]. This device in its earliest generation has been around for more than a decade and was initially approved in the US by the Food and Drug Administration based on one study [44]. It is approved for use in patients who are at transient high risk of SCD such as those awaiting cardiac transplantation or in patients who meet established indications for defibrillator therapy but fall in a blanking period such as being within 40 days of an acute myocardial infarction or within 90 days of coronary revascularization. Also, the wearable defibrillator is frequently used in patients who undergo extraction of implantable defibrillator system for infection [43, 45].

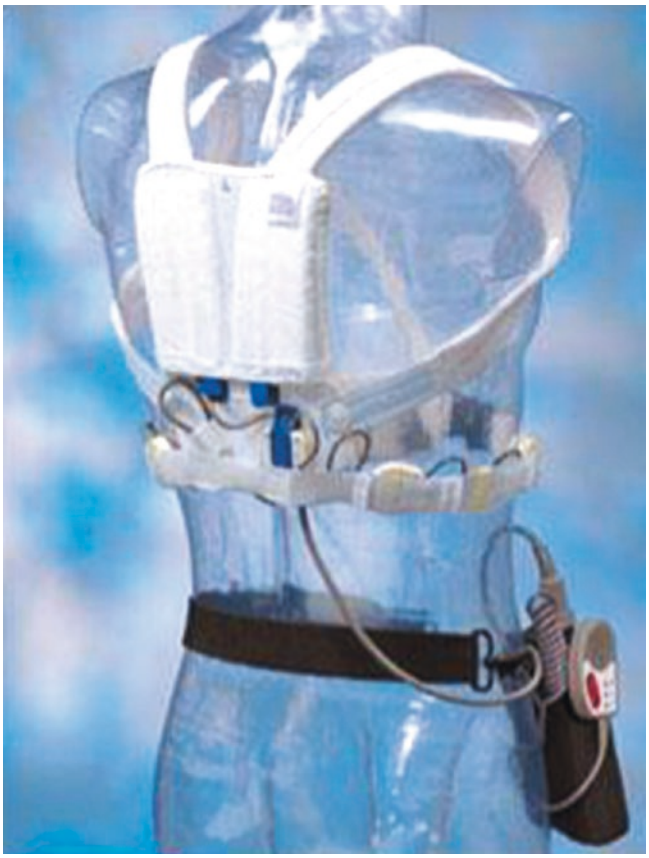


Fig. 11.6 This figure shows the wearable defibrillator (LifeVest) which consists of straps, holding non-adhesive sensing electrodes and dry shocking electrodes that release conductive gel prior to shock delivery. The monitor is worn on the waist. In the event of arrhythmia detection, it will provide auditory, visual, and tactile alarms. If conscious, the patient can press two buttons simultaneously to prevent a shock

Compared to automatic external defibrillators, the wearable defibrillator offers a significant advantage in that it detects and treats arrhythmias automatically without the need for bystander recognition of the cardiac arrest or activation of the system, such as placing the pads on the patient's chest, turning on the device, and following commands. One limitation for the use of the wearable defibrillator is the potential poor compliance of patients with it because it is not very comfortable to wear and it often alarms for false positive detections due to electrode noise. To date, there are no randomized controlled trials demonstrating mortality benefit from the wearable defibrillator. The bulk of available information is limited to registry data and case reports [46–48].

Conclusion

In a span of three decades, outcomes for cardiac arrest have improved considerably as a result of advances in defibrillator technology and clinical implementation strategies. Evidence based medicine based on large, randomized, controlled trials have established the survival benefit of ICD therapy in selected populations of cardiac patients. Data for the subcutaneous ICD and wearable cardioverter defibrillator are currently less robust. Future research will focus on expanding indications to patients with milder forms of cardiomyopathy and improved risk stratification techniques. At the same time improved strategies for each of these forms of defibrillation therapy will continue to evolve. Finally, further analysis related to cost-effectiveness and impact on quality of life of defibrillation therapies will further refine implementation strategies.

References

1. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Braunwald E, editor. Heart disease: a textbook of cardiovascular medicine. 4th ed. Philadelphia: W.B. Saunders; 1992. p. 756–89.
2. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. Circulation. 1992;85(Suppl 1):I2–10.
3. Zhang ZJ, Croft JB, Giles WH, et al. Sudden cardiac death in the United States, 1989 to 1998. Circulation. 2001;104:2158.
4. Estes NAM. Predicting and preventing sudden death. Circulation. 2011;124:651–6.
5. Kuck, KH, Cappato, R, Siebels, J, et al., for the CASH Investigators. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest. The Cardiac Arrest Study Hamburg (CASH). Circulation. 2000;102:748.
6. Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000;101:1297.
7. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337:1576.
8. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Circulation. 2008;117:e350.
9. Epstein AE, JP DM, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2013;127:e283–352.
10. Costantini O, Hohnloser SH, Kirk MM, et al., ABCD Trial Investigators. The ABCD (Alternans Before Cardioverter Defibrillator) Trial: strategies using T-wave alternans to improve efficiency of sudden cardiac death prevention. J Am Coll Cardiol. 2009;53:471–9.
11. Chow T, Kereiakes DJ, Onufer J, et al., MASTER Trial Investigators. Does microvolt T-wave alternans testing predict ventricular tachyarrhythmias in patients with ischemic cardiomyopathy and prophylactic defibrillators? The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial. J Am Coll Cardiol. 2008;52:1607–15.
12. La Rovere MT, Bigger JT Jr, Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet. 1998;351:478–84.
13. http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=110&ncdver=3&NCAId=148&NcaName=Implantable+Defibrillators&IsPopup=y&bc=AAAAAAAAIAAA&. Accessed 31 Aug 2015.
14. https://www.acls.net/aclsalg.htm
15. Matchett M, Sears SF, Hazelton G, Kirian K, Wilson E, Nekkanti R. The implantable cardioverter defibrillator: its history, current psychological impact and future. Expert Rev Med Devices. 2009;6:43–50.
16. van Welsenes GH, Borleffs CJ, van Rees JB, Atary JZ, Thijssen J, van der Wall EE, Schalij MJ. Improvements in 25 years of implantable cardioverter defibrillator therapy. Neth Heart J. 2011;19:24–30.
17. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm321755.htm
18. Bigger JT, for the Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. N Engl Med J. 1997;337:1569–75.
19. Moss, AJ, Hall, WJ, Cannom, DS, et al., for the Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med. 1996;335:1933.
20. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 1999;341:1882.

21. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877.
22. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225.
23. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004;351:2481.
24. Steinbeck G, Andresen D, Seidl K, et al., for the IRIS Investigators. Defibrillator implantation early after myocardial infarction. N Engl J Med. 2009;361:1427–36.
25. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia—AMIOVIRT. J Am Coll Cardiol. 2003;41:1707.
26. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation. 2002;105:1453.
27. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004;350:2151.
28. Abraham W, Young J, León A, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation. 2004;110:2864–8.
29. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140.
30. Moss AJ, Hall WJ, Cannom DS, et al., for the MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361:1329–38.
31. Tang A, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010;363:2385–95.
32. Linde C, Abraham WT, Gold MR, St John Sutton M, Daubert C, REVERSE Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol. 2008;52:1834–43.
33. Beshai JF, Grimm RA, Nagueh SF, Baker JH 2nd, Beau SL, Greenberg SM, Pires LA, Tchou PJ, RethinQ Study Investigators. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med. 2007;357:2461–71.
34. Frank Ruschitzka, William T. Abraham, Jagmeet P. Singh, Jeroen J. Bax, Jeffrey S. Borer, Josep Brugada, Kenneth Dickstein, Ian Ford, John Gorcsan III, Daniel Gras, Henry Krum, Peter Sogaard Johannes Holzmeister, for the EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013;369:1395–1405.
35. Maisel WH. Implantable cardioverter-defibrillator lead complication: when is an outbreak out of bounds? Heart Rhythm. 2008;5:1673–4.
36. Byrd CL, Wilkoff B, Love CJ, et al. Intravascular extraction of problematic or infected permanent pacemaker leads: 1994–1996, U.S. Extraction Database, MED Institute. Pacing Clin Electrophysiol. 1999;22:1348–57.
37. Wazni O, Epstein LM, Carrillo RG, et al. Lead extraction in the contemporary setting: the LExICon study: an observational retrospective study of consecutive laser lead extractions. J Am Coll Cardiol. 2010;55:579–86.
38. Gold MR, Weiss R, Theuns DA, Smith W, Leon A, Knight BP, Carter N, Husby M, Burke MC. Use of a discrimination algorithm to reduce inappropriate shocks with a subcutaneous implantable cardioverter-defibrillator. Heart Rhythm. 2014;11:1352–8.
39. Killingsworth CR, Litovsky SH, Melnick SB, et al. Shocks delivered via a subcutaneous defibrillation system cause less acute injury than transvenous leads in swine. Heart Rhythm. 2010;7:S186.
40. Bardy GH, Smith WM, Hood MA, et al. An entirely subcutaneous implantable cardioverter–defibrillator. N Engl J Med. 2010;363:36–44.
41. Weiss R, Knight BP, Gold MR, Leon AR, Herre JM, Hood M, Rashtian M, Kremers M, Crozier I, Lee KL, Smith W, Burke MC. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. Circulation. 2013;128:944–53.
42. Burke MC, Gold MR, Knight BP, Barr CS, Theuns DA, Boersma LV, Knops RE, Weiss R, Leon AR, Herre JM, Husby M, Stein KM, Lambiase PD. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE Study and EFFORTLESS Registry. J Am Coll Cardiol. 2015;65:1605–15.
43. Adler A, Halkin A, Viskin S. Wearable cardioverter-defibrillators. Circulation. 2013;127:854–60.
44. Feldman AM, Klein H, Tchou P, Murali S, Hall WJ, Mancini D, Boehmer J, Harvey M, Heilman MS, Szymkiewicz SJ, Moss AJ, WEARIT Investigators and Coordinators; BIROAD Investigators and Coordinators. Use of a wearable defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: results of the WEARIT/BIROAD. Pacing Clin Electrophysiol. 2004;27:4–9.
45. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC Jr, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, American College of Cardiology/American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114:e385–484.
46. Chung MK, Szymkiewicz SJ, Shao M, et al. Aggregate national experience with the wearable cardioverter-defibrillator: event rates, compliance, and survival. J Am Coll Cardiol. 2010;56:194–203.
47. Klein HU, Meltendorf U, Reek S, et al. Bridging a temporary high risk of sudden arrhythmic death. Experience with the wearable cardioverter defibrillator (WCD). Pacing Clin Electrophysiol. 2010;33:353–567.
48. Lee BK, Olgin JE. Role of wearable and automatic external defibrillators in improving survival in patients at risk for sudden cardiac death. Curr Treat Options Cardiovasc Med. 2009;11:360–5.

Atrial Fibrillation Ablation

12

Abhishek J. Deshmukh and Douglas L. Packer

Abstract

Atrial fibrillation (AF), an accruing epidemic, is projected to have an incidence of approximately 16 million by 2050. A 15% increase in the hospitalization rate for AF was reported during the past decade implying significant burden on health care delivery system. According to the 2014 AHA/ACC/HRS guidelines for management of AF, catheter ablation is indicated in patients with symptomatic, paroxysmal AF who have not responded to or tolerated antiarrhythmic medications and in selected patients with symptomatic, paroxysmal AF *prior* to a trial of medical therapy, provided that it can be performed at an experienced center. In this chapter, we summarize the state of the art of catheter ablation and how it may utilized to its maximum advantage in patients with this common arrhythmia.

Keywords

Atrial fibrillation • Pulmonary veins • Ablation

Introduction

Atrial fibrillation (AF), an accruing epidemic, is projected to have an incidence of approximately 16 million by 2050 [1]. A 15% increase in the hospitalization rate for AF was reported during the past decade implying significant burden on health care delivery system [2]. Multiple studies have shown catheter ablation to be superior to anti arrhythmic therapy in the management of patients with AF [3–6]. According to the 2014 AHA/ACC/HRS guidelines for management of AF, catheter ablation is indicated in patients with symptomatic, paroxysmal AF who have not responded to or tolerated antiarrhythmic medications (Class I) and in selected patients with symptomatic, paroxysmal AF *prior* to a trial of medical therapy, provided that it can be performed at an experienced center (Class IIa) [7]. The past decade saw electrophysiologists pursuing high success rates with extensive ablation. This helped us understand certain adverse sequelae such has, recurrent left sided flutters, pulmonary vein stenosis, atrioesophageal fistula, silent strokes and stiff left atrial syndrome. In current times, we are challenged to further clarify the complex mechanisms of AF to make ablation of

A.J. Deshmukh, M.D. • D.L. Packer, M.D. (✉)
Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic/St. Marys Campus,
200 First Street SW, Rochester, MN 55905, USA
e-mail: deshmuhk.abhishek@mayo.edu; packer@mayo.edu

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_12

AF safer and effective. The irrefragable litmus test for success for any technology or innovation in this field is to provide a viable choice for our patients. The ultimate idea is to go beyond "one size fits all" ablation strategy and tailor to the particular AF mechanism of the particular patient. In the following sections, we discuss the current paradigm of atrial fibrillation, recent advances and a brief look into the future.

Basis for Pulmonary Vein Isolation

The seminal observation that rapid depolarizations from the pulmonary veins (PVs) can initiate and maintain AF led to the development of novel mechanistic and therapeutic paradigms [8] (Fig. 12.1).

It is well established that the PVs play a major role in triggering and maintaining AF, as established by animal and human models, especially in the setting of paroxysmal AF. Fibrillatory conduction is likely initiated by rapid discharges from one or several focal sources within the atria; in most patients with AF (94%), the focus is in one of the PVs. The role of PVs in the initiation and perpetuation of persistent AF seems less prominent than in the setting of paroxysmal AF, likely secondary to the electrical and structural remodeling associated with persistent AF (Fig. 12.2). Evidence exists to suggest that the PVs are capable of sustaining automaticity. Blom et al. [9] studying the human embryo using monoclonal antibodies to stain conducting tissue, documented the presence of cardiac conduction tissue within the PV during embryonic development. However, although node-like cells have been observed in the PVs of rats, a detailed histology of the atrial myocardial sleeves in human hearts has thus far failed to reveal any node-like structures. Experiments have demonstrated early and delayed after-depolarization and automatic high-frequency irregular rhythms related to calcium-sensitive inward currents following infusion of ryanodine, atrial distension, rapid atrial pacing, or congestive heart failure, but most groups have not observed these in normal PV cardiomyocytes [10]. A possible role for re-entry has been implicated in the genesis of spontaneous activity from the PV. Conduction delay and block (source—sink mismatch) have been associated with changing myocardial fiber orientation, producing nonuniform anisotropy and fractionated electrograms in PVs and at the PV-left atrial (LA) junction. Optical mapping studies of normal canine PVs, demonstrated both anisotropic conduction and repolarization heterogeneity [11]. Clinically, ectopy-initiating episodes of AF have been largely localized to the distal PV musculature from multiple PVs or from multiple sites within a given PV, which after isolation could occur proximal to the ablated site. Chen et al. demonstrated that the distal PV had significantly shorter refractory periods than the adjacent LA [12]. Jais et al. demonstrated distinctive electrophysiologic properties in the PVs of patients with AF (compared with controls), with shorter PV refractory periods, more frequent and greater decremental conduction to the LA, and a propensity for PV extrastimuli to initiate AF [13]. Based on these clinical and basic electrophysiologic findings, the mechanisms of PV arrhythmogenesis is likely to be a combination of abnormal automaticity, triggered activity, and multiple reentrant circuits.

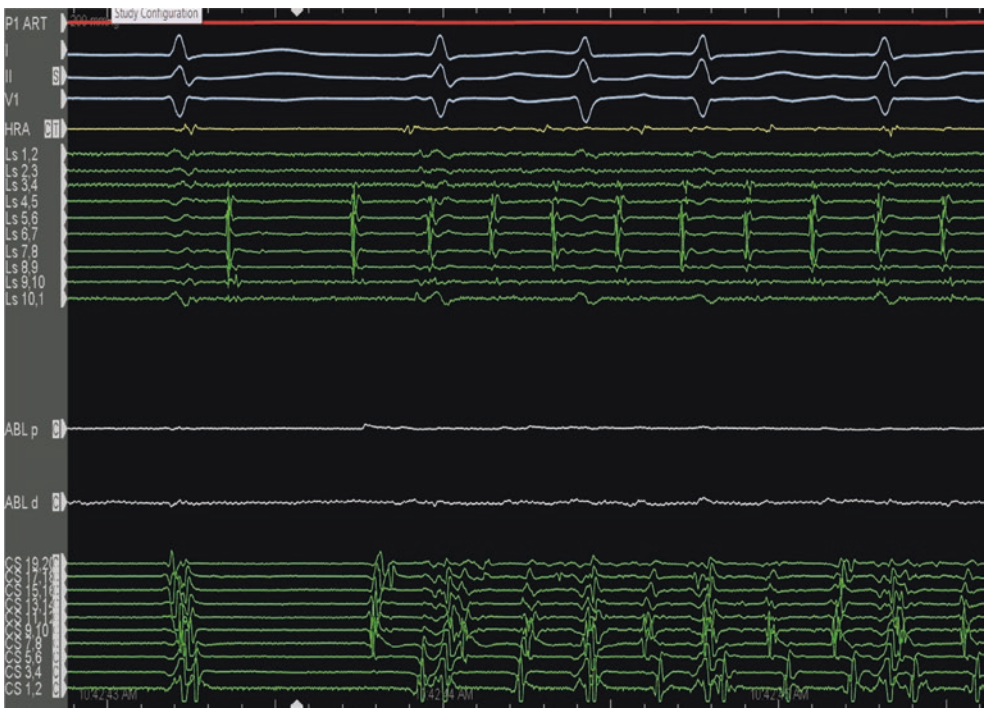


Fig. 12.1 Initiation of atrial fibrillation. Circular mapping catheter is placed in left superior pulmonary vein. Trigger noted earliest from this vein resulting in induction of atrial fibrillation

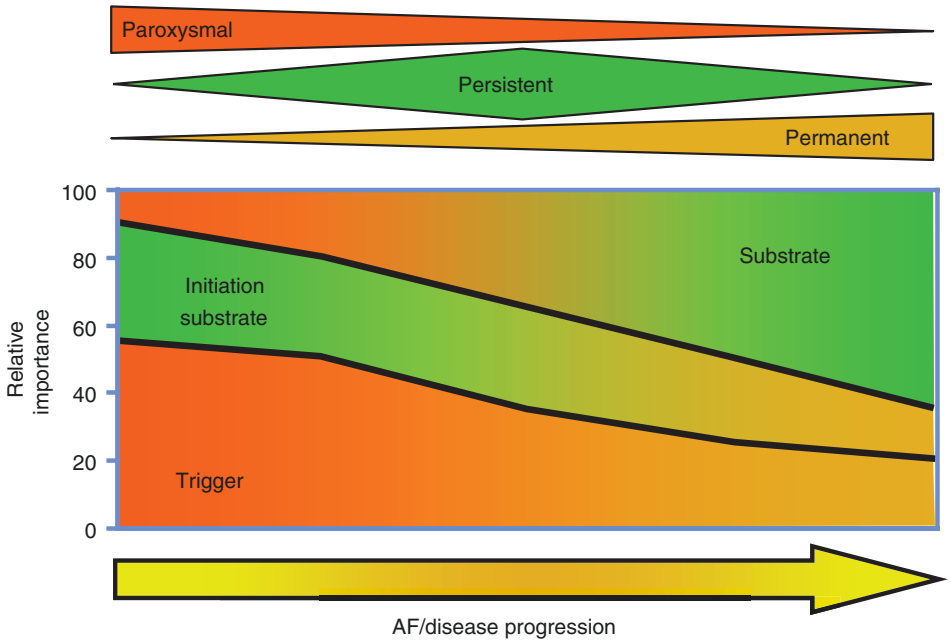


Fig. 12.2 Underlying pathogenesis of atrial fibrillation. AF is a two part disease of trigger and substrate

Pulmonary Vein Anatomy and Signals Assessment

The most important anatomic landmark relevant to AF ablation is the PV ostium. Thus regardless of the mechanism, ablation is frequently targeted to electrically isolate this substrate from the rest of the atrium. The venoatrial junctions of the pulmonary and other thoracic veins are highly complex structures [14]. Syncytial atrial myocardium extends into the veins however the orientation of the fibers typically changes around the venoatrial junction. This transition in fiber orientation, however, is gradual, and no distinct anatomic landmark (valves, ridge, etc.) clearly demarcates vein from atrium. Hence identification of true PV ostium is not possible despite advanced imaging. In some patients, the PVs may first drain into a common antrum, which then connects to the remainder of the atrium. Histologically and developmentally, the antrum, and for that matter, the proximal PVs, are no different from the atria itself showing venous and atrial myocardial components suggesting common developmental origin. During embryonic development, the common PV (sinus venosus origin) is incorporated into the left atrium. An immunohistochemical study demonstrated that the histologic characteristics of the PVs and the smooth-walled portion of the left atrium are identical explaining why the antral regions of the PVs and the posterior left atrium also are arrhythmogenic [15].

Assessing PV Potentials

PV's have its own unique electrical signature. Characteristic electrograms are recorded with single-electrode or multi-electrode mapping catheters placed within the PV. These electrograms will depend on the vein mapped, type of mapping catheter and if prior ablation has been performed. However generally an initial far-field electrogram followed by an isoelectric period, and then a sharp near-field deflection called the PV potential is recorded. The far-field signal usually represents left atrial activation. The exact reason of the isoelectric period between the left atrial potential and the PV potential is unknown, but possible explanations include ostial delay secondary to fiber orientation, ostial fibrosis, remnant nodal tissue, and a smooth muscle and cardiac syncytial interface. This delay is even better assessed with incremental coronary sinus pacing. Due to the anatomic proximity of the PVs to several other electrically active structures, complex signals may be picked up by catheter placed in the PV. For example, a catheter placed in the left upper PV may record electrical activity in the left atrial appendage, ipsilateral PV, vein of Marshall, and left atrium. In general, only the PV potential itself is near-field; all other structures picked up by the "antenna" of the mapping catheter are blunted and far-field. A mapping catheter placed in the right upper PV may record electrical activity in the right upper PV, right middle PV, right lower PV (particularly a superior branch), right atrium, left atrium, superior vena cava, and azygos vein. In fact, the far-field electrogram seen on a circumferential mapping catheter placed in the right upper PV almost always is a right atrial electrogram (not left atrial). However, this criterion alone is insufficient for identifying the true PV potential. If a catheter is deep within a PV where no PV musculature is present, then left atrial appendage electrograms will appear relatively near-field. Similarly, when radiofrequency ablation has already been performed, edema near the PV os and inadvertent ablation within the PV (more frequent than typically realized) will cause PV potentials to be less

sharp and less near-field in character. Various pacing maneuvers such as paravenous, perivenous, differential pacing are utilized to decipher each potential. We refer you to the classic reviews by Dr. Samuel Asirvatham on pulmonary vein pacing maneuvers [14, 16–18].

Techniques and Results of PVI

The initial description of PV trigger ablation consisted of focal ablation within the PVs. Initial isolation approaches were targeting specific pulmonary vein triggers utilizing induction strategies. These pulmonary vein triggers were then targeted with either focal or segmental isolation [8, 12]. However an induction strategy as a stepwise approach to pulmonary vein isolation was fraught with difficulties such as consistently initiating the arrhythmogenic foci during the electrophysiology study. In addition, during subsequent studies in patients with AF recurrence, different ectopic foci from the same or different pulmonary veins were often found to be active contributors to the arrhythmia. This approach had minimal long-term benefit, and was associated with a significant risk of PV stenosis. Subsequent evolution of the procedure involved segmental ablation at the anatomic ostium of the PVs, as defined by angiography or ICE, to isolate muscle sleeve connections between the PV and left atrium electrically. This approach is commonly referred to as segmental ostial PVI.As such, empiric isolation of all pulmonary veins became the preferred strategy [19]. However, it is important to recognize that a close examination of long-term outcomes does not demonstrate that empiric isolation of all pulmonary veins is superior to treating only those veins that are arrhythmogenic [20]. The technique further evolved targeting the left atrial tissue more proximal to the PV ostium, in a region defined as the PV antrum [21]. To achieve antral PVI, multiple approaches with different mapping systems have been described. These include electroanatomic mapping using three-dimensional nonfluoroscopic systems, and circular mapping techniques guided by imaging the PVs through ICE or angiography. Wide antral PV isolation (WACA) guided by recordings from a circular mapping catheter has been demonstrated superior to other ablation techniques in studies of direct comparison [22]. With circumferential PV ablation strategies, contiguous lesions can sometimes be created without necessarily achieving complete conduction block. Thus, post-ablation reentrant atrial tachycardias have been reported in up to 20% of patients treated with this approach [23]. Wide antral PVI is more efficacious than ostial PVI in achieving freedom from any atrial tachyarrhythmia recurrence at long-term follow-up [24]. The importance of a wider antral isolation encompassing the posterior wall between the PVs has been suggested in several preliminary studies. The main advantage of wide antral PVI is the empirical elimination of triggers arising from the left atrial posterior wall, which should be considered as an extension of the PVs from an embryologic, anatomic, and electrophysiologic standpoint. Preclinical studies have demonstrated rotors and high-frequency AF sources within the left atrial posterior wall, and observations from intraoperative AF ablation have confirmed a significant role of the posterior wall in triggering and maintaining the arrhythmia [25].

As mentioned, the majority of the studies investigating the role of PVI for the long-term maintenance of sinus rhythm have predominantly enrolled patients with paroxysmal AF; the role of PV triggers in patients with nonparoxysmal AF has not been investigated in a systematic fashion.

Pulmonary Veins Reconnection

The original promise and likely potential for this groundbreaking discovery remains largely unfulfilled due to PV reconnection. Indeed, increasing pessimism with regard to the long term outcomes for curing AF now appears to be the norm. What has remained unclear is, if our lack of progress is a fundamental flaw in the hypothesis of PV-based arrhythmogenesis, or whether we simply do not know how to permanently isolate the pulmonary veins. One basic assumption made when raising the question if pulmonary vein isolation is enough for a "cure" or durable therapy for AF is that the index ablation procedure resulted in permanent isolation of the pulmonary veins. Reconnection of the PVs represents the dominant mechanism of arrhythmia recurrence after PVI. Observational studies reporting the findings at repeat procedures showed a prevalence of PV reconnection ranging from 80 to 100% of patients [26]. In long-term follow-up study that investigated the rate of pulmonary vein reconnection after initial isolation, 53% of 161 patients were free of AF. In 66 patients, a repeat ablation was performed for repeat arrhythmia. The rate of pulmonary vein reconnection was strikingly high at 94% (62 of 66 patients) [27]. The importance of pulmonary vein reconnection has been confirmed in other studies and has led to the postulate that electrical reconnection of the veins is an important mechanism if not the sole reason for AF recurrence following catheter ablation [27, 28]. There are several potential mechanisms that may underlie pulmonary vein reconnection. First, it is possible that the initial procedure failed to achieve complete electrical isolation of the pulmonary vein. Incomplete isolation is felt to result from residual gap(s) within the encircling lesion set or lack of transmural lesions [29, 30]. As such, it is could be inferred that early recurrence of AF post ablation may be an early marker of incomplete procedural pulmonary vein isolation. This hypothesis is supported by an interesting study of 12 patients that underwent a maze procedure after a failed radiofrequency ablation. Importantly, myocardial biopsies showed anatomic gaps and/or nontransmural lesions in pulmonary veins that had reconnected [31]. Enhanced

post-procedural imaging has also added further supported to this hypothesis. In a canine study in which endocardial conduction block was demonstrated, post procedural MRI identified gaps within the line of ablation. Finally, long-term follow up data has demonstrated that those pulmonary veins with MRI identified gaps were more likely to become electrically reconnected with symptomatic recurrences [29]. Currently we can isolate the veins; however there is no real time marker to suggest if the lesions are transmural. Certain indirect assessments as discussed below can be used; however lack of real time assessment of transmural lesions remains the holy grail of modern day electrophysiology.

Maximizing Durable Pulmonary Vein Isolation

Based on available evidence, achievement of permanent PV isolation is considered the main goal of current ablation approaches for AF [32]. As of now, there are no proven ways to improve long-term durable pulmonary vein isolation, largely because we are just beginning to realize the frequency of reconnection in patients without recurrence of arrhythmia. There are several technologies and approaches that have been advocated to improve the likelihood of transmural lesion formation and durable pulmonary vein isolation. The efficacy of these technologies is largely based upon periprocedural data with the previously noted limitations, but the hope is that acute or periprocedural results will translate to enhanced long-term outcomes.

Open-irrigated catheters with contact force sensors (Thermocool® SmartTouch®, Biosense Webster, Inc., and TactiCath™, Endosense SA, Meyrin, Switzerland) have been made recently available for clinical use. These catheters contain sensors that provide real-time information on the tissue-catheter contact force and have the potential to significantly increase the safety and efficacy of PVI [33, 34]. In the Touch+ for Catheter Ablation (TOCCATA) trial, a multicenter feasibility and safety study, 32 patients with paroxysmal AF underwent PVI with the TactiCath catheter [35, 36]. In this study, tissue-catheter contact force over time (evaluated as force-time interval) was a predictor of arrhythmia-free survival over follow-up. In particular, the analysis of the force-interval integral showed a recurrence rate of 75% in patients treated with <500 g compared to 31% of patients treated with >1000 g contact force. These results have been replicated by Neuzil et al. in the EFFICAS-I trial [33]. These authors studied 46 patients with paroxysmal AF undergoing PVI with the TactiCath catheter, and operators were blinded to the contact-force information. All patients underwent a second procedure at 3 months to evaluate the presence of persistent PVI and the location of ablation gaps. Of note, 26/40 patients undergoing a repeat procedure over follow-up showed the presence of ≥1 ablation gaps; gaps were more frequently found at regions where ablation lesions were delivered with <20 g initial force and <400 g of contact force-time integral. Natale et al. recently reported the results of the SMART-AF trial evaluating the Thermocool SmartTouch catheter. In this multicenter study, 172 patients with drug-refractory symptomatic paroxysmal AF underwent PVI. At 12 months, the cumulative freedom from any atrial tachyarrhythmia recurrence was 72.5%. Of note, in this study the investigators could select the contact force parameters discretionally; when the contact force employed was in the preselected working ranges ≥80% of the time, outcomes were 4.25-times more likely to be successful [34]. A subsequent metaanalysis showed that the use of contact force technology decreases AF recurrence at a median follow-up of 12 months and also led to decreased use of RF during ablation. There was no difference in total procedure length and fluoroscopy exposure.

Methods of checking for durable lesion sets have also been explored. Dormant conduction can be identified by use of intravenous adenosine that hyperpolarizes atrial cell membranes allowing transient conduction at sites with partial ablation. Adenosine reduces LA and PV action potential duration but significantly hyperpolarizes RMP only in PV cells. This differential action on RMP is due to larger IKAdo in PV than in LA and PV cells having smaller IK1 (and therefore less negative RMPs) than LA cells. Ablation by RF energy significantly changes cellular electrophysiological properties, producing potentially reversible membrane depolarization and loss of cellular excitability. Hyperpolarization facilitates the closure of the inactivated sodium channels, making them available for activation. This results in resumption of conduction in tissue where reversible thermal heating has occurred. This premise has been used by multiple studies to assess gap in the ablation line. Although further ablation at these sites may improve AF-free period, paradoxically it also identifies those patients with a greater likelihood of AF recurrence despite additional ablation reflecting suboptimal ablation [37]. Macle et al. have recently reported the benefit of adenosine testing after initial PV isolation to improve outcomes in patients with paroxysmal AF [38]. They found that adenosine unmasked dormant PV conduction in 53% of patients studied. Further, iterative elimination of the elicited PV conduction significantly reduced the recurrence of symptomatic atrial arrhythmia after a single ablation procedure (success rate 69.4% with additional ablation vs. 42.3% with no further ablation). This absolute risk reduction of 27% translates into needing to treat 3.7 patients for benefit [38]. However no significant reduction in the 1-year incidence of recurrent atrial tachyarrhythmias by ATP-guided PVI compared with conventional PVI by another recent study [39].

Another approach to treat potential conduction gaps is to perform further ablation at sites that demonstrate pace capture along the ablation line. In a recent study investigators were able to achieve PVI in 95% of PV's using pace-guidance

alone, as assessed by circular mapping catheter data that was blinded to the operator [40]. In a prospective randomized study, same group noted 82.7% patients were free of AF at 1 year in the pace map group [41].

Beyond identification of gaps, efforts have also been directed in preventing these gaps during ablation. Steerable sheaths were designed to improve access to and contact with ablation target sites. One randomized controlled trial compared the use of steerable sheaths with the use of non-steerable sheaths in AF ablations [42]. Although the rate of acute PV isolation and total RF application time did not differ between the two groups, single procedure success was significantly higher in patients treated with a steerable sheath (76% vs. 53% at 6 months), which highlights the importance of good wall contact to achieve transmural and durable lesions.

The optimum time for ablation at each site without collateral damage is still not known. Surrogates of transmural lesions such as impedance drop change in unipolar electrograms have been studied [43–45].

Beyond electrophysiological innovation, the adoption of general anesthesia is has been shown to improve the procedural success. In a multicenter trial, Di Biase et al. randomized 257 consecutive patients undergoing a first AF ablation procedure to general anesthesia or conscious sedation. At 17 ± 8 month follow-up, 69% patients assigned to conscious sedation were free of atrial arrhythmias off antiarrhythmic drugs, as compared with 88% patients randomized to general anesthesia ($P < 0.001$). In this study, all patients with recurrence had a second procedure. Interestingly, at the repeat procedure, 42% of PVs in the conscious sedation arm had recovered PV conduction compared with 19% in the general anesthesia group ($P = 0.003$) [46]. Better and more stable tissue-catheter contact due to controlled breathing patterns and elimination of patient movements may provide an explanation to these findings. Hutchinson et al. showed similar results in an observational study [47]. The authors reported that the systematic implementation of general anesthesia and high-frequency jet ventilation together with the use of steerable sheaths and anatomic image integration with merged computed tomography/magnetic resonance imaging scans resulted in significantly better long-term arrhythmia-free survival compared to historical controls undergoing ablation under conscious sedation.

Complex Fractionated Atrial Electrograms

Complex fractionated atrial electrograms (CFAEs) during AF are thought to represent either continuous reentry of the fibrillation waves into the restricted area or an overlap of different wavelets entering the same area at different times [48]. These complex electrical activities have a relatively short cycle length and heterogeneous temporal and spatial distribution in humans. Ablation of these electrograms has been performed with the aim of eliminating wavelet reentry, thus preventing AF from perpetuating. Nademanee et al. were the first to report the success of pure CFAE ablation [49]. CFAEs are defined as low voltage atrial electrograms (ranging from 0.04 to 0.25 mV) that have fractionated electrograms composed of two deflections or more, and/or have a perturbation of the baseline with continuous deflection of a prolonged activation complex. CFAE have a very short cycle length (≤120 ms) with or without multiple potentials; however, when compared to the rest of the atria, this site has the shortest cycle length. The following key areas have demonstrated a predominance of CFAE: (1) the proximal coronary sinus; (2) superior vena cava–RA junction; (3) septal wall anterior to the right superior and inferior PVs; (4) anterior wall medial to the LA appendage; (5) area between the LA appendage and left superior PV; and (6) posterosuperior wall medial to the left superior PV. A customized software package to assist in the process of mapping (CFAE software module, CARTO, Biosense-Webster, Diamond Bar, CA, USA) has been developed [50]. The software analyzes data on atrial electrograms collected from the ablation catheter over a 2.5-s recording window and interprets it according to two variables: (1) shortest complex interval (SCL) minus the shortest interval found (in milliseconds), out of all intervals identified between consecutive CFAE complexes; and (2) interval confidence level (ICL) minus the number of intervals identified between consecutive complexes identified as CFAE, where the assumption is that the more complex intervals that are recorded—that is, the more repetitions in a given time duration—the more confident the categorization of CFAE. Information from these variables is projected on a three-dimensional electroanatomic shell according to a color-coded scale. This allows targeting and retargeting of areas of significant CFAE.

Nandemanee reported a single-procedure success rate of 63% at 12 months that improved to 77% with repeat procedures in 19 of the 64 patients. Nevertheless, similar results at that magnitude have not been replicated by other studies. Subsequent studies analyzed the additive effect of CFAE ablation to PVI. Hayward et al. performed a metaanalysis of eight controlled studies comparing the effect of PVI with CFAE ablation versus PVI alone in patients with paroxysmal and non-paroxysmal AF ($N = 481$). The authors found a slight benefit with the addition of CFAE ablation, with a relative risk of 1.15 (CI 1.2–1.31, $P = 0.03$). This statistical difference was primarily driven by studies on patients with non-paroxysmal AF. Similar results were published in a meta-analysis by Kong et al., yet this group also analyzed the drawbacks of this technique and showed that adjunctive CFAE ablation increased procedural, fluoroscopy, and RFA times [51]. Recently the STAR AF collaborators randomized patients with persistent atrial fibrillation, and found

no reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary-vein isolation.

Linear Ablation

Linear ablation paradigm is based on compartmentalization of the atria with the aim of preventing the formation of macroreentrant circuits. Ablation lines include a roof line, a mitral isthmus line, posterior box line, anterior line or any other line which could be used to compartmentalize the atrium further. Issues involved beyond collateral damage are to ensure presence of bidirectional block. If the line is not blocked, then it can further promote macroreentrant flutters.

Roof Line

Hocini et al. was the first to describe the benefits of a complete linear block by creating a roof line joining the right and left superior PVs in patients with paroxysmal AF [52]. This prospective randomized study demonstrated the feasibility of achieving complete linear block at the LA roof, which resulted in the prolongation of the fibrillatory cycle, termination of AF, and subsequent non inducibility of this arrhythmia in the electrophysiology laboratory. Roof line was also associated with an improved clinical outcome compared with PVI alone (87% vs. 69%, P = 0.04) [53].

Mitral Line

In a study by Jais et al., mitral isthmus block was achieved in 92% of patients. At 1 year after the last procedure, 87% patients with mitral isthmus ablation versus 69% without (P = 0.002) were arrhythmia free, with mitral isthmus ablation being the only factor associated with long-term success [54]. Fassini et al. showed that patients who had additional mitral isthmus ablation but did not achieve bi-directional block did not fare better than patients who had pulmonary vein isolation only [55]. In a randomized trial, Pappone et al. found that additional linear ablation (roof and mitral isthmus) significantly reduced the incidence of macroreentrant flutters without affecting AF recurrence [56, 57]. A gap in the mitral isthmus line is undoubtedly a pre-requisite for the development of postprocedure macroreentrant peri mitral flutter. It is observed from several studies that these "gaps" do not always lead to clinical tachycardia. In fact, the majority of these "gaps" do not manifest as peri mitral flutter [58]. It may be because "gaps" alone are not sufficient to support macroreentrant tachycardia and other factors may be necessary for initiation and/or perpetuation of macroreentry. In fact, Bai et al. suggested that for treatment of peri mitral flutter, the strategy of eliminating PV and non-PV triggers may be superior to mitral isthmus ablation [59].

Role of Non-PV Sources

Despite persistent PV isolation, a subset of patients may still continue to experience recurrent arrhythmia. In a recent study, Dukkipati et al. reported a 1-year AF recurrence rate of 29% despite proven permanent PVI [60]. The reasons underlying the lack of sustained response to PVI are still unclear, although the occurrence of triggers outside the PV region has been shown to play an important role in observational studies. High dose isoproterenol infusion (up to 20 μg/min) together with cardioversion of induced AF is the protocol we follow to provoke latent non-PV triggers. Typically, non-PV triggers cluster in specific regions such as the coronary sinus, the inferior mitral annulus, the interatrial septum particularly at the fossa ovalis/limbus region, the left atrial appendage, the Eustachian ridge, the crista terminalis region, and the superior vena cava [61, 62]. Other sites responsible for AF triggers are the persistent left superior vena cava and its remnant, the ligament of Marshall [63, 64]. Empirical ablation at common origins of trigger did not improve outcomes in a recent randomized trial and is not part of the standard ablation strategy at this time [62]. The optimal strategy to target non-PV sources varies according to the site of origin of the triggers. While for many areas focal ablation is typically sufficient to eliminate the triggers, isolation for triggers arising from the coronary sinus and the left atrial appendage has resulted in improved success. Once all the arrhythmia triggers have been eliminated, the incremental value of additional substrate modification with linear ablation and/ or ablation of complex fractionated atrial electrograms remains unproven [61].

Ganglion Plexi Modification

Autonomic nervous system (both sympathetic and parasympathetic) plays and important role in modulating AF triggers and substrate. High-frequency stimulation of epicardial autonomic plexuses can induce triggered activity from the PVs and potentially shorten the atrial refractory periods to provide a substrate for the conversion of PV firing into sustained AF. High-frequency stimulation is performed in the LA adjacent to the antral region of the PVs. Once identified, the location of a ganglionated plexus is tagged on the electroanatomical map. Generally, the four major LA ganglionated plexuses can be identified and localized using high-frequency stimulation in the majority of patients; though, it is not

uncommon that one or more ganglionated plexuses cannot be identified, especially in patients with persistent AF. RF is delivered after all ganglionated plexus sites have been identified. At present, no reports have suggested that targeting of ganglionated plexuses as a stand-alone procedure will consistently terminate AF or prevent its reinitiation. On the other hand, several studies combining ganglionated plexus mapping and ablation with PV-based ablation procedures for the treatment of AF have produced promising but variable results. For example, in a study of 242 paroxysmal AF patients, three groups were compared; (1) standard pulmonary vein isolation; (2) ablation of the main ganglion plexi of the left atrium; and (3) both pulmonary vein isolation and left atrial ganglion plexi ablation. Over a 2-year follow-up period freedom from AF or atrial tachycardia was achieved in 56%, 48%, and 74% of the patients, respectively (P = 0.004) [65]. Although there was increased benefit with combining ablation with ganglion plexi modification, success rates without pulmonary vein isolation were worse than the standard approach. The synergy noted with ablation of both targets may be explained in a study of 63 patients with paroxysmal AF. Ganglion plexi ablation alone before pulmonary vein isolation significantly decreased the occurrence of pulmonary vein firing in 75% of patients and reduced the inducibility of sustained AF in 68% [66].

Focal Impulse and Rotor Modulation

Localized sources for AF were postulated by Garrey, Mines, and Lewis in the early twentieth century, and reported in seminal canine studies by Schuessler, Cox, and Boineau who showed that AF is often sustained by stable, relatively large drivers [67]. Narayan et al. hypothesized that human AF may be sustained by localized sources such as electrical rotors and focal impulses. Focal Impulse and Rotor Modulation (FIRM) mapping is a novel technique to identify patient-specific AF mechanisms, by recording AF electrograms in a wide field-of-view across the majority of both atria then using physiologically-directed computational methods to produce maps of AF propagation. FIRM records AF in both atria using direct contact electrodes, the gold standard particularly for low-amplitude AF electrograms, in the form of 64-pole basket catheters each of 8 splines containing 8 electrodes. Basket catheters are advanced from the femoral vein into the right atrium (RA) or, transseptally, to the left atrium (LA). Recordings are made sequentially using one basket in each atrium in turn. Electrodes are separated by 4–6 mm along each spline and by 4–10 mm between splines. Catheters are manipulated to ensure good electrode contact and electrode locations are verified within the atrial geometry using fluoroscopy or electroanatomic mapping [68]. In an extended follow-up study, patients who underwent FIRM-guided ablation maintained higher freedom from AF versus those who underwent conventional ablation [68]. Overall, FIRM mapping revealed AF rotors or focal sources in 98% of the patients, for 1.9 ± 1.1 concurrent sources per patient, 67% of which were in the left atrium and 33% in the right atrium [68]. Importantly, AF sources were analyzed to be coincidentally ablated in 45% of conventional cases (e.g., at the LA roof or near the PVs). These data might help explain why wide area PVI is more effective than more distal PVI, and especially, why patients might remain free of AF recurrences despite PV re-connection. The encouraging results obtained by elimination of patient-specific rotors were recently confirmed in a multicenter study [69].

In the CONFIRM trial, these sources were detected in 97% of 107 patients undergoing paroxysmal or persistent AF ablation [68]. The acute end point (AF termination or consistent slowing) was achieved in 86% of cases guided by focal impulse and rotor modulation (FIRM) versus 20% of conventional ablation cases (P < 0.001). During a median follow-up of 273 days following a single procedure, FIRM-guided cases had higher freedom from AF (82.4% vs. 44.9%; P < 0.001). Interestingly, a different group from Taiwan using a distinctive optical mapping system also demonstrated the possibility of localizing rotors in the LA in a canine heart failure model in which AF was induced by infusing acetylcholine. Epicardial ablation of the rotor anchoring sites suppressed AF inducibility in 12 out of 13 Langendorff-perfused left PV–LA preparations [70]. The use of rotor mapping and ablation should be considered investigational, and a large, multicenter, randomized controlled trial comparing FIRM versus conventional ablation versus FIRM and PVI must be designed and conducted to validate the efficacy and safety of this technique.

Balloon Based Technology

Cryoballoon

Balloon-based ablation technologies have been developed with the aim of achieving PVI in shorter time and minimizing the operator dependency of manual procedures. The cryoablation balloon catheter (cryoballoon) has been evaluated quite extensively in clinical studies. The *cryoballon* is available in two diameter sizes, namely, 23 and 28 mm. Once the balloon is inflated at the ostium of the PVs, it is capable of achieving PVI within few (usually 2) cryoablation. The most important clinical study evaluating the effectiveness of ablation of AF with the cryoballoon has been the Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP-AF) trial, which has been recently published [71]. In this study, 245 patients with at least two documented episodes of drug-refractory paroxysmal AF were randomized in a 2:1 ratio to the cryoablation group or the antiarrhythmic drug therapy group. Over 12 months of follow-up, 69.9% of patients

treated with cryoablation were free of AF, compared with only 7.3% of the antiarrhythmic drug group ($P < 0.001$ for comparison). Twenty-nine patients (11.2%) developed post-procedural phrenic nerve palsy, which persisted beyond 12 months in four patients [71]. More recently, Metzner and co-workers reported a 12% incidence of esophageal thermal lesions at routine esophagogastroduodenoscopy in patients who underwent cryoballoon PVI with the 28-mm device [72, 73]. In addition, cases of atrioesophageal fistula have been reported with the cryoballoon technology [74–76]. This might reflect the higher power of the new cryoablation platform, and would suggest routine esophageal temperature monitoring also with the cryoballoon device. Prospective and retrospective large study didn't find any difference in freedom from AF when compared to radiofrequency energy [77, 78]. Further research is warranted to better evaluate the long-term arrhythmia-free survival and the safety profile of the cryoballoon device.

Laser-Balloon Ablation

The balloon-based laser ablation system (CardioFocus, Inc., Marlborough, MA) is a 12-F balloon catheter with a 2-F endoscope at the proximal end of the balloon. The balloon is designed to be inflated at the ostium of the PV to occlude the blood flow and deliver circumferential ablation. The last generation of the laser-balloon catheter is a compliant and sizeable balloon that has the capacity of delivering spot laser lesions over a wider range of energies. Dukkipati and co-workers recently reported their clinical experience with the compliant laser-balloon system in 200 patients with drug-refractory paroxysmal AF [79]. Successful PVI was achieved in 78.4% of cases with a single encircling lesion, and in 98.8% after an average of 1.3 attempts/PV. A total of 181 patients completed the 12-month follow-up achieving an arrhythmia-free survival off antiarrhythmic drugs of 60.2% (95% CI 52.7–67.4%). Phrenic nerve injury occurred in five patients, and was permanent in only one case. In addition, pericardial effusion occurred in six patients, and required pericardiocentesis in four cases [79]. In conclusion, the clinical experience with the laser-balloon catheter is very promising. It is important to emphasize that the reported results reflect the experience of high-volume institutions, and whether the reported safety and effectiveness can be generalized to less experienced operators and lower volume institutions warrants further investigation.

Complications

The specific risks of AF ablation reflect potentially extensive ablation as well as the proximity of atria to structures such as the esophagus, phrenic nerves, and other vasculature [14, 16]. Awareness of these risks has improved procedural technique, e.g., eliminating PV stenosis by ablating widely outside PVs instead of close to the thin-walled PVs, while better sheath management and anticoagulation can reduce thromboembolic risk and use of esophageal temperature probe to prevent esophageal injury. Accordingly, AF ablation procedural safety has increased with very low mortality in multicenter survey and data from both the US and Europe [80–82]. Data have consistently shown and that procedural outcomes improve with center experience. US claims data from over 93,000 patients in the U.S. national inpatient sample database showed an *in-hospital* mortality rate of 0.42%, and an overall complication rate of 6.29% which were lower in high-volume centers [83]. The possibility that complication rates are trending higher in some studies (driven by hospital volumes), although not others, may reflect treatments in less experienced centers or more complex, older patients with persistent AF in whom widespread ablation and long procedure times may cause complications. This again argues for a more targeted, mechanistic approach to AF ablation and performed by experienced operators.

Risk Factor Modification

Recently there has been interest in risk factor management to prevent recurrence of AF. Within the last decade, data on the relationship between AF and obesity, obstructive sleep apnea (OSA), alcohol consumption, and cardiometabolic risk factors have emerged [84–87]. Increased LA pressure and volume, and shortened ERP in the left atrium and PV are potential factors facilitating and perpetuating AF in obese patients with AF [88]. Furthermore, in a recently published randomized clinical study, weight reduction plus intensive general risk factor management (RFM) resulted in reduced AF symptom burden and severity. AF also has a genetic component, and a primary fibrotic atrial cardiomyopathy was described as a specific disease supplying substrates for AF, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications [89]. Pathak et al. reported the results of the ARREST-AF Cohort Study (Aggressive Risk Factor Reduction Study for Atrial Fibrillation) and their implications for catheter ablation outcomes [90]. This study comprised consecutive patients with body mass index ≥ 27 kg/m^2 and ≥ 1 risk factor (hypertension, glucose intolerance/diabetes mellitus, hyperlipidemia, OSA, smoking, or alcohol excess) undergoing catheter ablation for symptomatic AF, despite use of antiarrhythmic drugs. Patients in the RFM group ($n = 61$) attended an intensive physician-directed program in a RFM clinic, according to American College of Cardiology/American Heart Association guidelines [91]. The control group subjects ($n = 88$) continued RFM under the direction of their treating physician. RFM resulted in significantly greater weight and

blood pressure reductions, and better glycemic control and lipid profiles. Reviews were every 3 months for the first year and then every 6 months thereafter, including ambulatory 7-day monitoring at each review. At follow-up after catheter ablation, arrhythmia-free survival after single and multiple procedures was significantly greater in RFM patients compared with control subjects. On multivariate analysis, RFM was an independent predictor of arrhythmia-free survival, with an impressive hazard ratio of 4.8 [90]. This confirms and extends the growing body of evidence that a variety of cardiac risk factors affect procedural outcomes in patients with AF undergoing catheter ablation. Prior trials assessing antiarrhythmic therapy and ablation typically left these cardiometabolic risk factors untreated, these new data indicate that less invasive, lower risk, and beneficial interventions show substantial efficacy in treating AF.

Guidelines reserve ablation for patients with symptomatic AF and several studies show that ablation in such patients improves quality of life compared to pharmacologic therapy [6, 32]. Metrics of success is measured by eliminating asymptomatic and symptomatic AF. If the results of major ongoing studies, including CABANA (Clinicaltrials.gov: NCT00911508), CASTLE-AF (Clinicaltrials.gov: NCT00643188), and EAST (Clinicaltrials.gov: NCT01288352), show improved survival from ablation compared to pharmacological therapy, then AF ablation may be potentially extended to patients with asymptomatic AF.

Although cure rates remain disheartening, the remarkable success of ablation in many patients provides a foundation for future advancements. A mechanistic classification of AF will enable better guidance on how to tailor ablation in specific populations. Technical advances have already improved the ease of performing AF ablation, decreasing procedure times, and its safety profile. These trends are likely to further improve results from AF ablation in coming years as it becomes an increasingly important therapeutic option in many patients. Upstream and downstream risk factor modification has emerged as an important factor in maintaining sinus rhythm. The next few decades are exciting times for AF ablation, as it evolves from improved mechanistic understanding to innovative technology.

Disclosures Abhishek Deshmukh: None.

Douglas Packer: Dr. Packer in the past 12 months has provided consulting services for Abbott Laboratories/Topera, Abiomed, Aperture Diagnostics, Biosense Webster, Inc., Boston Scientific, CardioFocus, CardioInsight Technologies, Johnson & Johnson Healthcare Systems, Johnson & Johnson, MediaSphere Medical, LLC, Medtronic CryoCath, Siemens, St. Jude Medical, and Topera. Dr. Packer received no personal compensation for these consulting activities. Dr. Packer receives research funding from the American Heart Association Foundation Award, Biosense Webster, Boston Scientific/EPT, CardioInsight, CardioFocus, Endosense, Hansen Medical, Medtronic CryoCath LP, NIH, St. Jude Medical, Siemens and Thermedical. Dr. Packer also receives royalties from Wiley & Sons and St. Jude Medical.

References

1. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114(2):119–25.
2. Patel NJ, Deshmukh A, Pant S, Singh V, Patel N, Arora S, et al. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. Circulation. 2014;129(23):2371–9.
3. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009;2(4):349–61.
4. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA. 2014;311(7):692–700.
5. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med. 2012;367(17):1587–95.
6. Noheria A, Kumar A, Wylie JV Jr, Josephson ME. Catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation: a systematic review. Arch Intern Med. 2008;168(6):581–6.
7. Fuster V, Ryden LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation) Developed in Collaboration with the North American Society of Pacing and Electrophysiology. Circulation. 2001;104(17):2118–50.
8. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659–66.
9. Blom NA, Gittenberger-de Groot AC, DeRuiter MC, Poelmann RE, Mentink MM, Ottenkamp J. Development of the cardiac conduction tissue in human embryos using HNK-1 antigen expression: possible relevance for understanding of abnormal atrial automaticity. Circulation. 1999;99(6):800–6.
10. Hocini M, Ho SY, Kawara T, Linnenbank AC, Potse M, Shah D, et al. Electrical conduction in canine pulmonary veins: electrophysiological and anatomic correlation. Circulation. 2002;105(20):2442–8.
11. Arora R, Verheule S, Scott L, Navarrete A, Katari V, Wilson E, et al. Arrhythmogenic substrate of the pulmonary veins assessed by high-resolution optical mapping. Circulation. 2003;107(13):1816–21.
12. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, WC Y, et al. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation. 1999;100(18):1879–86.

13. Jais P, Hocini M, Macle L, Choi KJ, Deisenhofer I, Weerasooriya R, et al. Distinctive electrophysiological properties of pulmonary veins in patients with atrial fibrillation. Circulation. 2002; 106(19):2479–85.
14. Macedo PG, Kapa S, Mears JA, Fratianni A, Asirvatham SJ. Correlative anatomy for the electrophysiologist: ablation for atrial fibrillation. Part I: pulmonary vein ostia, superior vena cava, vein of Marshall. J Cardiovasc Electrophysiol. 2010;21(6): 721–30.
15. Douglas YL, Jongbloed MR, Gittenberger-de Groot AC, Evers D, Dion RA, Voigt P, et al. Histology of vascular myocardial wall of left atrial body after pulmonary venous incorporation. Am J Cardiol. 2006;97(5):662–70.
16. Macedo PG, Kapa S, Mears JA, Fratianni A, Asirvatham SJ. Correlative anatomy for the electrophysiologist: ablation for atrial fibrillation. Part II: regional anatomy of the atria and relevance to damage of adjacent structures during AF ablation. J Cardiovasc Electrophysiol. 2010;21(7):829–36.
17. Asirvatham SJ. Pulmonary vein-related maneuvers: part I. Heart Rhythm. 2007;4(4):538–44.
18. Asirvatham SJ. Pacing maneuvers for nonpulmonary vein sources: part II. Heart Rhythm. 2007;4(5):681–5.
19. Oral H, Scharf C, Chugh A, Hall B, Cheung P, Good E, et al. Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. Circulation. 2003;108(19):2355–60.
20. Zhang B, Zhen Y, Tao A, Zhang G. Efficacy of selective arrhythmogenic pulmonary veins isolation versus empirical all pulmonary veins isolation for atrial fibrillation: a meta-analysis of randomized and observational studies. J Interv Card Electrophysiol. 2014;39(3):233–40.
21. Pappone C, Santinelli V, Manguso F, Vicedomini G, Gugliotta F, Augello G, et al. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. Circulation. 2004;109(3):327–34.
22. Marrouche NF, Dresing T, Cole C, Bash D, Saad E, Balaban K, et al. Circular mapping and ablation of the pulmonary vein for treatment of atrial fibrillation: impact of different catheter technologies. J Am Coll Cardiol. 2002;40(3):464–74.
23. Chugh A, Oral H, Good E, Han J, Tamirisa K, Lemola K, et al. Catheter ablation of atypical atrial flutter and atrial tachycardia within the coronary sinus after left atrial ablation for atrial fibrillation. J Am Coll Cardiol. 2005;46(1):83–91.
24. Proietti R, Santangeli P, Di Biase L, Joza J, Bernier ML, Wang Y, et al. Comparative effectiveness of wide antral versus ostial pulmonary vein isolation: a systematic review and meta-analysis. Circ Arrhythm Electrophysiol. 2014;7(1):39–45.
25. Webb S, Kanani M, Anderson RH, Richardson MK, Brown NA. Development of the human pulmonary vein and its incorporation in the morphologically left atrium. Cardiol Young. 2001;11(6):632–42.
26. Santangeli P, Lin D. Catheter ablation of paroxysmal atrial fibrillation: have we achieved cure with pulmonary vein isolation? Methodist Debakey Cardiovasc J. 2015;11(2):71–5.
27. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation. 2010;122(23):2368–77.
28. Callans DJ, Gerstenfeld EP, Dixit S, Zado E, Vanderhoff M, Ren JF, et al. Efficacy of repeat pulmonary vein isolation procedures in patients with recurrent atrial fibrillation. J Cardiovasc Electrophysiol. 2004;15(9):1050–5.
29. Ranjan R, Kato R, Zviman MM, Dickfeld TM, Roguin A, Berger RD, et al. Gaps in the ablation line as a potential cause of recovery from electrical isolation and their visualization using MRI. Circ Arrhythm Electrophysiol. 2011;4(3):279–86.
30. McGann CJ, Kholmovski EG, Oakes RS, Blauer JJ, Daccarett M, Segerson N, et al. New magnetic resonance imaging-based method for defining the extent of left atrial wall injury after the ablation of atrial fibrillation. J Am Coll Cardiol. 2008;52(15):1263–71.
31. Kowalski M, Grimes MM, Perez FJ, Kenigsberg DN, Koneru J, Kasirajan V, et al. Histopathologic characterization of chronic radiofrequency ablation lesions for pulmonary vein isolation. J Am Coll Cardiol. 2012;59(10):930–8.
32. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. 2012;9(4):632–696.e21.
33. Neuzil P, Reddy VY, Kautzner J, Petru J, Wichterle D, Shah D, et al. Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study. Circ Arrhythm Electrophysiol. 2013;6(2):327–33.
34. Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. J Am Coll Cardiol. 2014;64(7):647–56.
35. Kuck KH, Reddy VY, Schmidt B, Natale A, Neuzil P, Saoudi N, et al. A novel radiofrequency ablation catheter using contact force sensing: Toccata study. Heart Rhythm. 2012;9(1):18–23.
36. Reddy VY, Shah D, Kautzner J, Schmidt B, Saoudi N, Herrera C, et al. The relationship between contact force and clinical outcome during radiofrequency catheter ablation of atrial fibrillation in the TOCCATA study. Heart Rhythm. 2012;9(11):1789–95.
37. McLellan AJ, Kumar S, Smith C, Morton JB, Kalman JM, Kistler PM. The role of adenosine following pulmonary vein isolation in patients undergoing catheter ablation for atrial fibrillation: a systematic review. J Cardiovasc Electrophysiol. 2013;24(7): 742–51.
38. Macle L, Khairy P, Weerasooriya R, Novak P, Verma A, Willems S, et al. Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial. Lancet. 2015;386:672–9.
39. Kobori A, Shizuta S, Inoue K, Kaitani K, Morimoto T, Nakazawa Y, et al. Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: the UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate (UNDER-ATP) trial. Eur Heart J. 2015;36:3276–87.
40. Steven D, Reddy VY, Inada K, Roberts-Thomson KC, Seiler J, Stevenson WG, et al. Loss of pace capture on the ablation line: a new marker for complete radiofrequency lesions to achieve pulmonary vein isolation. Heart Rhythm. 2010;7(3):323–30.
41. Steven D, Sultan A, Reddy V, Luker J, Altenburg M, Hoffmann B, et al. Benefit of pulmonary vein isolation guided by loss of pace capture on the ablation line: results from a prospective 2-center randomized trial. J Am Coll Cardiol. 2013;62(1):44–50.
42. Piorkowski C, Eitel C, Rolf S, Bode K, Sommer P, Gaspar T, et al. Steerable versus nonsteerable sheath technology in atrial

fibrillation ablation: a prospective, randomized study. Circ Arrhythm Electrophysiol. 2011;4(2):157–65.
43. Reichlin T, Knecht S, Lane C, Kuhne M, Nof E, Chopra N, et al. Initial impedance decrease as an indicator of good catheter contact: insights from radiofrequency ablation with force sensing catheters. Heart Rhythm. 2014;11(2):194–201.
44. Reichlin T, Lane C, Nagashima K, Nof E, Chopra N, Ng J, et al. Feasibility, efficacy, and safety of radiofrequency ablation of atrial fibrillation guided by monitoring of the initial impedance decrease as a surrogate of catheter contact. J Cardiovasc Electrophysiol. 2015;26(4):390–6.
45. Kumar S, Michaud GF. Unipolar electrogram morphology to assess lesion formation during catheter ablation of atrial fibrillation: successful translation into clinical practice. Circ Arrhythm Electrophysiol. 2013;6(6):1050–2.
46. Di Biase L, Conti S, Mohanty P, Bai R, Sanchez J, Walton D, et al. General anesthesia reduces the prevalence of pulmonary vein reconnection during repeat ablation when compared with conscious sedation: results from a randomized study. Heart Rhythm. 2011;8(3):368–72.
47. Hutchinson MD, Garcia FC, Mandel JE, Elkassabany N, Zado ES, Riley MP, et al. Efforts to enhance catheter stability improve atrial fibrillation ablation outcome. Heart Rhythm. 2013;10(3):347–53.
48. Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. Circulation. 1994;89(4):1665–80.
49. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol. 2004;43(11):2044–53.
50. Nademanee K, Schwab M, Porath J, Abbo A. How to perform electrogram-guided atrial fibrillation ablation. Heart Rhythm. 2006;3(8):981–4.
51. Li WJ, Bai YY, Zhang HY, Tang RB, Miao CL, Sang CH, et al. Additional ablation of complex fractionated atrial electrograms after pulmonary vein isolation in patients with atrial fibrillation: a meta-analysis. Circ Arrhythm Electrophysiol. 2011;4(2):143–8.
52. Hocini M, Jais P, Sanders P, Takahashi Y, Rotter M, Rostock T, et al. Techniques, evaluation, and consequences of linear block at the left atrial roof in paroxysmal atrial fibrillation: a prospective randomized study. Circulation. 2005;112(24):3688–96.
53. Lo LW, Scherlag BJ, Chang HY, Lin YJ, Chen SA, Po SS. Paradoxical long-term proarrhythmic effects after ablating the "head station" ganglionated plexi of the vagal innervation to the heart. Heart Rhythm. 2013;10(5):751–7.
54. Jais P, Hocini M, Hsu LF, Sanders P, Scavee C, Weerasooriya R, et al. Technique and results of linear ablation at the mitral isthmus. Circulation. 2004;110(19):2996–3002.
55. Fassini G, Riva S, Chiodelli R, Trevisi N, Berti M, Carbucicchio C, et al. Left mitral isthmus ablation associated with PV Isolation: long-term results of a prospective randomized study. J Cardiovasc Electrophysiol. 2005;16(11):1150–6.
56. Pappone C, Manguso F, Vicedomini G, Gugliotta F, Santinelli O, Ferro A, et al. Prevention of iatrogenic atrial tachycardia after ablation of atrial fibrillation: a prospective randomized study comparing circumferential pulmonary vein ablation with a modified approach. Circulation. 2004;110(19):3036–42.
57. Sawhney N, Anand K, Robertson CE, Wurdeman T, Anousheh R, Feld GK. Recovery of mitral isthmus conduction leads to the development of macro-reentrant tachycardia after left atrial linear ablation for atrial fibrillation. Circ Arrhythm Electrophysiol. 2011;4(6):832–7.
58. Rostock T, O'Neill MD, Sanders P, Rotter M, Jais P, Hocini M, et al. Characterization of conduction recovery across left atrial linear lesions in patients with paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2006;17(10):1106–11.
59. Bai R, Di Biase L, Mohanty P, Dello Russo A, Casella M, Pelargonio G, et al. Ablation of perimitral flutter following catheter ablation of atrial fibrillation: impact on outcomes from a randomized study (PROPOSE). J Cardiovasc Electrophysiol. 2012;23(2):137–44.
60. Dukkipati SR, Neuzil P, Kautzner J, Petru J, Wichterle D, Skoda J, et al. The durability of pulmonary vein isolation using the visually guided laser balloon catheter: multicenter results of pulmonary vein remapping studies. Heart Rhythm. 2012;9(6):919–25.
61. Dixit S, Lin D, Frankel DS, Marchlinski FE. Catheter ablation for persistent atrial fibrillation: antral pulmonary vein isolation and elimination of nonpulmonary vein triggers are sufficient. Circ Arrhythm Electrophysiol. 2012;5(6):1216–23. discussion 1223
62. Dixit S, Marchlinski FE, Lin D, Callans DJ, Bala R, Riley MP, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. Circ Arrhythm Electrophysiol. 2012;5(2):287–94.
63. Elayi CS, Fahmy TS, Wazni OM, Patel D, Saliba W, Natale A. Left superior vena cava isolation in patients undergoing pulmonary vein antrum isolation: impact on atrial fibrillation recurrence. Heart Rhythm. 2006;3(9):1019–23.
64. Choi JI, Pak HN, Park JH, Choi EJ, Kim SK, Kwak JJ, et al. Clinical significance of complete conduction block of the left lateral isthmus and its relationship with anatomical variation of the vein of Marshall in patients with nonparoxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2009;20(6):616–22.
65. Katritsis DG, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J Am Coll Cardiol. 2013;62(24):2318–25.
66. Nakagawa H, Scherlag BJ, Patterson E, Ikeda A, Lockwood D, Jackman WM. Pathophysiologic basis of autonomic ganglionated plexus ablation in patients with atrial fibrillation. Heart Rhythm. 2009;6(12 Suppl):S26–34.
67. Schricker AA, Lalani GG, Krummen DE, Narayan SM. Rotors as drivers of atrial fibrillation and targets for ablation. Curr Cardiol Rep. 2014;16(8):509.
68. Narayan SM, Baykaner T, Clopton P, Schricker A, Lalani GG, Krummen DE, et al. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). J Am Coll Cardiol. 2014;63(17):1761–8.
69. Miller JM, Kowal RC, Swarup V, Daubert JP, Daoud EG, Day JD, et al. Initial independent outcomes from focal impulse and rotor modulation ablation for atrial fibrillation: multicenter FIRM registry. J Cardiovasc Electrophysiol. 2014;25(9):921–9.
70. Chou CC, Chang PC, Wen MS, Lee HL, Chen TC, Yeh SJ, et al. Epicardial ablation of rotors suppresses inducibility of acetylcholine-induced atrial fibrillation in left pulmonary vein-left atrium preparations in a beagle heart failure model. J Am Coll Cardiol. 2011;58(2):158–66.
71. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol. 2013;61(16):1713–23.
72. Metzner A, Burchard A, Wohlmuth P, Rausch P, Bardyszewski A, Gienapp C, et al. Increased incidence of esophageal thermal lesions using the second-generation 28-mm cryoballoon. Circ Arrhythm Electrophysiol. 2013;6(4):769–75.
73. Furnkranz A, Bordignon S, Bohmig M, Konstantinou A, Dugo D, Perrotta L, et al. Reduced incidence of esophageal lesions by luminal esophageal temperature-guided second-generation cryoballoon ablation. Heart Rhythm. 2015;12(2):268–74.

74. Stockigt F, Schrickel JW, Andrie R, Lickfett L. Atrioesophageal fistula after cryoballoon pulmonary vein isolation. J Cardiovasc Electrophysiol. 2012;23(11):1254–7.
75. Lim HW, Cogert GA, Cameron CS, Cheng VY, Sandler DA. Atrioesophageal fistula during cryoballoon ablation for atrial fibrillation. J Cardiovasc Electrophysiol. 2014;25(2):208–13.
76. Kawasaki R, Gauri A, Elmouchi D, Duggal M, Bhan A. Atrioesophageal fistula complicating cryoballoon pulmonary vein isolation for paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2014;25(7):787–92.
77. Schmidt M, Dorwarth U, Andresen D, Brachmann J, Kuck KH, Kuniss M, et al. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. J Cardiovasc Electrophysiol. 2014;25(1):1–7.
78. Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hormann P, et al. Cryoballoon versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation: The Prospective, Randomised, Controlled, Non-Inferiority FreezeAF Study. Circulation. 2015;132:1311–9.
79. Dukkipati SR, Kuck KH, Neuzil P, Woollett I, Kautzner J, McElderry HT, et al. Pulmonary vein isolation using a visually guided laser balloon catheter: the first 200-patient multicenter clinical experience. Circ Arrhythm Electrophysiol. 2013;6(3):467–72.
80. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3(1):32–8.
81. Hoyt H, Bhonsale A, Chilukuri K, Alhumaid F, Needleman M, Edwards D, et al. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. Heart Rhythm. 2011;8(12):1869–74.
82. Bertaglia E, Stabile G, Pappone A, Themistoclakis S, Tondo C, De Sanctis V, et al. Updated national multicenter registry on procedural safety of catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol. 2013;24(10):1069–74.
83. Deshmukh A, Patel NJ, Pant S, Shah N, Chothani A, Mehta K, et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. Circulation. 2013;128(19):2104–12.
84. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA. 2004;292(20):2471–7.
85. Tsang TS, Barnes ME, Miyasaka Y, Cha SS, Bailey KR, Verzosa GC, et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur Heart J. 2008;29(18):2227–33.
86. Kodama S, Saito K, Tanaka S, Horikawa C, Saito A, Heianza Y, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. J Am Coll Cardiol. 2011;57(4):427–36.
87. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. J Am Coll Cardiol. 2014;64(3):281–9.
88. Munger TM, Dong YX, Masaki M, JK O, Mankad SV, Borlaug BA, et al. Electrophysiological and hemodynamic characteristics associated with obesity in patients with atrial fibrillation. J Am Coll Cardiol. 2012;60(9):851–60.
89. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013;310(19):2050–60.
90. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol. 2014;64(21):2222–31.
91. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation. 2002;106(3):388–91.

Ventricular Tachycardia Ablation

13

Samuel H. Baldinger, Usha B. Tedrow,
and William G. Stevenson

Abstract

While catheter ablation (CA) of ventricular arrhythmias (VAs) was in the past often only considered after pharmacological options had been exhausted, substantial progress has occurred and CA is now an option that should be considered early when therapy of recurrent arrhythmia is needed. In patients with VAs without structural heart disease CA is highly successful with a low rate of complications. In patients with heart disease efficacy is determined by the nature of the arrhythmia substrate, most often an area of scar. The current ability of mapping to identify substrate during stable sinus rhythm makes CA an option even when multiple and unstable ventricular tachycardias (VTs) are present. Its major role is in controlling of incessant VT and recurrent symptomatic VT in patients with implanted defibrillators. Continued advances in mapping and ablation methods are anticipated to continue to improve efficacy and safety.

Keywords

Ventricular tachycardia • Ventricular fibrillation • Mapping • Image integration • Catheter ablation • Radiofrequency ablation • Coronary artery disease • Non-ischemic cardiomyopathy • Focal ventricular tachycardia • Reentrant ventricular tachycardia

Introduction

In patients with structural heart disease (SHD) and implantable cardioverter defibrillators (ICDs) episodes of sustained ventricular tachycardia (VT) are associated with worsening heart failure, psychological morbidity and increased mortality [1–3]. In patients with no SHD ventricular arrhythmias can cause compromising symptoms and when very frequent may lead to decreased ventricular function [4, 5]. Antiarrhythmic medication can reduce arrhythmia burden and the frequency of ICD shocks but often are poorly tolerated [6]. Some antiarrhythmic drugs increase mortality in patients with SHD [7].

While catheter ablation (CA) was in the past often only considered after pharmacological options had been exhausted, current guidelines suggest consideration of VT ablation earlier in the course of the disease [8]. This chapter will discuss current strategies for CA in patients with sustained VT and will provide a perspective of potential future developments.

Technical Aspects of Catheter Ablation

Radiofrequency Ablation

The goal of catheter-based ablation therapy for VT is to create durable myocardial lesions at the ablation target. Radiofrequency (RF) ablation to treat cardiac arrhythmias was first introduced by Huang and coworkers in 1985 [9], and has revolutionized the treatment of cardiac arrhyth-

S.H. Baldinger, M.D. (✉) • U.B. Tedrow, M.D., M.Sc.
W.G. Stevenson, M.D.
Cardiovascular Division, Cardiac Arrhythmia Center,
Brigham and Women's Hospital, 75 Francis Street,
Boston, MA 02115, USA
e-mail: sbaldinger1@partners.org; utedrow@partners.org;
wstevenson@partners.org

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_13

mias. RF energy delivered between an electrode at the tip of the ablation catheter and a large grounding patch on the patient's skin, results in resistive heating of a 1- to 2-mm rim of tissue adjacent to the catheter tip and conductive heating of surrounding tissue causing thermal damage. Because of the rapid reduction in heating with distance, lesions created by RF energy are typically small and well circumscribed [10]. The catheter electrode temperature must be kept below 80° centigrade to avoid coagulum or char formation at the catheter tip. The development of RF catheters that cool the electrode with saline irrigation allows greater power delivery while minimizing heating of the catheter tip, and was a major technological advance. With cooling the zone of maximal heating is shifted deeper into the tissue, increasing the radius of resistive heating and resulting in larger and deeper lesions [11].

Lesion formation with RF ablation is critically determined by catheter–tissue contact. If the catheter is not in direct contact with myocardial tissue, virtually all energy will be dissipated in the blood pool without effective tissue heating. Newer ablation catheters incorporate contact force sensors to aid in catheter positioning [12, 13].

Alternative Energy Sources

Cryoablation destroys tissue by freezing and is an important method for surgical ablation, but is not commonly used for CA [14]. Laser catheter, high intensity focused ultrasound, and microwave ablation techniques are all under development and hold promise for increasing lesion size for scar-related VT.

Access Considerations

Depending on the location of the arrhythmia substrate ablation may require access of the right ventricle (RV), left ventricle (LV), aortic root, epicardial coronary venous system, or the pericardial space. Access to the LV can be achieved using a retrograde approach across the aortic valve or using a transseptal approach via the left atrium and through the mitral valve. For patients with peripheral vascular disease, a mechanical aortic valve or when insertion of multiple mapping catheters is desired, the transseptal approach is preferred. Percutaneous pericardial access is needed to allow CA of arrhythmias arising from the epicardial surface of the heart and is often needed in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and other non-ischemic cardiomyopathies [15]. Access is usually accomplished by a subxiphoid pericardial puncture using an epidural needle or micropuncture needle [16, 17]. Access is often not possible if pericardial adhesions, as from prior cardiac surgery, are present. Although epicardial access, mapping and ablation are commonly used in experienced centers it is associated with a 6–10% risk of complications, most frequently pericardial bleeding [15, 18].

Initial Considerations and Pre-procedural Workup for Patients Presenting with VT

VTs considered to be a target for CA most frequently are monomorphic. The optimal ablation approach and expected success rates are dependent on the location of the arrhythmia origin or substrate, which can often be anticipated from the electrocardiographic characteristics of the arrhythmia as well as the presence and type of underlying heart disease. Patients with SHD and sustained monomorphic VT usually, but not always have scar related reentrant VT, while patients with structurally normal hearts usually have a focal VT origin consistent with automaticity or triggered activity. Documentation of the spontaneous VT (commonly referred to as the "clinical VT") on 12-lead-ECG is helpful because the likely VT origin can be derived from the QRS morphology. If VT is terminated by an ICD, at least the cycle length of the clinical VT should be obtained.

The type and severity of underlying heart disease is a major determinant of prognosis and risk. A careful cardiac evaluation is therefore important and will influence the treatment approach. Pre-procedural planning is important to minimize risks. Transthoracic echocardiography gives a first impression regarding ventricular function, size and the location of areas of abnormal wall motion that could potentially contain arrhythmogenic scars; and is also useful to assess the presence of mobile left ventricular (LV) thrombi, which would prevent endocardial LV mapping. Contrast enhanced magnetic resonance imaging (MRI) may be used to identify ventricular abnormalities including scar, evident as delayed gadolinium enhancement, that is likely to contain the VT substrate which are areas that contain critical conduction pathways for reentry circuits (isthmus sites) that are targets for CA [19–21]. Images from MRI or cardiac CT can be imported into electro-anatomic mapping systems to help guide ablation procedures [22, 23]. Nuclear perfusion imaging may show areas of scar as perfusion defects [24]. Cardiac positron emission tomographic imaging (PET) with fluoro-deoxyglucose can reveal inflammatory disease, such as cardiac sarcoidosis.

In patients with coronary artery disease (CAD), the potential for ischemia, which could contribute to instability during the ablation procedure, should be addressed. Electrolyte disturbances, heart failure and fluid balance should be optimized, particularly because external irrigation catheters used for ablation administer additional volume with potential to aggravate heart failure. Discontinuation of antiarrhythmic

drug therapy is usually desirable to facilitate induction of VT and assessment of the ablation endpoint, but is not needed if VT is incessant or very frequent.

Complications of Catheter Ablation

In a retrospective analysis of a large U.S. administrative data base Palaniswamy et al. reported that the complication rate for CA has remained stable from 2001 to 2011 (total complications 11.2%; vascular: 6.9%, cardiac: 4.3%, and neurologic: 0.5%) with in-hospital mortality rates (1.6%) in the United States during 2002–2011 [25]. Most larger trials however reported lower complication rates [26–28]. Cardiac tamponade is usually related to ablation in the thin-walled RV or epicardial access. AV block can occur when targeting basal septal VTs with RF energy. In patients with structural heart disease, procedure-related mortality is approximately 2%, with most deaths being related to incessant, uncontrollable VT and cardiogenic shock [8].

Patients with Structurally Normal Hearts

In patients with idiopathic ventricular arrhythmias and no SHD, CA should be considered for symptomatic patients or those with frequent arrhythmia that is inducing cardiomyopathy, and is appropriate even as first line therapy [8]. Reported acute efficacy rates exceed 70% and complication rates are low and largely related to vascular access complications, although cardiac tamponade, coronary artery injury, and valvular injury can occur [29]. Efficacy and procedure risks are determined by the arrhythmia origin. Ablation failure is usually due to inability to induce the arrhythmia to allow mapping at the time of the procedure, often related to sedation, to the location of the arrhythmia focus in a location not accessible to the ablation catheter, or to the location of the focus adjacent to a coronary artery where CA attempted are precluded due to the risk of coronary injury.

Outflow Tract Arrhythmias

Most idiopathic monomorphic VTs or PVCs have a focal origin from the RV outflow tract (RVOT) [30]. The cellular mechanism is likely related to intracellular calcium overload and c-AMP related delayed after-depolarizations that lead to triggered activity. The tachycardia can often be terminated with overdrive pacing; administration of intravenous β-blockers, calcium-channel blockers, or adenosine [31, 32]. The QRS shows a left bundle branch block (LBBB) morphology in lead V1 with an inferior frontal plane axis and a precordial transition from rS to Rs typically at V3 or later. Because of an origin close to the conduction system, VTs coming from posterior sites of the RVOT usually show relatively narrow QRS complexes (≤140 ms) [33]. Sleeves of myocardium often extend above the pulmonary valve and may be the source for up to 50% of all arrhythmias classified as RVOT tachycardia [34, 35].

These focal arrhythmias are approached by activation mapping, which shows centrifugal activation of the ventricle emanating from the earliest site of activation, which typically precedes the surface QRS onset by 25–50 ms and shows a QS deflection on the unipolar recording. In addition, pacing at the source of the arrhythmia (pace-mapping) typically reproduces the morphology of the ventricular arrhythmia (Fig. 13.1); however the spatial resolution of pace-mapping is inferior to that of activation mapping and exact pace maps can be recorded up to 2 cm from the site of origin [36].

Less commonly VTs originate from the LV outflow tract (LVOT), most frequent from the left coronary cusp, followed by the commissure between the right and the left coronary cusp, the right coronary cusp and rarely the non-coronary cusp [37]. ECG algorithms have been proposed to identify the likely site of origin of outflow tract arrhythmias but exceptions occur [38–43]. LVOT VT usually shows a precordial transition with a prominent R wave at or before V3. Up to 15% of outflow tract arrhythmias have an epicardial site of origin that may be approached for CA from within an epicardial cardiac vein, usually the great cardiac vein, although these sites can be close to a coronary artery precluding ablation attempts [44]. Others originate from myocardium extending above the aortic valve that requires ablation from within the right or left sinus of Valsalva. Ablation targeting isolated potentials preceding the QRS and pace-mapping is not reliable and can be misleading in this region [45].

Other Idiopathic Ventricular Arrhythmias

Idiopathic focal arrhythmias can also arise from the LV or RV papillary muscles, the moderator band, sites along the mitral or tricuspid annulus, or the cardiac crux, an epicardial region corresponding to the intersection of the atrioventricular groove and posterior interventricular groove [46].

A less common form of idiopathic VT that is due to reentry in or near the LV fascicles of the Purkinje system is verapamil-sensitive left fascicular VT. It can be induced by atrial pacing, has a RBBB like morphology and left superior frontal plain axis with relatively narrow QRS width, and can be terminated by intravenous verapamil administration [47, 48]. Ablation targeting an area of presystolic Purkinje potentials during VT or rounded diastolic potentials usually found in the mid LV septum is very effective.

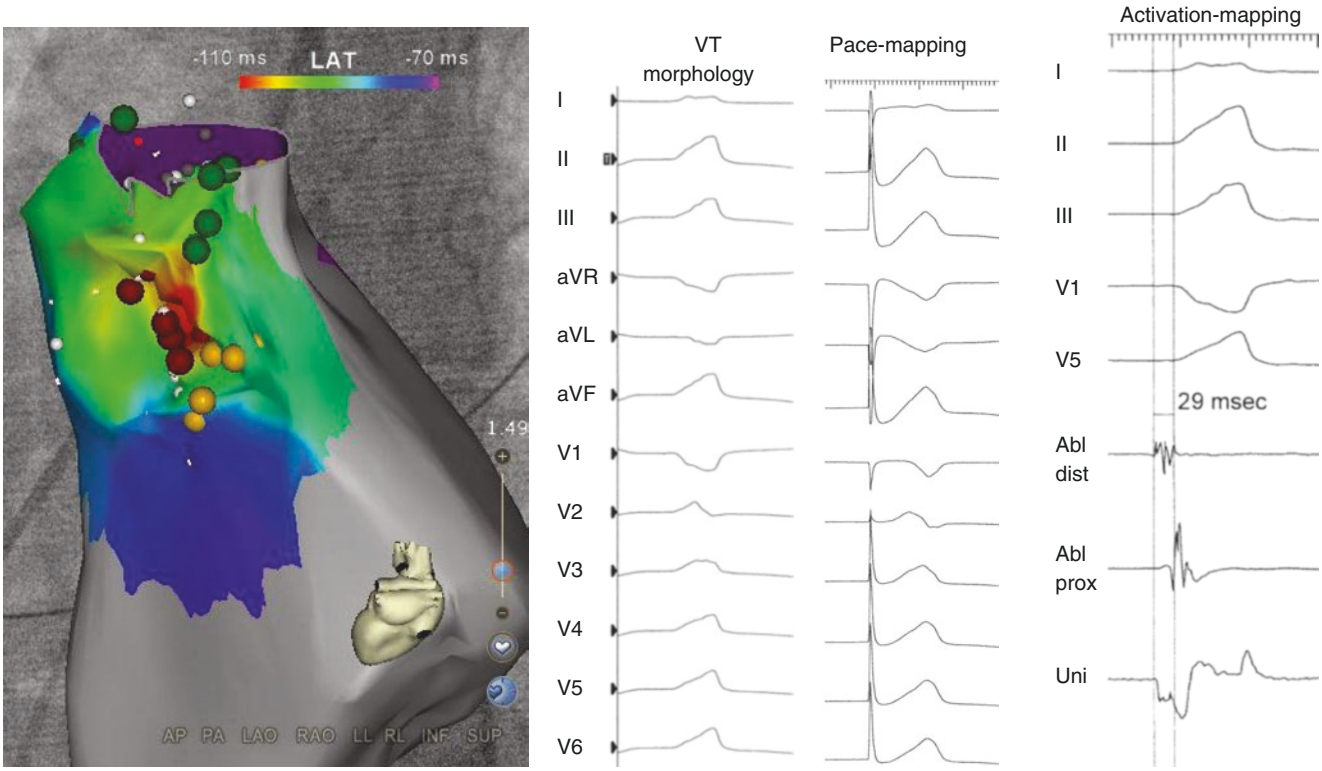


Fig. 13.1 Mapping of idiopathic VT originating from the RVOT. VT shows a left bundle branch block like morphology in V1 with inferior frontal plane axis and precordial transition at V2. Earliest ventricular activation (29 ms before the onset of the surface QRS) was recorded from the ablation catheter at the posterior RVOT. Pacing at that site shows good, however not perfect match of the paced QRS with the VT QRS. At the left is the electroanatomic map of the RV. Colors indicate activation time during VT, with *red* earliest, followed by *yellow*, *green*, *blue*, and *purple*. RF applications, marked as *red dots*, at the early site terminated and abolished VT. Abbreviations: *VT* ventricular tachycardia, *Abl* ablation catheter, *prox* proximal, *dist* distal, *Uni* unipolar recording

Sustained Monomorphic VT in Structural Heart Disease

Most sustained monomorphic VT in patients with structural heart disease is due to reentry in regions of ventricular scar. Patients are subject to recurrent episodes and an ICD is usually warranted. The major role of CA is to prevent or reduce VT recurrences. In most series, CA has been used late, after repeated episodes of VT have failed to be controlled with antiarrhythmic drugs, often after the patient has experienced repeated painful shocks. In a retrospective analysis combining 2061 patients with heart disease undergoing ablation at multiple centers, Tung et al. reported that 70% of patients were rendered from of recurrent VT at 1 year and there was a strong association between VT recurrence and death or heart transplantation that was independent of heart failure severity and cardiomyopathy type [49]. Table 13.1 summarizes selected clinical trials on CA scar related VT.

Recent guidelines recommend early consideration of CA when VT is recurrent and symptomatic [8]. Dinov et al. reported better acute and long-term success after CA of scar-related VT performed within 30 days after the first documented VT, although a mortality benefit was not observed [50]. Bunch et al. reported a lower risk of death and heart failure hospitalizations in patients treated with CA after an ICD shock compared to patients managed medically only [51]. Two randomized trials of CA after the first arrhythmia episode, around the time of ICD implantation in patients with prior myocardial infarction showed that CA reduced VT recurrences, although the number of patients was too small to assess any mortality effect [27, 28]. Use of ablation also should consider the underlying heart disease, disease severity, and risks, as discussed earlier.

Sustained Monomorphic VT due to Scar-Related Reentry

Poorly coupled surviving myofibers within scar regions creates an arrhythmia substrate characterized by slow conduction, areas of anatomically fixed or functional conduction block and unidirectional block required to support reentrant

Table 13.1 Selected clinical studies on catheter ablation in patients with structural heart disease

	Patients	Type of heart disease	Male	Age (years)	LVEF (%)	# of VTs induced at baseline	Adverse events	Non-inducible/ re-tested patients	Follow-up time (month)	VT recurrence	Overall mortality
Prospective, randomized trials											
Reddy et al. (SMASH-VT) 2008	64 in ablation group (128 total)	CAD	92%	68 ± 9	31 ± 10	n/a	5%	n/a	23 ± 6	12%	13%
Kuck et al. (VTACH) [28]	52 in ablation group (107 total)	CAD	96%	66 ± 8	34 ± 10	n/a	4%	9/11 (82%)	22 ± 9	47% VT free survival at 24 month	10%
Prospective, non-randomized trials											
Calkins et al. (Cooled RF) 2000	146	CAD/NICM	92%	65 ± 13	31 ± 13	3 ± 2	14%	63/85 (74%)	8 ± 5	45%	18%
Stevenson et al. (Thermocool VT) [26]	231	CAD/NICM	89%	68 (59–72)	25 (20–35)	3 (2–5)	17%	8/15 (53%)	6	47%	10%
Tanner et al. (Euro-VT) 2009	63	CAD	89%	64 ± 9	30 ± 13	3 ± 2	8%	17/21 (81%)	12 ± 3	49%	8%
Dinov et al. (HELP-VT) [50]	227	CAD: 164 NICM: 63	88% 83%	67 ± 10 59 ± 13	32 ± 11 34 ± 11	2.2 ± 1.3 2.1 ± 1.2	11% 11%	128/164 (78%) 42/63 (67%)	20 (16–36) 27(16–37)	43% VT free survival 23% VT free survival	8% 13%
Observational studies											
Sacher et al. (2008)	149	CAD: 212 NICM:149	88% 77%	67 ± 11 52 ± 15	28 ± 13 39 ± 6	2.2 ± 1.7	12% 6%	65% 51%	40 ± 29	n/a	35% 17%
Tokuda et al. (2012)	226	NICM	79%	52 ± 14	38 ± 17	2.7 ± 1.2	5%	124/204	53 ± 40	18%	22%

Abbreviations: *LVEF* left ventricular ejection fraction, *VT* ventricular tachycardia, *CAD* coronary artery disease, *NICM* non-ischemic cardiomyopathy

circuits [52–54]. Scars related to VT often border a valve annulus that forms a border segment for part of the circuit [55]. Reentry circuits often appear to have a protected isthmus where radiofrequency current lesions can interrupt reentry, an exit site where the isthmus meets the border of the scar region and from which the excitation wave activates the ventricles, determining the VT QRS morphology, and an entrance region where the circulating wave front returns back into the isthmus (Fig. 13.2a, b) [56].

Multiple potential paths can be contained within the scar region that can give rise to multiple VT morphologies and changes in activation remote form the circuit due to regions of functional block can alter VT QRS morphology [57, 58]. Slow, stable VTs are often due to relatively large macroreentry circuits spanning several centimeters [59].

Mapping to identify reentry circuit sites is facilitated by the use of electroanatomic mapping systems that allow for three-dimensional reconstructions of heart chambers, incor-

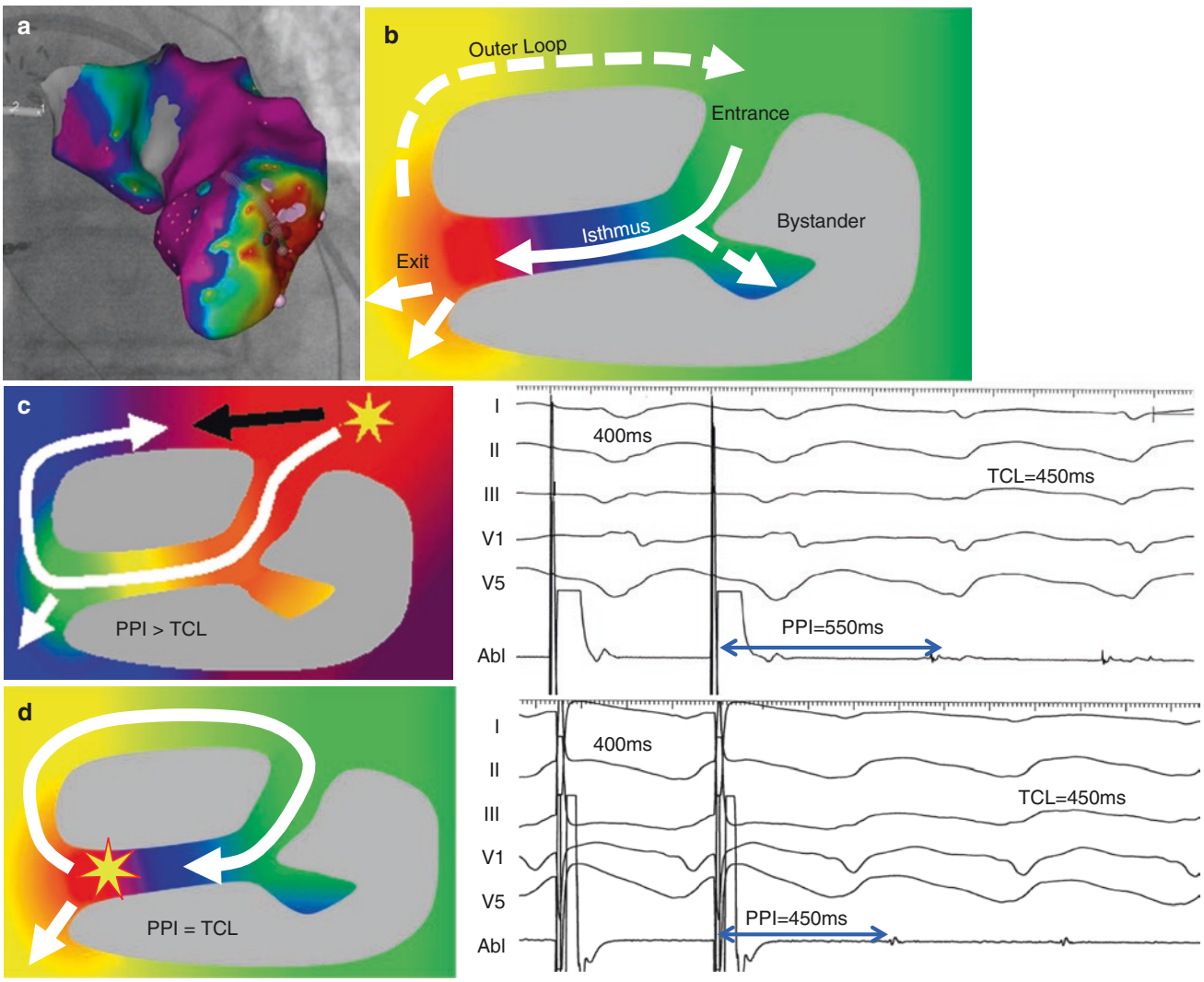


Fig. 13.2 Entrainment mapping of scar-related reentrant VT. Panel (**a**) shows an electroanatomic voltage map of a patient with prior lateral myocardial infarction. Colors indicate bipolar electrogram amplitude, with *purple* being normal (>1.5 mv) and *blue*, *green*, *yellow*, and *red*, being progressively lower amplitude. Fluoroscopic images were integrated in the mapping system. Panels (**b–d**) show a theoretic reentry circuit with areas of dense scar (*gray*) defining the circuit that has a protected isthmus, an exit site where the isthmus meets the border of the scar region, and an entrance region where the circulating wave front returns back into the isthmus. Colors indicate activation sequences with *red* being early and *purple* being late, relative to the exit site (**b**) or the pacing sites (**c** and **d**). (**c**) Pacing at a cycle length of 400 ms from a remote bystander site entrains the tachycardia and changes of the QRS morphology (overt fusion) because the paced, antidromic wavefront (*black arrow*) changes the ventricular activation sequence. The postpacing interval (PPI) is 550 ms, exceeding the VT cycle length by 100 ms. (**d**) When pacing at 400 ms cycle length from a site within the protected isthmus during a VT with a slightly different QRS morphology but the same cycle length of 450 ms, the tachycardia is entrained with no change in QRS morphology (concealed fusion) indicating that the ventricular activation sequence during pacing is the same as during VT. Capture is confirmed since the VT is accelerated to the paced cycle length. The PPI equals the VT cycle length. The short stimulus-to-QRS interval suggests a pacing site close to the exit. Abbreviations: *VT* ventricular tachycardia, *PPI* postpacing interval

porating voltage and activation-time data and provide for non-fluoroscopic localization of electrophysiologic catheters within the heart. The area of scar is recognized as having a bipolar electrogram voltage <1.5 mV (using present mapping catheters with a large tip electrode and filtered at 10–400 Hz) [58]. Correlation of voltage maps with MRI show that while, this is a reliable indicator of scar, a 2–3 mm rim of surviving endocardium can generate this voltage, and thus underlying intramural and epicardial scar is not delineated [23]. No, or very low amplitude electrograms may be recorded at areas of dense fibrosis bordering conduction channels, and these areas may be electrically unexcitable, such that pacing (10 mA at 2 ms pulse width with unipolar pacing) fails to capture [60–62]. However, electrically unexcitable scar cannot be detected reliably based on electrogram amplitude and morphology alone. Some abnormal electrograms suggesting a target site may be far-field signals from depolarization of a substantial mass of adjacent myocardium remote from the ablation [63]. Implementation of greater fidelity signal acquisition and processing methods may help differentiate far field from local electrogram sources [64].

If the patient is hemodynamically stable during induced VT, channels can be sought during VT using activation or entrainment mapping. Entrainment mapping tests the relation of a pacing site to the reentry circuit. Pacing at a rate slightly faster than the tachycardia continuously resets the reentry circuit, as confirmed by evidence of constant fusion between paced orthodromic and antidromic wave fronts. Pacing at increasing rates leads to greater activation of the ventricles by paced antidromic wavefronts, referred to as progressive fusion. Entrainment confirms reentry to be the tachycardia mechanism [65, 66]. The postpacing interval (PPI) following the last entrained beat indicates the proximity of the pacing site to the reentry circuit provided that pacing does not alter conduction in the VT circuit [56]. The last stimulated wave front propagates orthodromically through the circuit, and returns to the pacing site. Thus the time from the last pacing stimulus to the next activation at the pacing site is equal to the tachycardia cycle length plus the time it takes for conduction from the pacing site to the circuit and then back to the pacing site. For sites that are in the circuit, this conduction time from pacing site to circuit and back equals zero, and the PPI equals the tachycardia cycle length (Fig. 13.2c), whereas at pacing sites remote from the circuit, the PPI exceeds the tachycardia cycle length (Fig. 13.2d).

If VT is unstable for mapping due to hemodynamic intolerance, inability to induce VT, or frequent changes of VT morphologies, ablation targets can be sought based on mapping during sinus or paced rhythm, known as substrate mapping. Late or abnormal potentials and sites, where pacing (pace-mapping) replicates the VT QRS morphology and produces long S-QRS delays, indicate potential critical sites [67–69]. When pacing in the exit region, the QRS resembles that of VT and the interval between the stimulus and QRS onset is typically short, which is consistent with its location in the infarct border [70]. Ablation then aims to eliminate abnormal or late electrograms within scar tissue [71, 72], or "homogenize" the scar area completely with RF lesions [73]. The optimal strategy resulting in effective ablation while minimizing unnecessary RF application and procedure duration has not been established and there are complexities.

Mapping during unstable VTs can be performed with the use of hemodynamic support using percutaneous Left Ventricular Assist Devices (pLVAD). This approach is feasible, but it is not clear if it improves outcomes compared to substrate guided ablation approaches. In addition there is an increased risk of vascular complications [74–76]. A combination of mapping approaches is often used. Figure 13.3 shows the approach for VT ablation at our center.

Absence of inducible VT is a desirable procedural endpoint, but is not always attainable, and is not a reliable indicator of long-term freedom from VT. Non-inducibility has been suggested as an independent predictor long-term mortality [77, 78], however VT recurrence is observed in 29% of patients that could initially be rendered non-inducible [79]. In some cases recurrences are due to healing of the initial ablation injury.

When endocardial ablation fails, it is often due to origin of the VT deep to the endocardium, either from the epicardium or an intramural location. In patients with prior myocardial infarction, the QRS morphology of the VT is not reliable in identifying VTs that require epicardial ablation [80]. In NICM however a relatively wide QRS complex with a slow upstroke and a QS complex in leads reflecting the region of initial activation in VT suggest an epicardial VT origin [81–83]. Epicardial ablation has become an essential part in the ablation strategy especially for VT due to dilated cardiomyopathy (DCM) and ARVC. However a target for epicardial ablation cannot always be identified and coronary arteries or the left phrenic nerve can protect critical sites [18]. Image integration is potentially useful to minimize risks of phrenic nerve and coronary artery injury [84]. The phrenic nerve can successfully be displaced with an epicardially placed steerable sheath/catheter combination, or a balloon, allowing for targeting VT originating in close proximity to the phrenic nerve [85].

Transcoronary ethanol ablation or surgical cryoablation may be required to help control VT in patients in whom VT is refractory to anti-arrhythmic drugs and attempted endo- and epicardial CA, or in whom epicardial origin is suspected but access is prohibited due to adhesions from prior cardiac surgery [86]. Other methods to try to reach deep arrhythmia substrate are being assessed and developed including ablation across two catheters in a bipolar mode as well as an intramural needle electrode ablation catheter [87, 88].

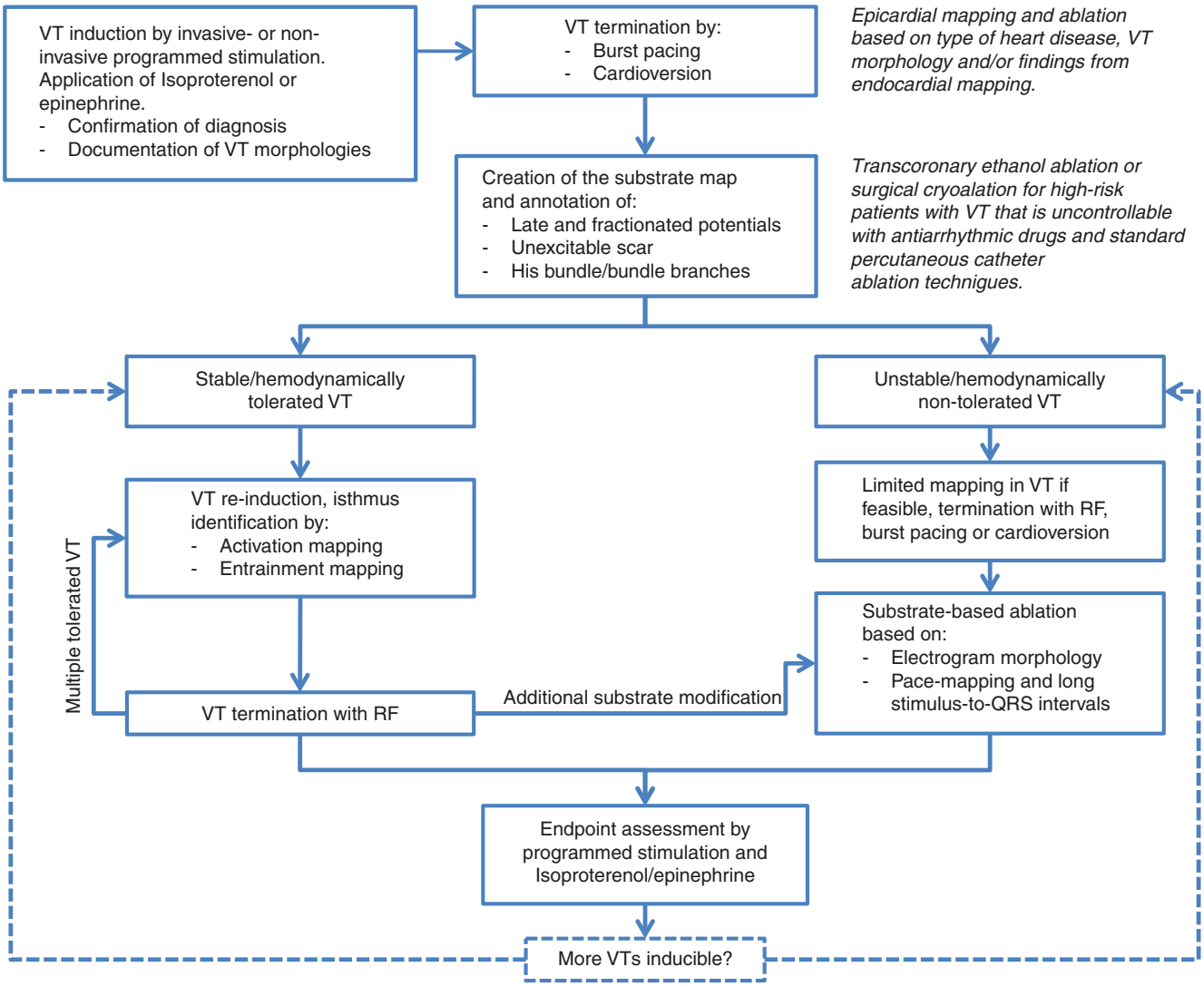


Fig. 13.3 Work flow for VT ablation procedures in patients with SHD. Abbreviations: *VT* ventricular tachycardia, *RF* radiofrequency

Ablation in Specific Disease

Ischemic Heart Disease

In post-infarct VT the location of critical arrhythmia substrate is governed by the infarct artery anatomy. VT circuits are typically located subendocardially, but can also be intramural or subepicardial in location (Fig. 13.4a) [89]. Reports of recurrence rates after post-infarct VT ablation procedures vary widely but typically range between 30 and 50% in larger studies. The frequency of VT is reduced in over two-thirds of patients.

Dilated Cardiomyopathy

Sustained monomorphic VTs in patients with DCM are most commonly the result of reentry associated with scar [90], with about 20% due to other mechanisms including bundle branch reentry (BBR) or enhanced automaticity [91]. The scar patterns observed in DCM, however, are different from those in ischemic cardiomyopathy, although the size of the scar influences the risk of ventricular arrhythmias for both [92–94]. Necropsy studies in humans have shown that only 14% of patients with DCM have grossly visible scars. Multiple patchy areas of replacement fibrosis are more common and involve the septum in the majority of cases [95]. The anatomic changes in DCM may occur as a continuous and progressive process, with increasing amounts of scarring over time [96]. Fibrosis most commonly affects the basal segments of the LV and is distributed predominantly in the mid-myocardium and epicardium (Fig. 13.4b) [97–100]. The pattern and extent of myocardial fibrosis is a predictor of both inducible and spontaneous VT independent of LV ejection fraction [101, 102]. Piers et al. showed that DCM patients exhibit two predominant scar patterns anteroseptal

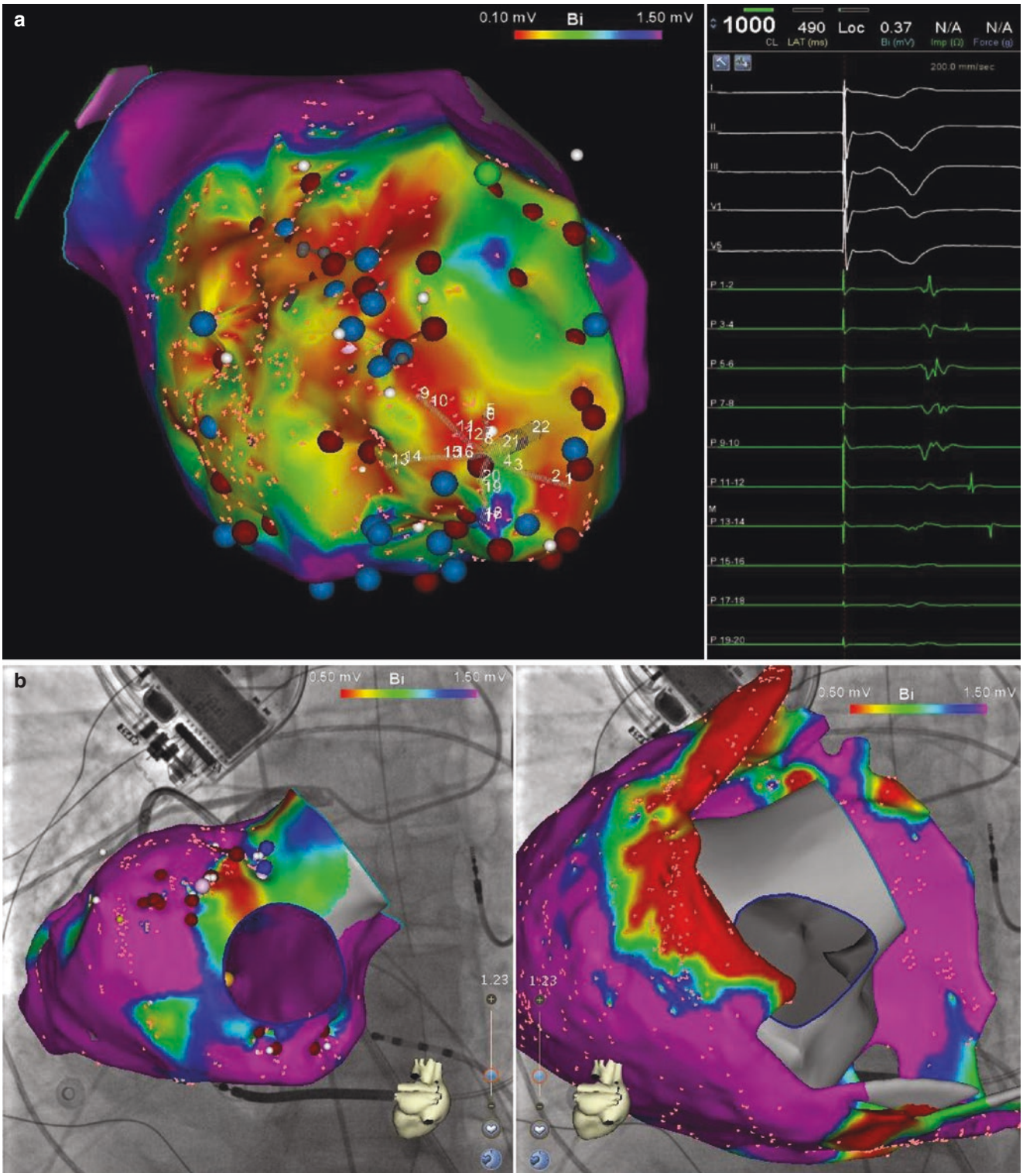


Fig. 13.4 VT substrate in patients with CAD and DCM. Shown are voltage maps with colors indicating bipolar electrogram amplitude, with *purple* being normal (>1.5 mv) and *blue*, *green*, *yellow*, and *red*, being progressively lower amplitude. Panel (**a**) shows a typical example of a patient with CAD and a large antero-septal and apical low-voltage region, consistent with infarct scar. At the right, recordings from the multispline catheter positioned in the scar show fractionated and late potentials, indicating poorly coupled myocardial tissue. Panel (**b**) shows endocardial (*left*) and epicardial (*right*) voltage maps from a patient with peri-aortic and peri-mitral scar, predominantly in the epicardium as typically seen in patients with DCM. Fluoroscopic images were integrated with the electroanatomic map. Abbreviations: *VT* ventricular tachycardia, *CAD* coronary artery disease, *DCM* dilated cardiomyopathy

and inferolateral that count for 89% of arrhythmogenic substrate in such patients. Anteroseptal scars were most effectively approached from the LV endocardium, whereas inferolateral scars frequently required an epicardial approach for ablation [99]. Patients with apical VTs compared to non-apical VTs have a worse prognosis though to be due to a larger voltage abnormality extending from the base further toward the apex [103]. Success rates of CA in non-ischemic cardiomyopathy are lower than patients with CAD although the VT burden can often be significantly reduced [104].

Arrhythmogenic RV Cardiomyopathy (ARVC)

ARVC can be a diagnostic challenge in its early phase because it may present as VT with a morphology similar to idiopathic outflow tract VT that can be triggered by adrenergic stimulation [105]. A left ventricular dominant form also occurs [106]. The arrhythmia substrate involves both the epicardium and endocardium. Ablation on both endocardial and epicardial surfaces of the heart is usually required to abolish all VTs and is followed by a significant reduction in the burden of VT [107].

Cardiac Sarcoidosis

Cardiac sarcoidosis can produce scar in any cardiac chamber. It can preferentially involve the RV and be clinically indistinguishable from ARVC. CA is usually effective in terminating VT storms and reducing VT in the majority of patients, but recurrences are common. Epicardial and endocardial ablation is often required [108].

Hypertrophic Cardiomyopathy

Sudden death in HCM is usually related to a polymorphic VT or VF. Sustained monomorphic VT is rare and usually related to reentry in a region of scar. CA has been shown to be helpful in reducing recurrences in these uncommon patients [109].

Repaired Congenital Heart Disease

Sustained VT is an important cause of late morbidity and mortality in patients with repaired congenital heart disease, most commonly tetralogy of Fallot. The disorder and its repair create anatomically defined isthmuses bordered by unexcitable tissue [110]. Transecting these isthmuses by CA is safe and highly effective in abolishing VT acutely and during follow up [111].

Purkinje-Related Monomorphic VTs

Purkinje-related monomorphic VTs can be classified into four groups: (1) verapamil-sensitive interfascicular VT in patients with structurally normal hearts (see above), (2) Purkinje fiber participation in scar-related VT, usually after infarction, (3) BBR and inter-fascicular reentry VTs, and (4) focal Purkinje VT (often beta-blocker-sensitive automatic VT) [112].

BBR-VT is usually encountered in patients with advanced heart disease and evidence of a diseased Purkinje system. The VT is often rapid (>200 bpm). The sinus rhythm ECG usually shows an intraventricular conduction abnormality, typically complete or incomplete LBBB [113, 114]. The mechanism of BBR-VT is a circuit with propagation anterogradely over the right bundle and retrogradely over the left bundle; the His bundle is adjacent to but separate from the circuit. BBR-VT therefore usually shows typical LBBB QRS morphology with a normal frontal plane axis or left axis deviation. The reverse sequence of conduction can also occur, leading to VT with a RBBB appearance. During mapping, a His bundle potential before each QRS onset and a PPI of 30 ms or less when entraining the tachycardia form the RV apex suggests the possibility of bundle branch reentry [115].

BBR-VT is often resistant to antiarrhythmic drugs; in contrast CA of the right bundle branch effectively eliminates the tachycardia [114]. Many patients have a predilection for other, scar-related VTs and in addition often have significant ventricular dysfunction, and an ICD with or without cardiac resynchronization should usually be considered according to the current guidelines [116].

Catheter Ablation for Polymorphic VT and Ventricular Fibrillation (VF)

Recurrent polymorphic VT or VF most commonly occurs during acute myocardial ischemia but can also occur early or late after a myocardial infarction as well as in the setting of idiopathic VF or an inherited arrhythmia syndrome, including long QT syndromes, short QT syndrome, Brugada syndrome and catecholaminergic polymorphic VT. Polymorphic VT and VF are often initiated by short-coupled premature beats from one or a few foci that can be targeted for ablation when they are occurring with sufficient frequency. These triggering beats often arise from the His–Purkinje system [117]. Sharp potentials consistent with Purkinje activation can then often recorded at foci in the LV or RV. Less frequently, triggers are located in the outflow tracts [118]. In selected patients, approximately 90% of patients are free from recurrences during follow-up [119–122].

Summary

CA in patients with idiopathic VTs with no SHD has a high efficacy and is reasonable to consider, even as first line therapy for symptomatic patients or those who have a high density of arrhythmia that is reducing ventricular function. In patients with SHD CA remains more challenging, but is a useful therapy for patients with incessant VT or VT that has elicited ICD shocks and should be considered when suppressive therapies, including antiarrhythmic drugs, are being considered. Advanced mappings strategies and image integration, and ablation technologies should continue to improve outcomes.

References

1. Moss AJ, Greenberg H, Case RB, Zareba W, Hall WJ, Brown MW, Daubert JP, McNitt S, Andrews ML, Elkin AD. Multicenter Automatic Defibrillator Implantation Trial IIRG. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. Circulation. 2004;110(25):3760–5. doi:10.1161/01.CIR.0000150390.04704.B7.
2. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, Talajic M, Wilber DJ, Fishbein DP, Packer DL, Mark DB, Lee KL, Bardy GH. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med. 2008;359(10):1009–17. doi:10.1056/NEJMoa071098.
3. Sood N, Ruwald AC, Solomon S, Daubert JP, McNitt S, Polonsky B, Jons C, Clyne CA, Zareba W, Moss AJ. Association between myocardial substrate, implantable cardioverter defibrillator shocks and mortality in MADIT-CRT. Eur Heart J. 2014;35(2):106–15. doi:10.1093/eurheartj/eht451.
4. Yarlagadda RK, Iwai S, Stein KM, Markowitz SM, Shah BK, Cheung JW, Tan V, Lerman BB, Mittal S. Reversal of cardiomyopathy in patients with repetitive monomorphic ventricular ectopy originating from the right ventricular outflow tract. Circulation. 2005;112(8):1092–7. doi:10.1161/CIRCULATIONAHA.105.546432.
5. Takemoto M, Yoshimura H, Ohba Y, Matsumoto Y, Yamamoto U, Mohri M, Yamamoto H, Origuchi H. Radiofrequency catheter ablation of premature ventricular complexes from right ventricular outflow tract improves left ventricular dilation and clinical status in patients without structural heart disease. J Am Coll Cardiol. 2005;45(8):1259–65. doi:10.1016/j.jacc.2004.12.073.
6. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, Thorpe K, Champagne J, Talajic M, Coutu B, Gronefeld GC, Hohnloser SH, Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients I. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. JAMA. 2006;295(2):165–71. doi:10.1001/jama.295.2.165.
7. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med. 1991;324(12):781–8. doi:10.1056/NEJM199103213241201.
8. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E, Della Bella P, Hindricks G, Jais P, Josephson ME, Kautzner J, Kay GN, Kuck KH, Lerman BB, Marchlinski F, Reddy V, Schalij MJ, Schilling R, Soejima K, Wilber D, European Heart Rhythm A, Registered Branch of the European Society of C, Heart Rhythm S, American College of C, American Heart A. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart Rhythm. 2009;6(6):886–933. doi:10.1016/j.hrthm.2009.04.030.
9. Huang SK, Bharati S, Graham AR, Lev M, Marcus FI, Odell RC. Closed chest catheter desiccation of the atrioventricular junction using radiofrequency energy—a new method of catheter ablation. J Am Coll Cardiol. 1987;9(2):349–58.
10. Haines DE. The biophysics of radiofrequency catheter ablation in the heart: the importance of temperature monitoring. Pacing Clin Electrophysiol. 1993;16(3 Pt 2):586–91.
11. d'Avila A, Houghtaling C, Gutierrez P, Vragovic O, Ruskin JN, Josephson ME, Reddy VY. Catheter ablation of ventricular epicardial tissue: a comparison of standard and cooled-tip radiofrequency energy. Circulation. 2004;109(19):2363–9. doi:10.1161/01.CIR.0000128039.87485.0B.
12. Hoffmayer KS, Gerstenfeld EP. Contact force-sensing catheters. Curr Opin Cardiol. 2015;30(1):74–80. doi:10.1097/HCO.0000000000000131.
13. Sacher F, Wright M, Derval N, Denis A, Ramoul K, Roten L, Pascale P, Bordachar P, Ritter P, Hocini M, Dos Santos P, Haissaguerre M, Jais P. Endocardial versus epicardial ventricular radiofrequency ablation: utility of in vivo contact force assessment. Circ Arrhythm Electrophysiol. 2013;6(1):144–50. doi:10.1161/CIRCEP.111.974501.
14. Choi EK, Nagashima K, Lin KY, Kumar S, Barbhaiya CR, Baldinger SH, Reichlin T, Michaud GF, Couper GS, Stevenson WG, John RM. Surgical cryoablation for ventricular tachyarrhythmia arising from the left ventricular outflow tract region. Heart Rhythm. 2015;12(6):1128–36. doi:10.1016/j.hrthm.2015.02.016.
15. Sacher F, Roberts-Thomson K, Maury P, Tedrow U, Nault I, Steven D, Hocini M, Koplan B, Leroux L, Derval N, Seiler J, Wright MJ, Epstein L, Haissaguerre M, Jais P, Stevenson WG. Epicardial ventricular tachycardia ablation a multicenter safety study. J Am Coll Cardiol. 2010;55(21):2366–72. doi:10.1016/j.jacc.2009.10.084.
16. Sosa E, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. J Cardiovasc Electrophysiol. 1996;7(6):531–6.
17. Kumar S, Bazaz R, Barbhaiya CR, Enriquez AD, Helmbold AF, Chinitz JS, Baldinger SH, Mahida S, McConville JW, Tedrow UB, John RM, Michaud GF, Stevenson WG. "Needle-in-needle" epicardial access: preliminary observations with a modified technique for facilitating epicardial interventional procedures. Heart Rhythm. 2015;12(7):1691–7. doi:10.1016/j.hrthm.2015.03.045.
18. Baldinger SH, Kumar S, Barbhaiya CR, Mahida S, Epstein LM, Michaud GF, John R, Tedrow UB, Stevenson WG. Epicardial radiofrequency ablation failure during ablation procedures for ventricular arrhythmias—reasons and implications for outcomes. Circ Arrhythm Electrophysiol. 2015;8:1422–32. doi:10.1161/CIRCEP.115.003202.
19. Nazarian S, Bluemke DA, Lardo AC, Zviman MM, Watkins SP, Dickfeld TL, Meininger GR, Roguin A, Calkins H, Tomaselli GF, Weiss RG, Berger RD, Lima JA, Halperin HR. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in

nonischemic cardiomyopathy. Circulation. 2005;112(18):2821–5. doi:10.1161/CIRCULATIONAHA.105.549659.
20. Andreu D, Ortiz-Perez JT, Boussy T, Fernandez-Armenta J, de Caralt TM, Perea RJ, Prat-Gonzalez S, Mont L, Brugada J, Berruezo A. Usefulness of contrast-enhanced cardiac magnetic resonance in identifying the ventricular arrhythmia substrate and the approach needed for ablation. Eur Heart J. 2014;35(20):1316–26. doi:10.1093/eurheartj/eht510.
21. Tian J, Ahmad G, Mesubi O, Jeudy J, Dickfeld T. Three-dimensional delayed-enhanced cardiac MRI reconstructions to guide ventricular tachycardia ablations and assess ablation lesions. Circ Arrhythm Electrophysiol. 2012;5(2):e31–5. doi:10.1161/CIRCEP.111.968636.
22. Wijnmaalen AP, van der Geest RJ, van Huls van Taxis CF, Siebelink HM, Kroft LJ, Bax JJ, Reiber JH, Schalij MJ, Zeppenfeld K. Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration. Eur Heart J. 2011;32(1):104–14. doi:10.1093/eurheartj/ehq345.
23. Dickfeld T, Tian J, Ahmad G, Jimenez A, Turgeman A, Kuk R, Peters M, Saliaris A, Saba M, Shorofsky S, Jeudy J. MRI-guided ventricular tachycardia ablation: integration of late gadolinium-enhanced 3D scar in patients with implantable cardioverter-defibrillators. Circ Arrhythm Electrophysiol. 2011;4(2):172–84. doi:10.1161/CIRCEP.110.958744.
24. Dickfeld T, Lei P, Dilsizian V, Jeudy J, Dong J, Voudouris A, Peters R, Saba M, Shekhar R, Shorofsky S. Integration of three-dimensional scar maps for ventricular tachycardia ablation with positron emission tomography-computed tomography. JACC Cardiovasc Imaging. 2008;1(1):73–82. doi:10.1016/j.jcmg.2007.10.001.
25. Palaniswamy C, Kolte D, Harikrishnan P, Khera S, Aronow WS, Mujib M, Mellana WM, Eugenio P, Lessner S, Ferrick A, Fonarow GC, Ahmed A, Cooper HA, Frishman WH, Panza JA, Iwai S. Catheter ablation of postinfarction ventricular tachycardia: ten-year trends in utilization, in-hospital complications, and in-hospital mortality in the United States. Heart Rhythm. 2014;11(11):2056–63. doi:10.1016/j.hrthm.2014.07.012.
26. Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, Gonzalez MD, Worley SJ, Daoud EG, Hwang C, Schuger C, Bump TE, Jazayeri M, Tomassoni GF, Kopelman HA, Soejima K, Nakagawa H, Multicenter Thermocool VTATI. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. Circulation. 2008;118(25):2773–82. doi:10.1161/CIRCULATIONAHA.108.788604.
27. Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K, Kralovec S, Sediva L, Ruskin JN, Josephson ME. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med. 2007;357(26):2657–65. doi:10.1056/NEJMoa065457.
28. Kuck KH, Schaumann A, Eckardt L, Willems S, Ventura R, Delacretaz E, Pitschner HF, Kautzner J, Schumacher B, Hansen PS, VTACH Study Group. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. Lancet. 2010;375(9708):31–40. doi:10.1016/S0140-6736(09)61755-4.
29. Vestal M, Wen MS, Yeh SJ, Wang CC, Lin FC, Wu D. Electrocardiographic predictors of failure and recurrence in patients with idiopathic right ventricular outflow tract tachycardia and ectopy who underwent radiofrequency catheter ablation. J Electrocardiol. 2003;36(4):327–32.
30. Kim RJ, Iwai S, Markowitz SM, Shah BK, Stein KM, Lerman BB. Clinical and electrophysiological spectrum of idiopathic ventricular outflow tract arrhythmias. J Am Coll Cardiol. 2007;49(20):2035–43. doi:10.1016/j.jacc.2007.01.085.
31. Lerman BB, Belardinelli L, West GA, Berne RM, DiMarco JP. Adenosine-sensitive ventricular tachycardia: evidence suggesting cyclic AMP-mediated triggered activity. Circulation. 1986;74(2):270–80.
32. Katra RP, Laurita KR. Cellular mechanism of calcium-mediated triggered activity in the heart. Circ Res. 2005;96(5):535–42. doi:10.1161/01.RES.0000159387.00749.3c.
33. Kamakura S, Shimizu W, Matsuo K, Taguchi A, Suyama K, Kurita T, Aihara N, Ohe T, Shimomura K. Localization of optimal ablation site of idiopathic ventricular tachycardia from right and left ventricular outflow tract by body surface ECG. Circulation. 1998;98(15):1525–33.
34. Sekiguchi Y, Aonuma K, Takahashi A, Yamauchi Y, Hachiya H, Yokoyama Y, Iesaka Y, Isobe M. Electrocardiographic and electrophysiologic characteristics of ventricular tachycardia originating within the pulmonary artery. J Am Coll Cardiol. 2005;45(6):887–95. doi:10.1016/j.jacc.2004.10.071.
35. Liu CF, Cheung JW, Thomas G, Ip JE, Markowitz SM, Lerman BB. Ubiquitous myocardial extensions into the pulmonary artery demonstrated by integrated intracardiac echocardiography and electroanatomic mapping: changing the paradigm of idiopathic right ventricular outflow tract arrhythmias. Circ Arrhythm Electrophysiol. 2014;7(4):691–700. doi:10.1161/CIRCEP.113.001347.
36. Bogun F, Taj M, Ting M, Kim HM, Reich S, Good E, Jongnarangsin K, Chugh A, Pelosi F, Oral H, Morady F. Spatial resolution of pace mapping of idiopathic ventricular tachycardia/ectopy originating in the right ventricular outflow tract. Heart Rhythm. 2008;5(3):339–44. doi:10.1016/j.hrthm.2007.11.011.
37. Yamada T, McElderry HT, Doppalapudi H, Murakami Y, Yoshida Y, Yoshida N, Okada T, Tsuboi N, Inden Y, Murohara T, Epstein AE, Plumb VJ, Singh SP, Kay GN. Idiopathic ventricular arrhythmias originating from the aortic root prevalence, electrocardiographic and electrophysiologic characteristics, and results of radiofrequency catheter ablation. J Am Coll Cardiol. 2008;52(2):139–47. doi:10.1016/j.jacc.2008.03.040.
38. Park KM, Kim YH, Marchlinski FE. Using the surface electrocardiogram to localize the origin of idiopathic ventricular tachycardia. Pacing Clin Electrophysiol. 2012;35(12):1516–27. doi:10.1111/j.1540-8159.2012.03488.x.
39. Betensky BP, Park RE, Marchlinski FE, Hutchinson MD, Garcia FC, Dixit S, Callans DJ, Cooper JM, Bala R, Lin D, Riley MP, Gerstenfeld EP. The V(2) transition ratio: a new electrocardiographic criterion for distinguishing left from right ventricular outflow tract tachycardia origin. J Am Coll Cardiol. 2011;57(22):2255–62. doi:10.1016/j.jacc.2011.01.035.
40. Ouyang F, Fotuhi P, Ho SY, Hebe J, Volkmer M, Goya M, Burns M, Antz M, Ernst S, Cappato R, Kuck KH. Repetitive monomorphic ventricular tachycardia originating from the aortic sinus cusp: electrocardiographic characterization for guiding catheter ablation. J Am Coll Cardiol. 2002;39(3):500–8.
41. Lin D, Ilkhanoff L, Gerstenfeld E, Dixit S, Beldner S, Bala R, Garcia F, Callans D, Marchlinski FE. Twelve-lead electrocardiographic characteristics of the aortic cusp region guided by intracardiac echocardiography and electroanatomic mapping. Heart Rhythm. 2008;5(5):663–9. doi:10.1016/j.hrthm.2008.02.009.
42. Yamada T, Yoshida N, Murakami Y, Okada T, Muto M, Murohara T, McElderry HT, Kay GN. Electrocardiographic characteristics of ventricular arrhythmias originating from the junction of the left and right coronary sinuses of Valsalva in the aorta: the activation pattern as a rationale for the electrocardiographic characteristics. Heart Rhythm. 2008;5(2):184–92. doi:10.1016/j.hrthm.2007.09.029.

43. Yoshida N, Yamada T, McElderry HT, Inden Y, Shimano M, Murohara T, Kumar V, Doppalapudi H, Plumb VJ, Kay GN. A novel electrocardiographic criterion for differentiating a left from right ventricular outflow tract tachycardia origin: the V2S/V3R index. J Cardiovasc Electrophysiol. 2014;25(7):747–53. doi:10.1111/jce.12392.
44. Baman TS, Ilg KJ, Gupta SK, Good E, Chugh A, Jongnarangsin K, Pelosi F Jr, Ebinger M, Crawford T, Oral H, Morady F, Bogun F. Mapping and ablation of epicardial idiopathic ventricular arrhythmias from within the coronary venous system. Circ Arrhythm Electrophysiol. 2010;3(3):274–9. doi:10.1161/CIRCEP.109.910802.
45. Yamada T, Platonov M, McElderry HT, Kay GN. Left ventricular outflow tract tachycardia with preferential conduction and multiple exits. Circ Arrhythm Electrophysiol. 2008;1(2):140–2. doi:10.1161/CIRCEP.108.778563.
46. Kawamura M, Gerstenfeld EP, Vedantham V, Rodrigues DM, Burkhardt JD, Kobayashi Y, Hsia HH, Marcus GM, Marchlinski FE, Scheinman MM, Badhwar N. Idiopathic ventricular arrhythmia originating from the cardiac crux or inferior septum: epicardial idiopathic ventricular arrhythmia. Circ Arrhythm Electrophysiol. 2014;7(6):1152–8. doi:10.1161/CIRCEP.114.001704.
47. Belhassen B, Rotmensch HH, Laniado S. Response of recurrent sustained ventricular tachycardia to verapamil. Br Heart J. 1981;46(6):679–82.
48. Zipes DP, Foster PR, Troup PJ, Pedersen DH. Atrial induction of ventricular tachycardia: reentry versus triggered automaticity. Am J Cardiol. 1979;44(1):1–8.
49. Tung R, Vaseghi M, Frankel DS, Vergara P, DiBiase L, Nagashima K, Yu R, Vangala S, Tseng CH, Choi EK, Khurshid S, Patel M, Mathuria N, Nakahara S, Tzou WS, Sauer WH, Vakil K, Tedrow U, Burkhardt D, Tholakanahalli V, Saliaris A, Dickfeld T, Weiss JP, Bunch TJ, Reddy M, Kanmanthareddy A, Callans D, Lakkireddy D, Natale A, Marchlinski F, Stevenson WG, Della Bella P, Shivkumar K. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: An International VT Ablation Center Collaborative Group study. Heart Rhythm. 2015;12:1997–2007. doi:10.1016/j.hrthm.2015.05.036.
50. Dinov B, Arya A, Bertagnolli L, Schirripa V, Schoene K, Sommer P, Bollmann A, Rolf S, Hindricks G. Early referral for ablation of scar-related ventricular tachycardia is associated with improved acute and long-term outcomes: results from the Heart Center of Leipzig ventricular tachycardia registry. Circ Arrhythm Electrophysiol. 2014;7(6):1144–51. doi:10.1161/CIRCEP.114.001953.
51. Bunch TJ, Weiss JP, Crandall BG, Day JD, May HT, Bair TL, Osborn JS, Mallender C, Fischer A, Brunner KJ, Mahapatra S. Patients treated with catheter ablation for ventricular tachycardia after an ICD shock have lower long-term rates of death and heart failure hospitalization than do patients treated with medical management only. Heart Rhythm. 2014;11(4):533–40. doi:10.1016/j.hrthm.2013.12.014.
52. de Bakker JM, van Capelle FJ, Janse MJ, van Hemel NM, Hauer RN, Defauw JJ, Vermeulen FE, Bakker de Wekker PF. Macroreentry in the infarcted human heart: the mechanism of ventricular tachycardias with a "focal" activation pattern. J Am Coll Cardiol. 1991;18(4):1005–14.
53. de Bakker JM, van Capelle FJ, Janse MJ, Wilde AA, Coronel R, Becker AE, Dingemans KP, van Hemel NM, Hauer RN. Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation. Circulation. 1988;77(3):589–606.
54. de Bakker JM, van Capelle FJ, Janse MJ, Tasseron S, Vermeulen JT, de Jonge N, Lahpor JR. Slow conduction in the infarcted human heart. 'Zigzag' course of activation. Circulation. 1993;88(3):915–26.
55. Marchlinski FE. Perivalvular fibrosis and monomorphic ventricular tachycardia: toward a unifying hypothesis in nonischemic cardiomyopathy. Circulation. 2007;116(18):1998–2001. doi:10.1161/CIRCULATIONAHA.107.731125.
56. Stevenson WG, Khan H, Sager P, Saxon LA, Middlekauff HR, Natterson PD, Wiener I. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. Circulation. 1993;88(4 Pt 1):1647–70.
57. Soejima K, Suzuki M, Maisel WH, Brunckhorst CB, Delacretaz E, Blier L, Tung S, Khan H, Stevenson WG. Catheter ablation in patients with multiple and unstable ventricular tachycardias after myocardial infarction: short ablation lines guided by reentry circuit isthmuses and sinus rhythm mapping. Circulation. 2001;104(6):664–9.
58. Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. Circulation. 2000;101(11):1288–96.
59. de Chillou C, Lacroix D, Klug D, Magnin-Poull I, Marquie C, Messier M, Andronache M, Kouakam C, Sadoul N, Chen J, Aliot E, Kacet S. Isthmus characteristics of reentrant ventricular tachycardia after myocardial infarction. Circulation. 2002;105(6):726–31.
60. Soejima K, Stevenson WG, Maisel WH, Sapp JL, Epstein LM. Electrically unexcitable scar mapping based on pacing threshold for identification of the reentry circuit isthmus: feasibility for guiding ventricular tachycardia ablation. Circulation. 2002;106(13):1678–83.
61. Arenal A, del Castillo S, Gonzalez-Torrecilla E, Atienza F, Ortiz M, Jimenez J, Puchol A, Garcia J, Almendral J. Tachycardia-related channel in the scar tissue in patients with sustained monomorphic ventricular tachycardias: influence of the voltage scar definition. Circulation. 2004;110(17):2568–74. doi:10.1161/01.CIR.0000145544.35565.47.
62. Hsia HH, Lin D, Sauer WH, Callans DJ, Marchlinski FE. Anatomic characterization of endocardial substrate for hemodynamically stable reentrant ventricular tachycardia: identification of endocardial conducting channels. Heart Rhythm. 2006;3(5):503–12. doi:10.1016/j.hrthm.2006.01.015.
63. Baldinger SH, Nagashima K, Kumar S, Barbhaiya CR, Choi EK, Epstein LM, Michaud GF, John R, Tedrow UB, Stevenson WG. Electrogram analysis and pacing are complimentary for recognition of abnormal conduction and far—field potentials during substrate mapping of infarct—related ventricular tachycardia. Circ Arrhythm Electrophysiol. 2017;10 doi:10.1161/CIRCEP.114.002714.
64. Das M, Downar E, Masse S, Harris L, Cameron D, Nair K, Chauhan VS, Spears DA, Ha AC, Jackson N, Nanthakumar K. Temporal-component analysis of diastolic electrograms in ventricular tachycardia differentiates nonvulnerable regions of the circuit. Heart Rhythm. 2015;12(8):1737–44. doi:10.1016/j.hrthm.2015.05.004.
65. Stevenson WG, Friedman PL, Sager PT, Saxon LA, Kocovic D, Harada T, Wiener I, Khan H. Exploring postinfarction reentrant ventricular tachycardia with entrainment mapping. J Am Coll Cardiol. 1997;29(6):1180–9.
66. Morady F, Kadish A, Rosenheck S, Calkins H, Kou WH, De Buitleir M, Sousa J. Concealed entrainment as a guide for catheter ablation of ventricular tachycardia in patients with prior myocardial infarction. J Am Coll Cardiol. 1991;17(3):678–89.
67. Kocovic DZ, Harada T, Friedman PL, Stevenson WG. Characteristics of electrograms recorded at reentry circuit sites and bystanders during ventricular tachycardia after myocardial infarction. J Am Coll Cardiol. 1999;34(2):381–8.
68. Bogun F, Bahu M, Knight BP, Weiss R, Goyal R, Daoud E, Man KC, Strickberger SA, Morady F. Response to pacing at sites of isolated diastolic potentials during ventricular tachycardia in

patients with previous myocardial infarction. J Am Coll Cardiol. 1997;30(2):505–13.
69. Harada T, Stevenson WG, Kocovic DZ, Friedman PL. Catheter ablation of ventricular tachycardia after myocardial infarction: relation of endocardial sinus rhythm late potentials to the reentry circuit. J Am Coll Cardiol. 1997;30(4):1015–23.
70. Brunckhorst CB, Delacretaz E, Soejima K, Maisel WH, Friedman PL, Stevenson WG. Identification of the ventricular tachycardia isthmus after infarction by pace mapping. Circulation. 2004;110(6):652–9. doi:10.1161/01.CIR.0000138107.11518.AF.
71. Jais P, Maury P, Khairy P, Sacher F, Nault I, Komatsu Y, Hocini M, Forclaz A, Jadidi AS, Weerasooryia R, Shah A, Derval N, Cochet H, Knecht S, Miyazaki S, Linton N, Rivard L, Wright M, Wilton SB, Scherr D, Pascale P, Roten L, Pederson M, Bordachar P, Laurent F, Kim SJ, Ritter P, Clementy J, Haissaguerre M. Elimination of local abnormal ventricular activities: a new end point for substrate modification in patients with scar-related ventricular tachycardia. Circulation. 2012;125(18):2184–96. doi:10.1161/CIRCULATIONAHA.111.043216.
72. Vergara P, Trevisi N, Ricco A, Petracca F, Baratto F, Cireddu M, Bisceglia C, Maccabelli G, Della Bella P. Late potentials abolition as an additional technique for reduction of arrhythmia recurrence in scar related ventricular tachycardia ablation. J Cardiovasc Electrophysiol. 2012;23(6):621–7. doi:10.1111/j.1540-8167.2011.02246.x.
73. Di Biase L, Santangeli P, Burkhardt DJ, Bai R, Mohanty P, Carbucicchio C, Dello Russo A, Casella M, Mohanty S, Pump A, Hongo R, Beheiry S, Pelargonio G, Santarelli P, Zucchetti M, Horton R, Sanchez JE, Elayi CS, Lakkireddy D, Tondo C, Natale A. Endo-epicardial homogenization of the scar versus limited substrate ablation for the treatment of electrical storms in patients with ischemic cardiomyopathy. J Am Coll Cardiol. 2012;60(2):132–41. doi:10.1016/j.jacc.2012.03.044.
74. Aryana A, Gearoid O'Neill P, Gregory D, Scotti D, Bailey S, Brunton S, Chang M, d'Avila A. Procedural and clinical outcomes after catheter ablation of unstable ventricular tachycardia supported by a percutaneous left ventricular assist device. Heart Rhythm. 2014;11(7):1122–30. doi:10.1016/j.hrthm.2014.04.018.
75. Miller MA, Dukkipati SR, Mittnacht AJ, Chinitz JS, Belliveau L, Koruth JS, Gomes JA, d'Avila A, Reddy VY. Activation and entrainment mapping of hemodynamically unstable ventricular tachycardia using a percutaneous left ventricular assist device. J Am Coll Cardiol. 2011;58(13):1363–71. doi:10.1016/j.jacc.2011.06.022.
76. Reddy YM, Chinitz L, Mansour M, Bunch TJ, Mahapatra S, Swarup V, Di Biase L, Bommana S, Atkins D, Tung R, Shivkumar K, Burkhardt JD, Ruskin J, Natale A, Lakkireddy D. Percutaneous left ventricular assist devices in ventricular tachycardia ablation: multicenter experience. Circ Arrhythm Electrophysiol. 2014;7(2):244–50. doi:10.1161/CIRCEP.113.000548.
77. Yokokawa M, Kim HM, Baser K, Stevenson W, Nagashima K, Della Bella P, Vergara P, Hindricks G, Arya A, Zeppenfeld K, de Riva Silva M, Daoud EG, Kumar S, Kuck KH, Tilz R, Mathew S, Ghanbari H, Latchamsetty R, Morady F, Bogun FM. Predictive value of programmed ventricular stimulation after catheter ablation of post-infarction ventricular tachycardia. J Am Coll Cardiol. 2015;65(18):1954–9. doi:10.1016/j.jacc.2015.02.058.
78. Dinov B, Arya A, Schratter A, Schirripa V, Fiedler L, Sommer P, Bollmann A, Rolf S, Piorkowski C, Hindricks G. Catheter ablation of ventricular tachycardia and mortality in patients with nonischemic dilated cardiomyopathy: can noninducibility after ablation be a predictor for reduced mortality? Circ Arrhythm Electrophysiol. 2015;8(3):598–605. doi:10.1161/CIRCEP.114.002295.
79. Della Bella P, Baratto F, Tsiachris D, Trevisi N, Vergara P, Bisceglia C, Petracca F, Carbucicchio C, Benussi S, Maisano F, Alfieri O, Pappalardo F, Zangrillo A, Maccabelli G. Management of ventricular tachycardia in the setting of a dedicated unit for the treatment of complex ventricular arrhythmias: long-term outcome after ablation. Circulation. 2013;127(13):1359–68. doi:10.1161/CIRCULATIONAHA.112.000872.
80. Martinek M, Stevenson WG, Inada K, Tokuda M, Tedrow UB. QRS characteristics fail to reliably identify ventricular tachycardias that require epicardial ablation in ischemic heart disease. J Cardiovasc Electrophysiol. 2012;23(2):188–93. doi:10.1111/j.1540-8167.2011.02179.x.
81. Berruezo A, Mont L, Nava S, Chueca E, Bartholomay E, Brugada J. Electrocardiographic recognition of the epicardial origin of ventricular tachycardias. Circulation. 2004;109(15):1842–7. doi:10.1161/01.CIR.0000125525.04081.4B.
82. Valles E, Bazan V, Marchlinski FE. ECG criteria to identify epicardial ventricular tachycardia in nonischemic cardiomyopathy. Circ Arrhythm Electrophysiol. 2010;3(1):63–71. doi:10.1161/CIRCEP.109.859942.
83. Bazan V, Gerstenfeld EP, Garcia FC, Bala R, Rivas N, Dixit S, Zado E, Callans DJ, Marchlinski FE. Site-specific twelve-lead ECG features to identify an epicardial origin for left ventricular tachycardia in the absence of myocardial infarction. Heart Rhythm. 2007;4(11):1403–10. doi:10.1016/j.hrthm.2007.07.004.
84. Yamashita S, Sacher F, Mahida S, Berte B, Lim HS, Komatsu Y, Amraoui S, Denis A, Derval N, Laurent F, Montaudon M, Hocini M, Haissaguerre M, Jais P, Cochet H. Role of high-resolution image integration to visualize left phrenic nerve and coronary arteries during epicardial ventricular tachycardia ablation. Circ Arrhythm Electrophysiol. 2015;8(2):371–80. doi:10.1161/CIRCEP.114.002420.
85. Kumar S, Barbhaiya CR, Baldinger SH, Koplan BA, Maytin M, Epstein LM, John RM, Michaud GF, Tedrow UB, Stevenson WG. Epicardial phrenic nerve displacement during catheter ablation of atrial and ventricular arrhythmias: procedural experience and outcomes. Circ Arrhythm Electrophysiol. 2015;8(4):896–904. doi:10.1161/CIRCEP.115.002818.
86. Kumar S, Barbhaiya CR, Sobieszczyk P, Eisenhauer AC, Couper GS, Nagashima K, Mahida S, Baldinger SH, Choi EK, Epstein LM, Koplan BA, John RM, Michaud GF, Stevenson WG, Tedrow UB. Role of alternative interventional procedures when endo- and epicardial catheter ablation attempts for ventricular arrhythmias fail. Circ Arrhythm Electrophysiol. 2015;8(3):606–15. doi:10.1161/CIRCEP.114.002522.
87. Sapp JL, Beeckler C, Pike R, Parkash R, Gray CJ, Zeppenfeld K, Kuriachan V, Stevenson WG. Initial human feasibility of infusion needle catheter ablation for refractory ventricular tachycardia. Circulation. 2013;128(21):2289–95. doi:10.1161/CIRCULATIONAHA.113.003423.
88. Koruth JS, Dukkipati S, Miller MA, Neuzil P, d'Avila A, Reddy VY. Bipolar irrigated radiofrequency ablation: a therapeutic option for refractory intramural atrial and ventricular tachycardia circuits. Heart Rhythm. 2012;9(12):1932–41. doi:10.1016/j.hrthm.2012.08.001.
89. Kaltenbrunner W, Cardinal R, Dubuc M, Shenasa M, Nadeau R, Tremblay G, Vermeulen M, Savard P, Page PL. Epicardial and endocardial mapping of ventricular tachycardia in patients with myocardial infarction. Is the origin of the tachycardia always subendocardially localized? Circulation. 1991;84(3):1058–71.
90. Soejima K, Stevenson WG, Sapp JL, Selwyn AP, Couper G, Epstein LM. Endocardial and epicardial radiofrequency ablation of ventricular tachycardia associated with dilated cardiomyopathy: the importance of low-voltage scars. J Am Coll Cardiol. 2004;43(10):1834–42. doi:10.1016/j.jacc.2004.01.029.
91. Stevenson WG, Soejima K. Catheter ablation for ventricular tachycardia. Circulation. 2007;115(21):2750–60. doi:10.1161/CIRCULATIONAHA.106.655720.

92. Fernandez-Armenta J, Berruezo A, Mont L, Sitges M, Andreu D, Silva E, Ortiz-Perez JT, Tolosana JM, de Caralt TM, Perea RJ, Calvo N, Trucco E, Borras R, Matas M, Brugada J. Use of myocardial scar characterization to predict ventricular arrhythmia in cardiac resynchronization therapy. Europace. 2012;14(11):1578–86. doi:10.1093/europace/eus104.
93. McCrohon JA, Moon JC, Prasad SK, McKenna WJ, Lorenz CH, Coats AJ, Pennell DJ. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. Circulation. 2003;108(1):54–9. doi:10.1161/01.CIR.0000078641.19365.4C.
94. Hsia HH, Callans DJ, Marchlinski FE. Characterization of endocardial electrophysiological substrate in patients with nonischemic cardiomyopathy and monomorphic ventricular tachycardia. Circulation. 2003;108(6):704–10. doi:10.1161/01.CIR.0000083725.72693.EA.
95. Roberts WC, Siegel RJ, McManus BM. Idiopathic dilated cardiomyopathy: analysis of 152 necropsy patients. Am J Cardiol. 1987;60(16):1340–55.
96. Liuba I, Frankel DS, Riley MP, Hutchinson MD, Lin D, Garcia FC, Callans DJ, Supple GE, Dixit S, Bala R, Squara F, Zado ES, Marchlinski FE. Scar progression in patients with nonischemic cardiomyopathy and ventricular arrhythmias: scar progression in NICM. Heart Rhythm. 2014;11:755–62. doi:10.1016/j.hrthm.2014.02.012.
97. Bogun FM, Desjardins B, Good E, Gupta S, Crawford T, Oral H, Ebinger M, Pelosi F, Chugh A, Jongnarangsin K, Morady F. Delayed-enhanced magnetic resonance imaging in nonischemic cardiomyopathy: utility for identifying the ventricular arrhythmia substrate. J Am Coll Cardiol. 2009;53(13):1138–45. doi:10.1016/j.jacc.2008.11.052.
98. Masci PG, Barison A, Aquaro GD, Pingitore A, Mariotti R, Balbarini A, Passino C, Lombardi M, Emdin M. Myocardial delayed enhancement in paucisymptomatic nonischemic dilated cardiomyopathy. Int J Cardiol. 2012;157(1):43–7. doi:10.1016/j.ijcard.2010.11.005.
99. Piers SR, Tao Q, van Huls van Taxis CF, Schalij MJ, van der Geest RJ, Zeppenfeld K. Contrast-enhanced MRI-derived scar patterns and associated ventricular tachycardias in nonischemic cardiomyopathy: implications for the ablation strategy. Circ Arrhythm Electrophysiol. 2013;6(5):875–83. doi:10.1161/CIRCEP.113.000537.
100. Bluemke DA. MRI of nonischemic cardiomyopathy. Am J Roentgenol. 2010;195(4):935–40. doi:10.2214/AJR.10.4222.
101. Iles L, Pfluger H, Lefkovits L, Butler MJ, Kistler PM, Kaye DM, Taylor AJ. Myocardial fibrosis predicts appropriate device therapy in patients with implantable cardioverter-defibrillators for primary prevention of sudden cardiac death. J Am Coll Cardiol. 2011;57(7):821–8. doi:10.1016/j.jacc.2010.06.062.
102. KC W, Weiss RG, Thiemann DR, Kitagawa K, Schmidt A, Dalal D, Lai S, Bluemke DA, Gerstenblith G, Marban E, Tomaselli GF, Lima JA. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. J Am Coll Cardiol. 2008;51(25):2414–21. doi:10.1016/j.jacc.2008.03.018.
103. Frankel DS, Tschabrunn CM, Cooper JM, Dixit S, Gerstenfeld EP, Riley MP, Callans DJ, Marchlinski FE. Apical ventricular tachycardia morphology in left ventricular nonischemic cardiomyopathy predicts poor transplant-free survival. Heart Rhythm. 2013;10(5):621–6. doi:10.1016/j.hrthm.2012.12.029.
104. Dinov B, Fiedler L, Schonbauer R, Bollmann A, Rolf S, Piorkowski C, Hindricks G, Arya A. Outcomes in catheter ablation of ventricular tachycardia in dilated nonischemic cardiomyopathy compared with ischemic cardiomyopathy: results from the Prospective Heart Centre of Leipzig VT (HELP-VT) Study. Circulation. 2014;129(7):728–36. doi:10.1161/CIRCULATIONAHA.113.003063.
105. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation. 2010;121(13):1533–41. doi:10.1161/CIRCULATIONAHA.108.840827.
106. Sen-Chowdhry S, Syrris P, Prasad SK, Hughes SE, Merrifield R, Ward D, Pennell DJ, McKenna WJ. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. J Am Coll Cardiol. 2008;52(25):2175–87. doi:10.1016/j.jacc.2008.09.019.
107. Philips B, Madhavan S, James C, Tichnell C, Murray B, Dalal D, Bhonsale A, Nazarian S, Judge DP, Russell SD, Abraham T, Calkins H, Tandri H. Outcomes of catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Arrhythm Electrophysiol. 2012;5(3):499–505. doi:10.1161/CIRCEP.111.968677.
108. Kumar S, Barbhaiya C, Nagashima K, Choi EK, Epstein LM, John RM, Maytin M, Albert CM, Miller AL, Koplan BA, Michaud GF, Tedrow UB, Stevenson WG. Ventricular tachycardia in cardiac sarcoidosis: characterization of ventricular substrate and outcomes of catheter ablation. Circ Arrhythm Electrophysiol. 2015;8(1):87–93. doi:10.1161/CIRCEP.114.002145.
109. Dukkipati SR, d'Avila A, Soejima K, Bala R, Inada K, Singh S, Stevenson WG, Marchlinski FE, Reddy VY. Long-term outcomes of combined epicardial and endocardial ablation of monomorphic ventricular tachycardia related to hypertrophic cardiomyopathy. Circ Arrhythm Electrophysiol. 2011;4(2):185–94. doi:10.1161/CIRCEP.110.957290.
110. Zeppenfeld K, Schalij MJ, Bartelings MM, Tedrow UB, Koplan BA, Soejima K, Stevenson WG. Catheter ablation of ventricular tachycardia after repair of congenital heart disease: electroanatomic identification of the critical right ventricular isthmus. Circulation. 2007;116(20):2241–52. doi:10.1161/CIRCULATIONAHA.107.723551.
111. Kapel GF, Reichlin T, Wijnmaalen AP, Piers SR, Holman ER, Tedrow UB, Schalij MJ, Stevenson WG, Zeppenfeld K. Re-entry using anatomically determined isthmuses: a curable ventricular tachycardia in repaired congenital heart disease. Circ Arrhythm Electrophysiol. 2015;8(1):102–9. doi:10.1161/CIRCEP.114.001929.
112. Nogami A. Purkinje-related arrhythmias part I: monomorphic ventricular tachycardias. Pacing Clin Electrophysiol. 2011;34(5):624–50. doi:10.1111/j.1540-8159.2011.03044.x.
113. Blanck Z, Dhala A, Deshpande S, Sra J, Jazayeri M, Akhtar M. Bundle branch reentrant ventricular tachycardia: cumulative experience in 48 patients. J Cardiovasc Electrophysiol. 1993;4(3):253–62.
114. Lopera G, Stevenson WG, Soejima K, Maisel WH, Koplan B, Sapp JL, Satti SD, Epstein LM. Identification and ablation of three types of ventricular tachycardia involving the his-purkinje system in patients with heart disease. J Cardiovasc Electrophysiol. 2004;15(1):52–8. doi:10.1046/j.1540-8167.2004.03189.x.
115. Merino JL, Peinado R, Fernandez-Lozano I, Lopez-Gil M, Arribas F, Ramirez LJ, Echeverria IJ, Sobrino JA. Bundle-branch reentry and the postpacing interval after entrainment by right ventricular apex stimulation: a new approach to elucidate the mechanism of wide-QRS-complex tachycardia with atrioventricular dissociation. Circulation. 2001;103(8):1102–8.
116. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L,

Keren A. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29(2):270–6. doi:10.1093/eurheartj/ehm342.

117. Haissaguerre M, Shah DC, Jais P, Shoda M, Kautzner J, Arentz T, Kalushe D, Kadish A, Griffith M, Gaita F, Yamane T, Garrigue S, Hocini M, Clementy J. Role of Purkinje conducting system in triggering of idiopathic ventricular fibrillation. Lancet. 2002;359(9307):677–8. doi:10.1016/S0140-6736(02)07807-8.
118. Van Herendael H, Zado ES, Haqqani H, Tschabrunn CM, Callans DJ, Frankel DS, Lin D, Garcia F, Hutchinson MD, Riley M, Bala R, Dixit S, Yadava M, Marchlinski FE. Catheter ablation of ventricular fibrillation: importance of left ventricular outflow tract and papillary muscle triggers. Heart Rhythm. 2014;11(4):566–73. doi:10.1016/j.hrthm.2013.12.030.
119. Haissaguerre M, Extramiana F, Hocini M, Cauchemez B, Jais P, Cabrera JA, Farre J, Leenhardt A, Sanders P, Scavee C, Hsu LF, Weerasooriya R, Shah DC, Frank R, Maury P, Delay M, Garrigue S, Clementy J. Mapping and ablation of ventricular fibrillation associated with long-QT and Brugada syndromes. Circulation. 2003;108(8):925–8. doi:10.1161/01.CIR.0000088781.99943.95.
120. Szumowski L, Sanders P, Walczak F, Hocini M, Jais P, Kepski R, Szufladowicz E, Urbanek P, Derejko P, Bodalski R, Haissaguerre M. Mapping and ablation of polymorphic ventricular tachycardia after myocardial infarction. J Am Coll Cardiol. 2004;44(8):1700–6. doi:10.1016/j.jacc.2004.08.034.
121. Marrouche NF, Verma A, Wazni O, Schweikert R, Martin DO, Saliba W, Kilicaslan F, Cummings J, Burkhardt JD, Bhargava M, Bash D, Brachmann J, Guenther J, Hao S, Beheiry S, Rossillo A, Raviele A, Themistoclakis S, Natale A. Mode of initiation and ablation of ventricular fibrillation storms in patients with ischemic cardiomyopathy. J Am Coll Cardiol. 2004;43(9):1715–20. doi:10.1016/j.jacc.2004.03.004.
122. Knecht S, Sacher F, Wright M, Hocini M, Nogami A, Arentz T, Petit B, Franck R, De Chillou C, Lamaison D, Farre J, Lavergne T, Verbeet T, Nault I, Matsuo S, Leroux L, Weerasooriya R, Cauchemez B, Lellouche N, Derval N, Narayan SM, Jais P, Clementy J, Haissaguerre M. Long-term follow-up of idiopathic ventricular fibrillation ablation: a multicenter study. J Am Coll Cardiol. 2009;54(6):522–8. doi:10.1016/j.jacc.2009.03.065.

Supraventricular Tachycardia

14

Ramanan Kumareswaran and Paul Dorian

Abstract

Supraventricular tachycardia (SVT) refers to any arrhythmia which involves a supraventricular structure for arrhythmia maintenance. Paroxysmal supraventricular tachycardia (PSVT) refers to a clinical syndrome with abrupt onset of rapid regular tachycardia which also terminates abruptly. The most common types of PSVT are atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant (reciprocating) tachycardia (AVRT) and atrial tachycardia (Page et al., J Am Coll Cardiol 67:S0735–S1097, 2016). Atrial tachycardia only requires the atrium for its maintenance. AVNRT maintenance is dependent on perinodal structures, and is independent of atrium and ventricle. AVRT requires both the atrium and ventricle for its maintenance. This chapter will discuss the clinical syndrome, typical scenarios of presentation, and then each type in more detail.

Keywords

Supraventricular tachycardia • AV node reentry • Atrioventricular reentry • Atrial tachycardia • SVT • Palpitations • Arrhythmias • Narrow complex tachycardias • Paroxysmal arrhythmias • Adenosine • Radiofrequency ablation

Supraventricular Tachycardia

Supraventricular tachycardia (SVT) refers to any arrhythmia which involves a supraventricular structure for arrhythmia maintenance. Paroxysmal supraventricular tachycardia (PSVT) refers to a clinical syndrome with abrupt onset of rapid regular tachycardia which also terminates abruptly. The most common types of PSVT are atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant (reciprocating) tachycardia (AVRT) and atrial tachycardia [1]. Atrial tachycardia only requires the atrium for its maintenance. AVNRT maintenance is dependent on perinodal structures, and is independent of atrium and ventricle. AVRT requires both the atrium and ventricle for its maintenance. This chapter will discuss the clinical syndrome, typical scenarios of presentation, and then each type in more detail.

Junctional tachycardia, inappropriate sinus tachycardia, sinoatrial reentrant tachycardia, nodofascicular or nodoventricular reentrant tachycardias are rare forms of SVT. Detailed discussions of these arrhythmias are beyond the scope of this chapter. Atrial fibrillation and atrial flutter are common atrial arrhythmias which will be discussed in detail in other sections of this textbook.

Clinical Presentation

The prevalence of PSVT in the United States is 2.25 per 1000 person years and the incidence is 35 per 100,000 person years. ANVRT is more frequent in women than men, and

R. Kumareswaran, M.D. (✉)
Department of Medicine/Cardiology, St. Michael's Hospital,
30 Bond Street, Toronto, ON, Canada, M5B 1W8
e-mail: ramk123@hotmail.com

P. Dorian, M.D., M.Sc., F.R.C.P.C.
Department of Medicine, University of Toronto,
Toronto, ON, Canada

Division of Cardiology, St. Michael's Hospital,
30 Bond Street, Toronto, ON, Canada, M5B 1W8
e-mail: dorianp@smh.ca

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_14

is more common in people who are middle aged or older. AVRT is more prevalent in adolescents [2].

The presentation and documentation of arrhythmia varies between patients and occurs in different circumstances. Some patients are initially seen with symptoms highly suggestive of SVT, but not documented, while others may be seen after an ECG has documented the arrhythmia, generally in an emergency room. In young patients (age less than 35 years), atrial fibrillation as the documented arrhythmia on an ECG may represent SVT leading to AF, and should be considered as the initiating cause.

Palpitations (a sensation of rapid and forceful or unpleasant awareness of cardiac action) is one of the most common presentations in cardiology. Taking a careful history can guide the clinician to the etiology of palpitations. First, a clinician should inquire if the symptom is continuous or intermittent, assessing if the etiology is likely sustained tachycardia as opposed to premature atrial, junctional or ventricular beats. Patients may describe sustained arrhythmia as sudden in onset, rapid, regular, lasting minutes to hours, often at rest, rarely recurring many times a day or lasting all day.

Other common symptoms experienced by patients include dizziness, shortness of breath, dyspnea on exertion, fatigue, and chest pain. Syncope can occur with PSVT, usually with a vagal component (similar to reflex mediated or neutrally mediated syncope) as opposed to hypotension caused by a rapid heart rate alone. Syncope and presyncope are more common in older patients with SVT. Patients experiencing these symptoms can also consider it as an obstacle for driving [3].

Patients may be aware of neck pounding or shirt 'flapping' which suggests that the atrium is contracting while the AV valves are closed, similar to cannon A waves. This presentation suggests that arrhythmia mechanism is likely AVNRT [1, 4].Typical AVNRT causes atrial electrical activation to occur simultaneously during ventricular activation due to rapid retrograde conduction in the fast pathway. This leads to simultaneous atrial and ventricular contraction.

In the absence of ECG documentation, the next step is to consider whether symptoms are due to PSVT or VT. A history of structural heart disease should raise the suspicion of VT. PSVTs are usually well tolerated and have better prognosis. However, patients with structural heart disease or other major comorbidities may not tolerate the rapid heart rates of PSVT leading to adverse events such as syncope, falls, and worsening heart failure. Infrequently, many hours (e.g. 6–12 h) of rapid PSVT, even in young individuals with a structurally normal heart, can lead to a troponin rise and transient left ventricular dysfunction.

Ultimately, obtaining symptom-rhythm correlation is paramount in making the correct diagnosis of palpitations. The ECG is the most valuable tool in the diagnosis of PSVT. Many patients may have an ECG recorded by emergency medical personnel or in the Emergency Department during initial presentation. However, arrhythmia in some patients may be transient and infrequent, which makes obtaining ECG during arrhythmia more difficult.

Obtaining Symptom Rhythm Correlation

If a 12 lead ECG during tachycardia is not available, then the next step is to obtain symptom-rhythm correlation via other monitoring strategies. The frequency of symptoms will determine the ideal monitoring strategy. If symptoms occur daily to many times a week, a 48–72 h Holter monitor can shed light on the etiology of palpitations. Symptoms that are infrequent may necessitate longer monitoring periods. An external loop recorder, usually worn for 2–4 weeks, can assist if the symptoms are frequent enough. Episodes that happen few times a year may warrant an Implantable Loop Recorder (ILR). The ILR is a minor invasive procedure whose utilization is ever increasing. If the suspicion for SVT is high and patient preference is to undergo catheter ablation if SVT is identified, a diagnostic electrophysiologic study is a reasonable option to consider.

Patterns of Presentation

Presentation in the Emergency Department with Ongoing Tachycardia

Narrow complex tachycardia is a common presentation to Emergency Departments. Patients with palpitations may feel unwell and unsafe enough to call and arrive by ambulance. An ECG needs to be performed in a timely manner and interpreted by physicians taking care of the patient. Assessing hemodynamic stability of the patient is the first step. Hemodynamically unstable patients with SVT may need emergent electrical cardioversion [5].

If the tachycardia involves AV nodal tissue, i.e. AVNRT and AVRT, then vagal maneuvers that lead to AV nodal block are helpful to diagnose and treat the patient [6]. Vagal maneuvers include Valsalva performed by patient or carotid sinus pressure (CSP) applied by the physician. CSP needs to be performed cautiously in elderly patients or patients with high likelihood of having carotid disease due to the risk of causing a stroke. The carotid artery needs to be auscultated for bruit prior to applying CSP. It is advisable not to perform CSP if bruit is present. Intravenous adenosine, which blocks AV nodal tissue, can also be given to diagnose and treat SVT [7]. Adenosine will terminate AVNRT and AVRT 80–90% of the time [2]. The effect of adenosine lasts only a few seconds but patients generally feel very unwell (often describing chest pressure or a sense of "impending doom") immediately after

administration. Ample warning to patients is recommended prior to administering adenosine.

Adenosine will help identify underlying atrial rhythm with AV block if the arrhythmia is atrial tachycardia or atrial flutter. The 12 lead morphology of flutter waves are more valuable than telemetry strips in terms of differentiating cavotricuspid isthmus dependent flutter vs other types of atypical flutter. The management of patients may differ depending on the type of flutter given the high success rate and low complication rate of catheter ablation for cavotricuspid isthmus dependent flutter.

Intravenous beta blockers or non-dihydropyridine calcium channel blockers can terminate all forms of SVT but may take time to take effect. These drugs can be useful in patients with immediate recurrences after IV adenosine. Oral forms are needed to be added for long term prevention. Antiarrhythmic medications are rarely needed to control incessant SVT acutely. Long term management is discussed below.

Further management is dependent on underlying medical condition of the patient. Patients who present with hemodynamic instability, who have underlying structural heart disease or other important morbidities may need admission with in-patient monitoring and cardiology/electrophysiology consultation. Patients with a structurally normal heart who otherwise tolerated the SVT can be discharged home with arrangements for out-patient follow up with an electrophysiologist. A rapid referral system to an electrophysiology clinic from the emergency department prevents loss to follow up and repeated presentation to emergency departments by patients.

Presentation to an Out Patient Clinic with Symptoms Suggestive of SVT

Careful history taking as detailed above will identify patients afflicted with SVT. Obtaining symptom rhythm correlation will be the first step. Occasionally, this may require multiple visits and ECG monitoring attempts. Some patients may have been misdiagnosed with sinus tachycardia, anxiety, or panic attacks, and suspicious symptoms should be followed closely until unambiguous symptom-rhythm correlation is obtained. Once symptom-rhythm correlation confirms SVT, the next step will be identifying the type of SVT, and management dictated by symptoms severity and frequency.

A Patient with Prior Documented SVT Presenting for Consultation and Management

In general, most patients with SVT begin to have episodes at a relatively young age, often in the second or third decades of life. Occasionally episodes begin in middle age or later; in these situations, atrial tachycardia should be suspected as the latter often occurs in the presence of atrial enlargement or underlying structural heart disease.

The pattern of episodes is extremely variable. Many patients tend to associate behavioral or lifestyle events with the occurrence of episodes of SVT; for example, many patients believe that stress, caffeine, certain foods, alcohol, weather changes, or other lifestyle events cause or are associated with SVT. It is useful to explain to patients that these associations are unlikely and their relation to arrhythmia frequency or pattern is not established. In occasional patients, exercise may precipitate SVT episodes, but usually this association is inconsistent and variable. Patients also need to be reminded that most SVT is not heritable, and that their siblings and children will not to be at particular risk.

It is useful, to reassure the patient, to explain that the triggers for SVT are generally atrial premature beats which occur randomly in most patients. The frequency and pattern of events can be extremely variable within and between patients. Some have episodes once every several years, others may have them daily. In general, AV nodal reentry tachycardia occurs with a greater frequency than atrioventricular reentry.

Patients can "manage" their condition by attempting Valsalva maneuver or splashing cold water on their face as soon as SVT symptoms occur. Bearing down against closed glottis (Valsalva) is the most common maneuver that is easy to teach and perform. Importantly, this will terminate ongoing SVT in at most 50% of patients. Cold water immersion of the face to elicit the diving reflex is very unpleasant and not recommended.

Many patients believe that a very rapid heart rate is immediately life-threatening; it is useful to remind patients that heart rates of 200 per minute or faster can be well tolerated, in otherwise healthy individuals, for many hours. Thus, long airplane flights, or being in a setting out of immediate available emergency medical care (such as hiking, camping, out of country travel, etc.) are generally safe and not contraindicated in patients with recurrent SVT. However, there are no well controlled studies of acute oral drug therapy that can be taken at the time of symptom occurrence ("pill in the pocket") and such treatment cannot be relied on to terminate ongoing SVT which does not respond to vagal maneuvers. Quality of life is often impaired in patients with SVT because of anxiety regarding the expectation of arrhythmia events, and concerns about their consequence. Allaying these anxieties is very important in the care process.

If the arrhythmia does not terminate spontaneously after the patient maneuvers above or after a relatively brief period of time, depending on the degree of symptoms, patients can be reminded that emergency room treatment of SVT with adenosine is simple, safe, and almost invariably effective.

Infrequent episodes of re-entrant arrhythmia that involves nodal tissue, most commonly AVNRT or AVRT, and which respond to vagal maneuvers, can be managed with a "watchful waiting" approach. If symptoms are frequent or impair quality of life, then the next step in management will be dependent on patient preference. Initiation and uptitration of oral beta blockers or non-dihydropyradine calcium channel blockers is the preferred choice of medications. Physically active patients may not tolerate beta blockers well and calcium channel blockers may be a better option for these patients [1]. Antiarrhythmic medications are rarely needed. Flecainide and propafenone are class Ic antiarrhythmic medications that can be used for patients without structural heart disease and without coronary artery disease [8, 9]. Dofetilide or sotalol are class III agents that can be used in patients with structural heart disease [9, 10]. Amiodarone is an alternative antiarrhythmic drug whose risk of toxicity increases with cumulative doses over many years [11]. Most of the antiarrhythmic medications can be proarrhythmic or result in unpleasant side effects. Therefore, close monitoring of patients on antiarrhythmics is warranted.

If patients prefer definitive treatment, then electrophysiology study with catheter ablation is the next step. Patients who fail medical therapy due to intolerance or ineffectiveness may also benefit from ablative therapy. Catheter ablation for SVT is relatively safe with high success rate (>95%) for AVRT and AVNRT [12]. It is nevertheless an invasive procedure, which can have serious but rare complications such as cardiac tamponade, emergent cardiac surgery, or stroke. Damage to the AV node, resulting in heart block and the need for a permanent pacemaker is not negligible with 0.5–0.7% risk for AVNRT ablation and 0.3% for AVRT ablation. It is important for patients to understand that the procedure is undertaken for symptom control and to improve quality of life. Success rates of the ablation procedures or atrial tachycardia are generally lower. Advent of three dimensional mapping systems has increased our ability to target focal and non-isthmus dependent reentrant atrial tachycardia.

SVT with Pronged QRS Duration/Wide Complex SVT

Supraventricular tachycardia can be associated with wide QRS complexes in the setting of aberrancy, antidromic AVRT or bystander pre-excitation. Aberrant conduction generally involves His-Purkinje system and therefore has typical bundle branch block or fascicular block morphology. SVT with aberrancy is treated the same way as narrow complex SVT.

Mechanisms of SVT

Atrial Tachycardia

The chamber of origin for atrial tachycardia is atrium and this arrhythmia is independent of other structures such as AV nodal tissue, His Purkinje system, or ventricles. The mechanism of atrial tachycardia can be abnormal automaticity, triggered activity, or micro-reentry. Atrial flutter is a special form of atrial tachycardia where macro-reentry is present in the atria, and is discussed elsewhere. Other forms of atrial tachycardia can involve any other structures of right atrium, left atrium, or venoatrial structures including pulmonary veins, coronary sinus, and superior venacava. Atrial tachycardia related P waves can be missed if 2:1 conduction to ventricle is present with every other P wave is masked by QRS, and if the tachycardia has a right atrial origin, the resultant rhythm misdiagnosed as sinus in origin.

AV Nodal Reentrant Tachycardia

AV nodal reentrant tachycardia involves reentry within AV nodal tissue. Fibers in AV nodal tissue and adjacent structures can exhibit longitudinal discontinuity to electrical propagation which can set up reentry. The most common dual properties of the fibers are called slow pathway and fast pathway. More than two pathways are also possible in AV nodal tissue due to multiple discontinuities. Slow pathway tissue is slow to conduct but fast to recover, i.e. shorter refractory period. Fast pathway tissue is fast to conduct but slow to recover. In a typical AVNRT circuit, premature atrial ectopy blocks in fast pathway which is slow to recover from previous atrial beat, but travels in slow pathway to reenter into fast pathway once it is ready to activate. This process starts a reentrant circuit that revolves around both slow and fast pathways. This form of activation is called typical or slow-fast ANVRT, to suggest that activation in the direction from atrium to ventricle is via slow pathway but from ventricle to atrium is by fast pathway. Other forms of AVNRT circuits are possible such as fast-slow and slow-slow.

The triangle of Koch is an anatomical region in right atrium where AV node and its extensions are located. The triangle is bounded by the coronary sinus, the tendon of Todaro, the septal tricuspid leaflet attachment, and the central fibrous body. The inferior extension of the AV node is located in anterior inferior margin of CS ostium in most patients. This is where slow pathway region is generally found. Slow pathway ablation cures AVNRT while leaving behind an intact fast pathway for normal atrioventricular conduction.

Atrioventricular Reciprocating Tachycardia

AVRT uses an accessory pathway between atrium and ventricle as part of the reentrant circuit. Electrical activation travels from atrium to ventricle and back to the atrium to complete the circuit. If the activation travelling to the ventricle is by AV nodal tissue but back to the atrium by accessory pathway then the QRS will be narrow. This form of AVRT is called orthodromic AVRT. If the activation to the ventricle from atrium is by the accessory pathway but back to the atrium by AV nodal tissue then the tachycardia will exhibit wide QRS complexes. Rarely one may encounter two different accessory pathways completing the circuit. AVRT is there for dependent on parts of atrium, AV nodal tissue, His-purkinje system, ventricle, and accessory pathway.

Junctional Tachycardia

Junctional tachycardia originates from AV nodal tissue or His bundle [13]. It is a very rare form of SVT. It is commonly encountered in post cardiac surgery, digitalis toxicity or other high catecholinergic states. The mechanism of this arrhythmia can be automaticity, triggered, or micro-reentry.

ECG

The 12 lead ECG remains vital in any arrhythmia diagnosis including SVT. SVT can present as both narrow and wide complex tachycardia but a vast majority of them are narrow. Table 14.1 summarizes ECG clues to the type of narrow complex tachycardia. Figure 14.1 shows a general approach to the ECG diagnosis of SVT, and Figs. 14.2, 14.3, and 14.4 illustrate typical examples of 12 lead ECGs recorded during various forms of SVT.

Table 14.1 ECG clues to SVT etiology

P wave morphology	Craniocaudal	Rules out AVNRT
	Caudocranial	Rules out sinus tachycardia
P/QRS ratio[a]	More P than QRS	Rules out AVRT
	More QRS than P	Rules out AT and AVRT
P to QRS timing	P is buried in QRS or Pseudo R′ in V1/aVR and/or S′ in inferior leads	Rules out AVRT
Tachycardia termination	Repeatedly terminates with non-premature p wave	AT is unlikely
Cycle length variations	Changes in RR cycle length precedes and predicts PP cycle length	Rules out AT
	Development of bundle branch block slows down tachycardia by 30 ms or more	AVRT utilizing accessory pathway on the same side as the blocked bundle

[a]Non-ectopic beats

Narrow complex tachycardia is defined as heart rate more than 100 beats per minute and QRS duration of less than or equal to 120 ms. Attention to details while reviewing the ECG can give clues to chamber of origin of tachycardia and essential chambers in sustaining the tachycardia circuit if the mechanism is re-entry.

P Wave Morphology

Identifying P waves during tachycardia provides very valuable information in terms of ruling in and/or ruling out mechanisms of tachycardia. Sinus tachycardia is expected to have atrial activation pattern that is consistent with sinus P waves. Negative P waves in inferior leads (lead 2, 3, aVF) with positive P waves in superior leads suggests that the activation of the atrium occurs in caudocranial fashion which rules out sinus tachycardia. Craniocaudal atrial activation, with positive P waves in inferior leads, rules out AVNRT.

Ratio of P Waves to QRS

The presence of more P waves than QRS complexes rules out AVRT, since the AVRT circuit involves atrial activation to travel to the AV node, His-Purkinje system, ventricle, accessory pathway and then back to the atrium in that order to maintain the reentry circuit. Any disruption along this circuit will terminate the tachycardia. Therefore it is impossible to have more P waves than QRS complexes in AVRT. Having more QRS complexes than P waves rules out AVRT for the same reason.

Timing of P Wave to QRS

If atrial depolarization occurs simultaneously with ventricular depolarization (i.e. with a very short R-P interval), then AVRT can be ruled out. It takes time for the activation wavefront in the ventricle to travel to the atrium via an accessory pathway given that these structures are being activated in series during AVRT. On the other hand, the AVNRT circuit is generally thought to be independent of majority of atrial tissue and all of ventricular myocardium. Thus the reentry circuit only involves AV nodal tissue, namely slow pathway and fast pathway; atria and ventricles are activated in parallel fashion and near simultaneously during typical AVNRT via a rapidly conducting fast pathway as a retrograde limb. Therefore the P waves can be buried in QRS complexes and

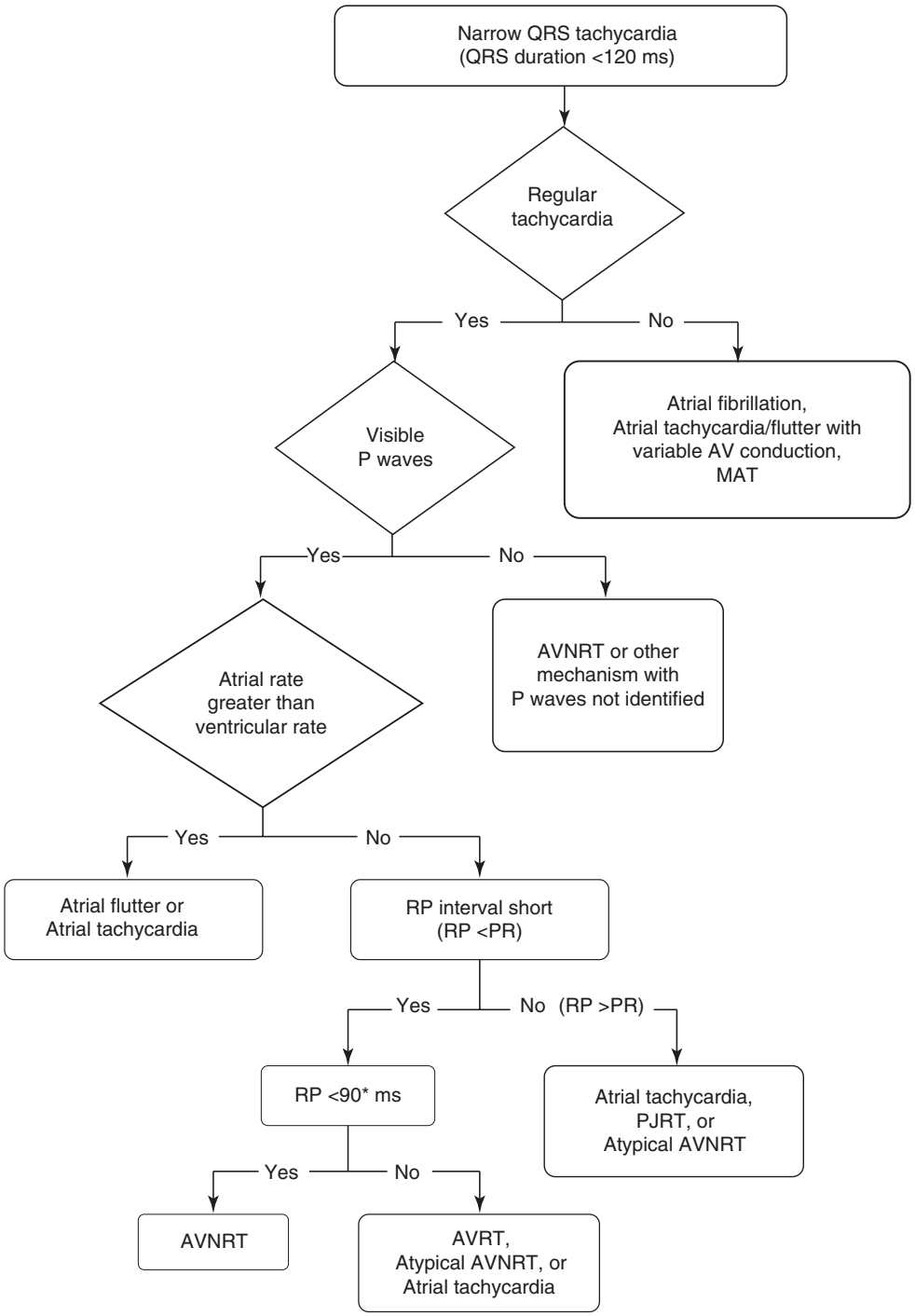


Fig. 14.1 Algorithm for the interpretation of a 12 lead ECG in a patient with narrow complex tachycardia. Patients with junctional tachycardia may mimic the pattern of slow–fast AVNRT and may show AV dissociation and/or marked irregularity in the junctional rate. * (*asterisk*) RP refers to the interval from the onset of surface QRS to the onset of visible P wave (note that the 90-ms interval is defined from the surface ECG, as opposed to the 70-ms ventriculoatrial interval that is used for intracardiac diagnosis)

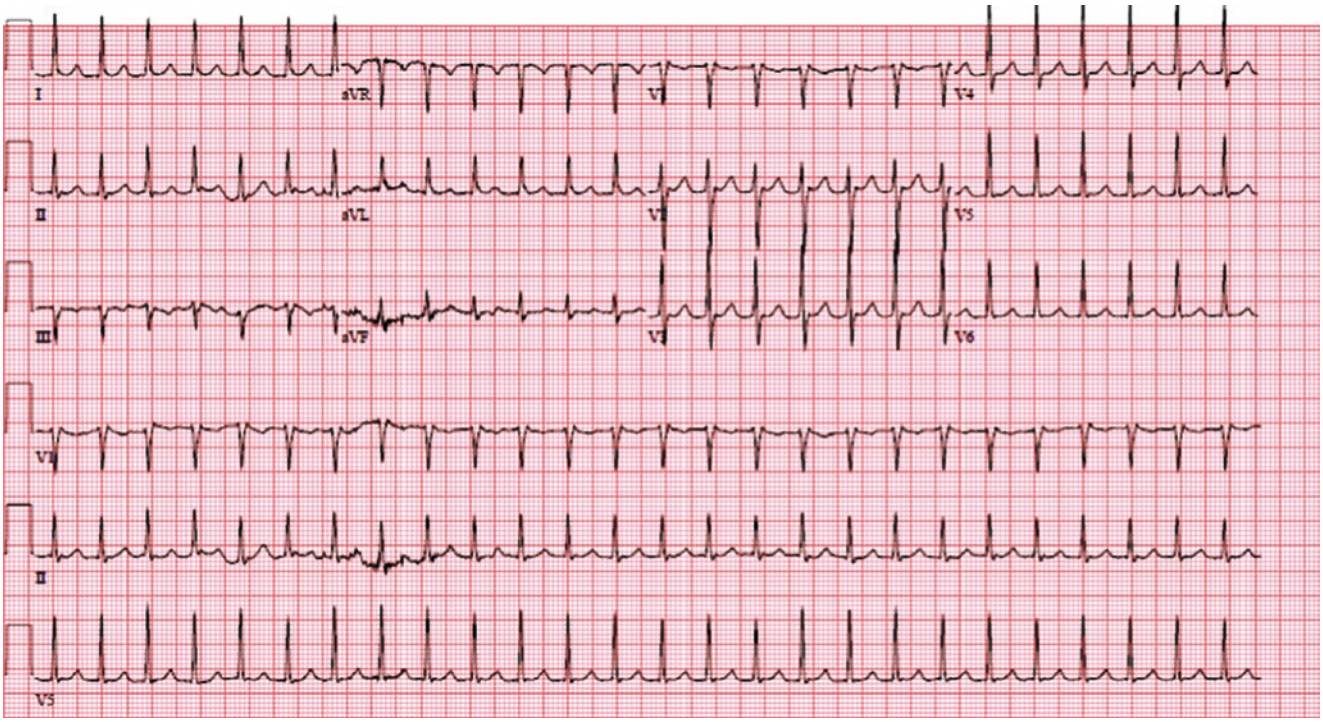


Fig. 14.2 AV node reentry tachycardia. Note small, high frequency deflections in the terminal portion of the QRS complex, most easily visible in leads V1, II

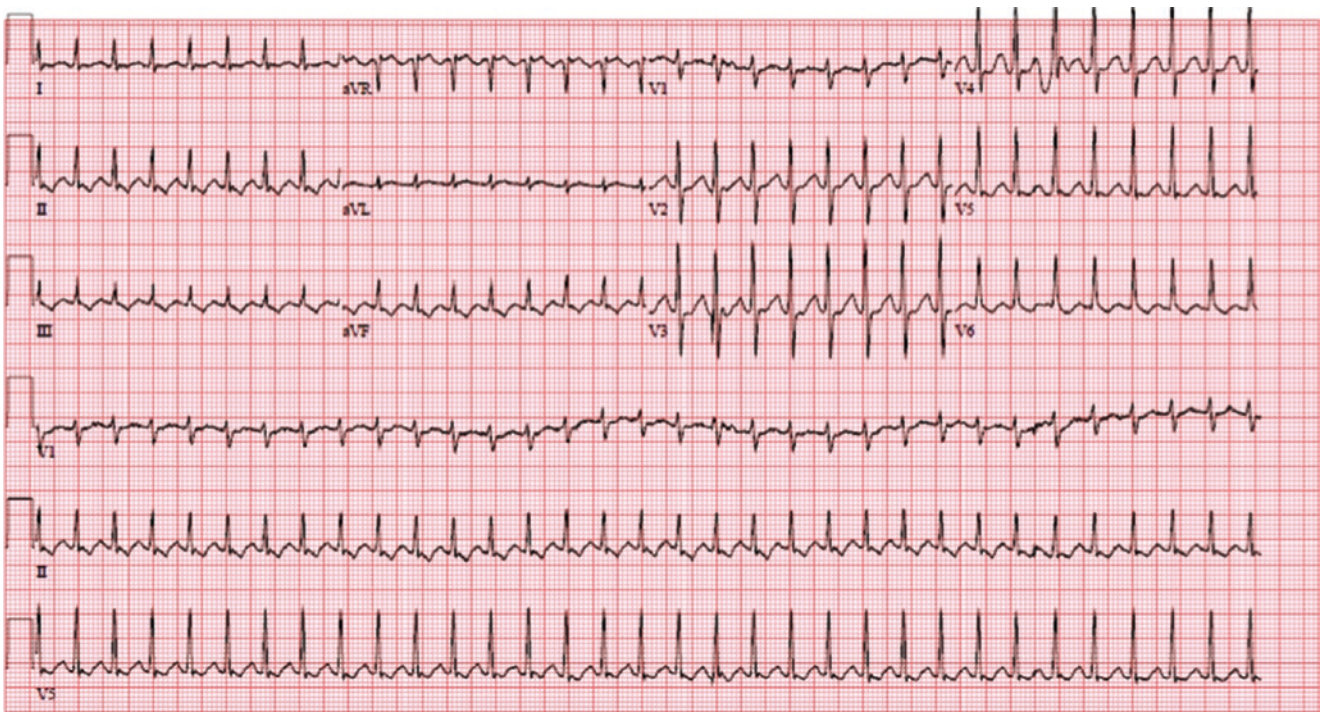


Fig. 14.3 Atrioventricular reentry tachycardia. Note retrograde P waves 120 ms after each QRS complex, most easily seen as small negative (*inverted*) P waves in the inferior leads

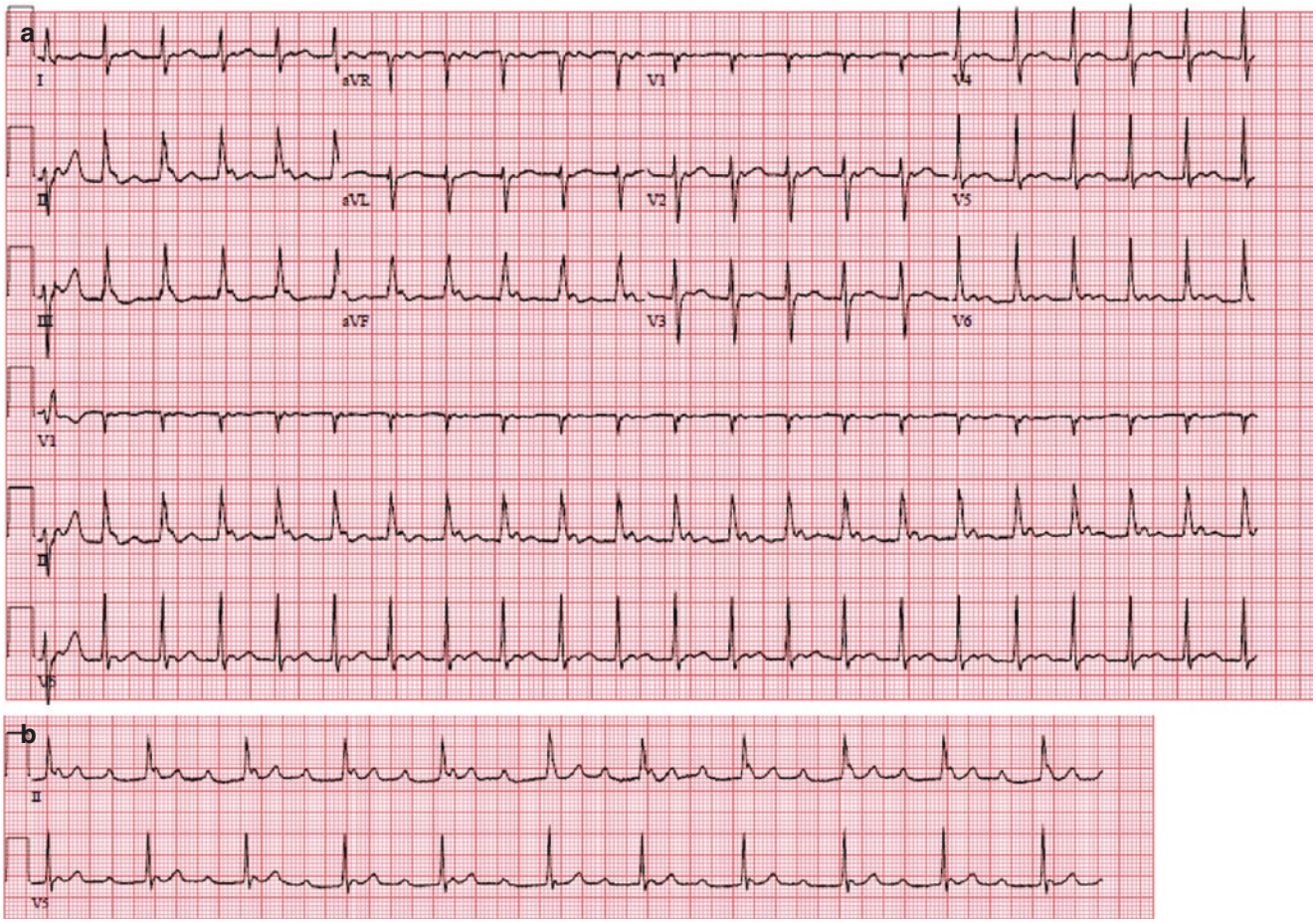


Fig. 14.4 Atrial tachycardia. (**a**) Note P waves immediately following each QRS complex. Positive (*upright*) P waves in the inferior leads signify craniocaudal direction of depolarization; (**b**) shows the P waves more clearly (2:1 AV block in the same patient immediately after IV Adenosine administration)

could be invisible or can only be visible at the end of the QRS as a 'pseudo S' in the inferior leads and 'pseudo R' in V1.

Initiation, Termination, and Cycle Length Variation

Catching initiation and termination of tachycardia can also yield clues to tachycardia etiology. Premature beats often initiate re-entry arrhythmia. A premature atrial ectopic beat that results in a markedly prolonged PR interval than expected, which then initiates tachycardia may suggest that the activation switched from fast pathway to slow pathway and may suggest typical AVNRT especially if the subsequent tachycardia has no visible P waves or P waves at the end of QRS.

Tachycardia that repeatedly terminates with a non-premature P wave rules out atrial tachycardia. Atrial tachycardia is independent of AV nodal conduction. The terminating P wave in tachycardia must have blocked in AV node to not have a QRS following it. It is extremely unlikely for the last P wave of atrial tachycardia to also repeatedly block in the AV node. However AVNRT and AVRT are both dependent on AV nodal conduction and therefore it is possible for both tachycardias to terminate with AV block (i.e. with non-premature P wave).

Changes in QRS that precede and predict the changes in atrial activation, i.e. R-R getting longer would then make P-P longer and R-R interval getting shorter then changes P-P to be shorter, suggest that atrium is not the site of origin of tachycardia and thereby rules out atrial tachycardia. If bundle branch block develops during narrow complex tachycardia and the cycle length of the tachycardia slows down by more than 30 ms, then the tachycardia is likely AVRT that utilizes accessory pathway on the same side as the blocked bundle [14]. The tachycardia rate is not expected to be affected by bundle branch block in atrial tachycardia, AVNRT, or JT given these arrhythmias are independent of ventricular activation.

VT vs. SVT with Aberrancy

Differentiating VT from SVT with aberrancy can sometimes be challenging. Hallmark of VT is AV dissociation. If discernible P waves have no association to wide complex QRS then VT is present. Fusion and capture beats are further evidence of AV dissociation. Fusion beat occurs when QRS due to conducted P wave fuses with VT QRS. Capture beat occurs when P wave is timed in such a way that ventricular myocardium is able to conduct it normally between VT beats. If AV dissociation is not evident then the morphology of QRS can suggest VT vs. SVT with aberrancy. Various morphologic criteria exist to identify VT but a simplified approach would be to determine whether the QRS complexes appear to be typical bundle/fascicular block pattern. If not, then the etiology is usually almost always VT especially if the patient has advanced age or evidence of structural heart disease.

Bystander Pre-excitation

Pre-excitation involves bypassing the native conduction system and presents as delta waves in electrocardiogram. Delta waves represent the activation of the myocardium that occurs to activation via His-Purkinje system. Given that bypass tracts generally insert in ventricular myocardium which is not specialized conduction tissue, activation is slow. Delta waves therefore occur prior to activation over the His Purkinje system, and are slurred. SVT can occur with bystander activation of the ventricle by an accessory pathway when the pathway itself is not needed for the initiation or maintenance of the tachycardia. An example of this would be an atrial tachycardia with bystander ventricular pre-excitation. Several localization algorithms exist in identifying the location of the pathways [15].

Accessory Pathways and Sudden Cardiac Death

Risk stratification for sudden cardiac death and management of reentrant arrhythmia are two different management aspects that need to be addressed in the presence of pre-excitation. Patients with pre-excitation are at risk for developing atrial fibrillation, possibly because of source-sink mismatch at the bypass tract insertion into ventricular tissue. Since antegrade bypass refractory periods can be short, thus permitting very rapid ventricular responses to atrial fibrillation or flutter, pre-excited atrial fibrillation is associated with increased risk of sudden cardiac death. The shorter the bypass refractory period, the greater the likelihood for extremely rapid ventricular rates during atrial fibrillation, which can degenerate into VF, causing sudden cardiac death. Shortest pre-excited RR intervals (SPRRI) during atrial fibrillation less than 250 ms are associated with increased likelihood of SCD [16]. Catheter ablation is recommended if SPRRI is less than 250 ms. An ablation procedure is also recommended for patients in high risk occupations such as pilots [1].

Pathways that show intermittent pre-excitation are unlikely to result in very rapid ventricular rates and to induce ventricular arrhythmia. Abrupt loss in pre-excitation during exercise can also assist in identifying low risk accessory pathways [17]. Exercise increases sympathetic tone and pathways, being made of myocardial cells are sensitive to sympathetic input. Exercise can thus enhance pathway conduction, resulting in the gradual appearance of a smaller contribution of activation over the bypass tract and a shorter or less clearly visible delta wave. It is important to distinguish this phenomenon from abrupt loss of pre-excitation, which occurs if the bypass tract becomes truly refractory at rapid rates during exercise.

During pre-excited tachycardia, it is important not to give medications that purely slow down AV nodal conduction or decrease blood pressure. These medications include calcium channel blockers, digoxin, and adenosine. Low blood pressure leads to a reflex increase in sympathetic tone which can lead to an increase in ventricular rates during atrial fibrillation by shortening the bypass tract refractory period. Intravenous beta blockers in pre-excited tachycardia may lead to similar phenomenon, with an indirect effect greater than a direct antiadrenergic effect, and are best avoided in this setting.

Although the mechanism is not established with certainty, reducing the number of impulses conducted over the AV node may reduce concealed conduction into the area near the ventricular insertion of the bypass tract, and indirectly lead greater shorter refractoriness, leading to an increased risk of ventricular fibrillation. Adenosine has been reported to lead to increased ventricular rates by directly shortening bypass tract refractoriness.

Procainamide is a class IA antiarrhythmic agent with proven efficacy and safety in pre-excited tachycardia [1]. It can be given acutely as IV bolus. Amiodarone can also be considered during these tachycardias, although its direct hypotensive effect may be undesirable as noted above. Pre-excited atrial fibrillation can be life threatening and therefore immediate cardioversion, either chemically with close monitoring or electrically, is mandated.

For the long term treatment of preexcitation, catheter ablation is a relatively safe procedure with high success rate in patients at increased risk for SCD or symptomatic SVT in the presence of accessory pathway. Flecainide or propafenone can be considered in patients without structural heart disease. Amiodarone, dofetilide, and sotalol are other antiarrhythmics that can be tried for long term control of arrhythmia.

Wide Complex Tachycardia with Accessory Pathways

Orthodromic AVRT (antegrade activation over the AV node and retrograde over a bypass tract) is usually narrow complex but can sometimes present as wide complex tachycardia due to aberrancy. AVRT can be antidromic when antegrade conduction, atrium to ventricle, is via an accessory pathway and retrograde conduction is via the AV node. Antidromic AVRTs are wide complex tachycardia given that they utilize non-specialized ventricular myocardium to activate the ventricle. The retrograde conduction back to atrium can use the AV node, or occasionally use another accessory pathway.

"Concealed" Bypass Tracts

Some accessory pathways may only conduct retrogradely, from ventricle to atrium.

In these patients, the ECG does not show preexcitation, but AVRT identical to that seen with manifest preexcitation can occur. Since there is no antegrade conduction over the bypass, there is no risk of life threateningly rapid rates during atrial fibrillation.

Permanent junctional reciprocating tachycardia (PJRT) is a rare form of orthodromic AVRT, most often seen in children and adolescents. The retrograde limb of the pathway is a concealed, slowly conducting retrograde pathway, most often located in the posteroseptal region; since the pathway conducts slowly, very long 'RP interval' is seen. This tachycardia is often incessant in nature and therefore best treated with catheter ablation. Other rare forms of pathways which may lead to PSVT include decrementally conducting atrioventricular pathways, atriofascicular pathways, nodofascicular or nodoventricular pathways, or fasciculoventricular pathways. These pathways are identified during EP study. All of these pathways except for fasciculoventricular pathway can participate in SVT. Catheter ablation can be successfully performed for all of these pathways.

References

1. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia: Executive Summary. J Am Coll Cardiol. 2016;16:S0735–1097.
2. Orejarena LA, Vidaillet H, DeStefano F, Nordstrom DL, Vierkant RA, Smith PN, et al. Paroxysmal supraventricular tachycardia in the general population. J Am Coll Cardiol. 1998;31:150–7.
3. Walfridsson U, Walfridsson H. The impact of supraventricular tachycardias on driving ability in patients referred for radiofrequency catheter ablation. Pacing Clin Electrophysiol. 2005;28:191–5.
4. Laurent G, Leong-Poi H, Mangat I, Korley V, Pinter A, Hu X, et al. Influence of ventriculoatrial timing on hemodynamics and symptoms during supraventricular tachycardia. J Cardiovasc Electrophysiol. 2009;20:176–81.
5. Roth A, Elkayam I, Shapira I, Sander J, Malov N, Kehati M, et al. Effectiveness of prehospital synchronous direct-current cardioversion for supraventricular tachyarrhythmias causing unstable hemodynamic states. Am J Cardiol. 2003;91:489–91.
6. Lim SH, Anantharaman V, Teo WS, Goh PP, Tan AT. Comparison of treatment of supraventricular tachycardia by Valsalva maneuver and carotid sinus massage. Ann Emerg Med. 1998;31:30–5.
7. DiMarco JP, Miles W, Akhtar M, Milstein S, Sharma AD, Platia E, et al. Adenosine for paroxysmal supraventricular tachycardia: dose ranging and comparison with verapamil. Assessment in placebo-controlled, multicenter trials. The Adenosine for PSVT Study Group. Ann Intern Med. 1990;113:104–10.
8. Dorian P, Naccarelli GV, Coumel P, Hohnloser SH, Maser MJ. A randomized comparison of flecainide versus verapamil in paroxysmal supraventricular tachycardia. The Flecainide Multicenter Investigators Group. Am J Cardiol. 1996;77:89A–95A.
9. Tendera M, Wnuk-Wojnar AM, Kulakowski P, Malolepszy J, Kozlowski JW, Krzeminska-Pakula M, et al. Efficacy and safety of dofetilide in the prevention of symptomatic episodes of paroxysmal supraventricular tachycardia: a 6-month double-blind comparison with propafenone and placebo. Am Heart J. 2001;142:93–8.
10. Wanless RS, Anderson K, Joy M, Joseph SP. Multicenter comparative study of the efficacy and safety of sotalol in the prophylactic treatment of patients with paroxysmal supraventricular tachyarrhythmias. Am Heart J. 1997;133:441–6.
11. Gambhir DS, Bhargava M, Nair M, Arora R, Khalilullah M. Comparison of electrophysiologic effects and efficacy of single-dose intravenous and long-term oral amiodarone therapy in patients with AV nodal reentrant tachycardia. Indian Heart J. 1996;48:133–7.
12. Spector P, Reynolds MR, Calkins H, Sondhi M, Xu Y, Martin A, et al. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. Am J Cardiol. 2009;104:671–7.
13. Ruder MA, Davis JC, Eldar M, Abbott JA, Griffin JC, Seger JJ, et al. Clinical and electrophysiologic characterization of automatic junctional tachycardia in adults. Circulation. 1986;73:930–7.
14. Coumel P, Attuel P. Reciprocating tachycardia in overt and latent preexcitation: influence of functional bundle branch block on the rate of the tachycardia. Eur J Cardiol. 1974;1(4):423–36.
15. Basiouny T, de Chillou C, Fareh S, Kirkorian G, Messier M, Sadoul N, et al. Accuracy and limitations of published algorithms using the twelve-lead electrocardiogram to localize overt atrioventricular accessory pathways. J Cardiovasc Electrophysiol. 1999;10(10):1340–9.
16. Pappone C, Vicedomini G, Manguso F, Saviano M, Baldi M, Pappone A, et al. Wolff-Parkinson-White syndrome in the era of catheter ablation: insights from a registry study of 2169 patients. Circulation. 2014;130:811–9.
17. Wackel P, Irving C, Webber S, Beerman L, Arora G. Risk stratification in Wolff-Parkinson-White syndrome: the correlation between noninvasive and invasive testing in pediatric patients. Pacing Clin Electrophysiol. 2012;35:1451–7.

Clinical Management of Atrial Fibrillation

15

E. Kevin Heist, Moussa Mansour, and Jeremy N. Ruskin

Abstract

Clinical care of patients with atrial fibrillation (AF) is complex and highly individualized. The initial assessment of a patient with AF centers on determination of AF type (paroxysmal or persistent), burden, symptoms, and risk for thromboembolism and stroke. Treatment strategies can then be selected focusing on rate vs. rhythm control and stroke risk reduction. Rate control is typically achieved with medical therapy, but AV junctional ablation and pacing are appropriate in selected patients. Rhythm control may involve cardioversion, antiarrhythmic drug therapy, catheter or surgical ablation, and, for some patients, a combination of these therapies. Stroke prevention has traditionally focused primarily on anticoagulation with warfarin, but novel oral anticoagulants and mechanical closure of the left atrial appendage now offer alternative approaches. A thorough understanding of the risks and benefits of all of these treatment approaches, as well as of the clinical status and preferences of each patient, is necessary to provide optimal individualized care to patients with AF.

Keywords

Antiarrhythmic drugs • Anticoagulation • Atrial fibrillation • Cardioversion • Catheter ablation • Left atrial appendage • Pacemaker • Rate control • Rhythm control • Stroke prevention • Thromboembolism

Disclosures: E.K.H. (all modest in amount): Biotronik (research grant, honoraria), Boston Scientific (research grant, consultant, honoraria), Janssen (consultant), Medtronic (honoraria), Sorin (consultant, honoraria), St. Jude Medical (research grant, consultant, honoraria).
M.M.: Biosense Webster (consultant, research grant), St Jude medical (consultant, research grant), Medtronic (consultant), Boston Scientific (consultant), Biotronik (consultant), Pfizer (research grant), Boehringer Ingelheim (research grant).
J.N.R.: Advanced Medical Education (Consultant); Cardiome (Consultant); Daiichi Sankyo (Consultant); Gilead Sciences (Data Monitoring Committee); InfoBionic (Scientific Advisory Board/Equity); Laguna Medical (Data Monitoring Committee); Medtronic (Scientific Advisory Board); Portola Pharmaceuticals (Consultant/Equity).

E. Kevin Heist, M.D., Ph.D. • J.N. Ruskin, M.D. (✉)
M. Mansour, M.D.
Cardiac Arrhythmia Service and Heart Center, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St., GRB 109, Boston, MA 02114, USA
e-mail: kheist@mgh.harvard.edu; jruskin@partners.org; mmansour@partners.org

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_15

Introduction

Atrial fibrillation (AF) is the most common arrhythmia requiring treatment, and is frequently encountered and managed by a variety of providers including internists, emergency medicine physicians and geriatricians in addition to cardiac electrophysiology specialists. Specific topics related to AF are included as separate chapters in this book, including AF pathophysiology, extended ECG monitoring, antiarrhythmic drugs, anticoagulation, and AF ablation. It is not the purpose of this chapter to summarize what is contained in these other sections, but rather to describe how an individual patient with AF is treated, taking into consideration the variety of ways in which AF can present and the large number of strategies available for AF management.

Assessment of the Patient with AF

In some cases, the diagnosis of AF can be made with certainty at the time of initial presentation, for example a patient presenting with an irregular pulse and found to be in AF when an EKG is performed. In other cases, however, the diagnosis of AF is not immediately clear and prolonged EKG monitoring may be necessary to make the diagnosis; examples of this include patients presenting with rare episodes of palpitations or cryptogenic stroke later found to be due to paroxysmal AF [1]. Depending on the frequency and duration of AF episodes, AF may thereby be diagnosed by EKG, by 24 h Holter monitoring, by event monitoring (typically with automatic triggering for AF) lasting typically for 2–4 weeks, or by implantable event monitoring with devices which may last for 3 or more years. The type of monitoring selected often depends on the symptom frequency, and longer duration monitors may be selected when shorter duration monitoring is not successful in identifying the relevant arrhythmia. The diagnosis of AF is typically straightforward when it is present on a monitor, but in some cases it can be difficult to differentiate AF from atrial tachycardia (particularly multifocal atrial tachycardia), especially when the arrhythmia is not sustained.

Current AF guidelines separate AF type into paroxysmal (episodes lasting 7 days or less and generally not requiring cardioversion), persistent (lasting more than 7 days but less than 1 year) and long-standing persistent (AF present continuously for more than 1 year) [2]. The term "permanent" AF is now less frequently used, as techniques such as ablation have been successful in restoring sinus rhythm in patients with very long-standing persistent AF [3]. Permanent AF generally implies very long-standing AF in which there is no plan for restoration of sinus rhythm. It should be noted that many patients will progress over time from paroxysmal to persistent AF, but in other patients AF can remain paroxysmal over decades while some patients will develop persistent AF with their first episode. The pathophysiologic bases for these differences are not yet elucidated, but paroxysms of AF may relate to AF triggers (most frequently from rapid electrical discharges from the pulmonary veins), whereas persistence of AF may relate more to the presence of AF drivers in an abnormal atrial substrate [2].

In many patients who are found to be in persistent AF, it can be difficult to determine with certainty the duration of the arrhythmia. Some patients may describe symptoms potentially attributable to AF such as fatigue or palpitations which suggest the onset of the arrhythmia, while other patients are not able to identify any new or different symptoms compared to when they were last known to be in sinus rhythm. AF symptoms most frequently include palpitations and rapid heart action, but other common symptoms are less specific and may include dyspnea, fatigue, weakness, dizziness or chest discomfort. Patients with rapid ventricular rates during AF are more likely to suffer from AF-related symptoms, although some patients are asymptomatic or minimally symptomatic despite high ventricular rates. These patients may be most likely to develop tachycardia-mediated cardiomyopathy [4], as they tend to come to medical attention only after developing symptoms of congestive heart failure. Other patients are severely affected by AF symptoms, despite well controlled ventricular rates. There are several major issues which must be addressed in each patient who is treated for AF (Table 15.1).

Table 15.1 Important considerations in the management of atrial fibrillation patients

1. Assessment of AF type (paroxysmal, persistent, long-standing persistent)
(a) EKG, Holter, event and device-based monitoring
(b) Frequency and duration of symptomatic AF
2. Determination of rate vs. rhythm control strategy
(a) Individualized risk/benefit assessment of each approach
(b) Patient preference
3. Approach to rate control
(a) Strict vs. lenient rate control
(b) Pharmacologic vs. AV nodal ablation/pacing
4. Approach to rhythm control
(a) Pharmacologic (antiarrhythmic drugs)
(b) Catheter ablation
(c) Surgical ablation
5. Determination of stroke and bleeding risk
(a) Utilization of scoring systems (CHADS2-VAS, HAS-BLED, etc.)
(b) Anticoagulation
(c) Left atrial appendage closure or excision

Choice of Rate Vs. Rhythm Control

One of the major decision points in treating a patient with AF is the selection of a rate vs. rhythm control strategy. Clinicians treating patients with AF will readily identify some individuals as obvious candidates for a rate control strategy and others as obvious candidates for rhythm control, while the decision can be quite difficult for some patients. Elderly patients with easily controlled AF rates and minimal AF symptoms are generally well served by a rate control approach. Conversely, patients with AF associated with disabling symptoms despite attempts at rate control generally require strategies directed at restoration and maintenance of sinus rhythm. An initial decision in favor of either rate or rhythm control does not commit a patient to continuing that strategy if the results with regard to control of AF symptoms are not satisfactory. While it is reasonable to switch from rate control to rhythm control, or vice-versa, it is worth keeping in mind that long periods of continuous AF generally reduces the efficacy of currently available rhythm control techniques.

While maintenance of sinus rhythm is a desirable goal, the "cure" (whether antiarrhythmic drugs or AF ablation) may, for some patients, be worse than the disease. The AFFIRM and RACE trials randomized patients with AF to either a rhythm control strategy with antiarrhythmic drugs or rate control. Both studies failed to show a benefit of the rhythm control strategy when compared with rate control [5, 6]. Importantly, the AFFIRM trial demonstrated a trend toward increased mortality in the rhythm control arm [5]. It should also be noted, however, that sinus rhythm maintenance (regardless of randomization arm) was associated with improved clinical outcomes in AFFIRM [7, 8], and that antiarrhythmic drugs were only modestly effective in maintaining sinus rhythm [5]. One possible conclusion from these studies is that the modest efficacy and toxicities of antiarrhythmic drugs counterbalance the benefit with regard to maintenance of sinus rhythm. Catheter ablation of AF is an alternative strategy with uniformly greater efficacy than antiarrhythmic drugs and one which avoids the long term risks and toxicity of these agents, but is associated with procedural risks. At the current time there are no available data comparable to AFFIRM and RACE with regard to rhythm control with catheter ablation vs. rate control; the ongoing CABANA trial is designed to answer this important question [9].

Approach to Rate Control

When the decision is made to proceed with a rate control strategy, it is important to define a ventricular rate target for each patient. The goals of rate control include the elimination or minimization of AF-related symptoms such as palpitations, rapid heart action, dyspnea, dizziness and chest discomfort, as well as the prevention of tachycardia-mediated cardiomyopathy [4]. Optimal ventricular rate targets have not been fully defined. The RACE 2 study randomized patients with persistent AF to lenient (resting heart rate <110 bpm) vs. strict (resting heart rate <80 bpm and heart rate during moderate exertion <110 bpm) rate control strategies [10]. The average heart rates which were achieved in each group were 93 ± 9 bpm in the lenient group and 76 ± 12 bpm in the strict group ($p < 0.001$). Over several years of clinical follow-up, there was no significant improvement in the combined endpoint of cardiovascular death, heart failure hospitalization, stroke, systemic embolism, bleeding or life-threatening arrhythmia with strict vs. lenient rate control, and symptoms attributable to AF were similar in both treatment arms. In addition, the strict rate control strategy required a greater number of medical visits to achieve desired rate control targets compared with the lenient strategy [10]. Whether the lenient rate control strategy of a target resting heart rate <110 bpm is satisfactory over longer periods of time than was evaluated in RACE 2 has not yet been determined. In addition, patients with congestive heart failure may benefit from more aggressive rate control targets than patients with normal ventricular function, although optimal heart rate targets for patients with heart failure have not been well defined [11].

While some patients with AF have well controlled ventricular rates due to the presence of underlying AV nodal disease, most patients require treatment to control their ventricular rates. For this latter group, the great majority are treated with AV nodal blocking drugs, most commonly beta-adrenergic receptor blockers, non-dihydropyridine calcium channel blockers (diltiazem and verapamil) and digitalis [2]. There is no clear consensus on whether beta blockers or calcium channel blockers are more effective in controlling the ventricular rate in AF. The relative effectiveness of beta blockers vs. calcium channel blockers is highly dependent on the particular drugs and doses used as well as patient characteristics, and both classes of drugs are acceptable first-line agents for rate control in most patients with AF. For some patients, side effects such as worsening of asthma with beta blockers or peripheral edema with calcium channel blockers may dictate which drug class is best suited to a particular patient. In patients with particularly difficult to control rates, a combination of a beta blocker and a calcium channel blocker may be employed, but this can result in profound bradycardia in some patients and should be used with caution in patients without the protection of a permanent pacemaker.

Digitalis, an extremely old drug first described more than 200 years ago from the purple foxglove plant (digitalis purpurea),

was for many decades the most widely and commonly used drug to treat AF. However, in recent years its use for rate control in AF has been called into question based on studies suggesting a higher mortality rate among AF patients treated with digitalis compared to other rate controlling medications [12]. In addition, digitalis tends to be less effective than other rate controlling medications, particularly during exertion or other states of high adrenergic tone. For these reasons, digitalis should rarely be used as a first line single agent for rate control in AF. Digitalis may have a role when added to another rate controlling agent, particularly for patients with systolic heart failure in whom the inotropic properties of digitalis may be beneficial [13]. Although amiodarone is an effective rate controlling agent, it is rarely used chronically for this purpose given its risk of organ toxicity and the availability of many less toxic rate controlling agents. Amiodarone has been demonstrated to be useful for achieving rapid rate control in acutely ill patients with AF with less associated hypotension compared to beta blockers or calcium channel blockers [14]. Beta blockers such as pindolol with intrinsic sympathomimetic activity may be considered for patients with tachy-brady syndrome to provide heart rate control with less potential for bradycardia.

For some AF patients, adequate rate control cannot be achieved by pharmacologic means alone. This may occur for a variety of reasons including: (1) inability to achieve acceptable rate control despite high doses of rate controlling medications; (2) intolerable medication related side effects and (3) periods of bradycardia in addition to tachycardia which limit the doses of rate controlling medications which can be used safely. In these situations, permanent cardiac pacing, either with or without AV junctional ablation, may allow the use of adequate doses of AV nodal blocking drugs to achieve acceptable rate control. Patients with a combination of bradycardia and tachycardia can usually be effectively treated with a combination of permanent cardiac pacing and rate and/or rhythm controlling medications. Patients with high ventricular rates which cannot be controlled with medications may require AV junctional ablation in addition to pacemaker placement to definitively control the ventricular rate [15]. Although some patients may have a slow junctional or ventricular escape rhythm after AV junctional ablation, many become pacemaker-dependent as a result of this procedure, so this approach is typically undertaken only as a last resort when other approaches to rate and/or rhythm control have proven ineffective. Cases of sudden death have been described in the early period after AV junctional ablation and pacemaker placement, which may relate to a pro-arrhythmic effect of a sudden drop in the heart rate at the time of AV nodal ablation [16]. For this reason, pacing at high ventricular pacing rates (typically 80–90 bpm) is now recommended in the initial weeks after AV junctional ablation, before more physiologic lower pacing rates are programmed.

AV junctional ablation typically results in nearly 100% ventricular pacing, which may cause or exacerbate systolic heart failure in some patients. Implantation of a cardiac resynchronization therapy (CRT) device with resultant pacing of both the left and right ventricles may ameliorate this problem as demonstrated in the randomized controlled PAVE study [17]. It is unclear whether CRT devices should be implanted in all patients undergoing AV junctional ablation, as left ventricular function remains preserved in many patients for long periods of time with right ventricular pacing alone and CRT devices carry additional implant complexity and risk and result in earlier battery depletion compared to conventional pacemakers. It seems reasonable to implant CRT devices initially at the time of AV junctional ablation in patients with pre-existing systolic heart failure (which is not believed to be caused by AF with rapid ventricular rates), and to upgrade to CRT devices in patients who develop systolic heart failure after a period of chronic right ventricular pacing following AV junctional ablation.

Approach to Rhythm Control

When the decision has been made to achieve and maintain sinus rhythm, a variety of strategies are available to the clinician for this purpose. Most commonly, these include electrical cardioversion, antiarrhythmic drug therapy, and catheter or surgical ablation [2]. A simplistic approach would be to use these strategies in this order for all patients for whom a rhythm control strategy is selected. However, patients are generally best served by an individualized approach based on patient-specific characteristics and shared decision making. It should also be noted that lifestyle factors can have a substantial impact on AF burden, and lifestyle modification can be an important element of AF treatment [18].

Modifiable factors such as obesity and sleep apnea can have a major impact on AF incidence, burden and progression, and a rhythm control strategy should address these factors as an integral part of the treatment plan in addition to whatever specific therapies are chosen to restore and maintain sinus rhythm. For some patients, an underlying condition such as sleep apnea may be a major trigger for AF and treatment of this condition may be all that is required to reduce or even eliminate AF. For many patients, however, treatment of obesity or sleep apnea may not be sufficient to prevent AF, but may enhance substantially success of other therapies used for sinus rhythm maintenance. Even after catheter ablation, a lifestyle modification program has been shown to substantially reduce AF recurrence [18].

Electrical cardioversion is a reasonable first line strategy for patients presenting with persistent AF when a rhythm control strategy has been selected. Although cardioversion alone in the absence of concomitant antiarrhythmic drug

therapy is rarely effective in achieving long-term maintenance of sinus rhythm, there are patients with rare episodes of persistent AF for whom occasional cardioversion procedures are sufficient to manage AF recurrences. Chemical cardioversion, most commonly with Class I antiarrhythmic drugs (which may also be used by the patient in combination with an AV nodal blocking agent as a "pill in the pocket" strategy) or IV ibutilide can also be used for patients with occasional episodes of persistent AF. In addition, for patients with persistent AF resulting from a well-defined and transient trigger (such as cardiac surgery), cardioversion may be sufficient to return the patient to sinus rhythm without the need for further long term therapy. Some patients present with persistent AF of unclear duration and with vague symptoms such as fatigue which may or may not be caused by the AF. For these patients, cardioversion can be extremely useful if it results in a sufficiently long period of sinus rhythm to determine whether symptoms are truly relate to AF and to thereby aid in the decision about a rhythm vs. rate control strategy if AF recurs following cardioversion.

Most patients with AF require more than cardioversion for sinus rhythm maintenance. For the majority of these patients, it is advisable to recommend a trial of antiarrhythmic drug therapy prior to proceeding with catheter ablation therapy. The most commonly used antiarrhythmic drugs for AF include class IC agents (flecainide and propafenone), class III agents (sotalol, dofetilide, amiodarone and dronedarone). While amiodarone and dronedarone are classified as class III agents, they exert effects on multiple ion channels including sodium and calcium channels in addition to potassium channels. Both drugs also have antiadrenergic effects. While notable exceptions exist in some patients, beta blockers and calcium channel blockers, the mainstays for rate control in AF, have not demonstrated substantial efficacy with regard to rhythm control. There are relatively few randomized head to head studies of rhythm control medications for AF patients. Amiodarone was found to be generally more effective than sotalol for maintenance of sinus rhythm in the SAFE-T study [19], and more effective than dronedarone in the DIONYSOS study [20], but the effectiveness of amiodarone must be counterbalanced with its greater risk for toxicity. AF patients with structurally normal hearts without coronary artery disease and with normal renal function typically have a wide choice of antiarrhythmic drug options, while the options for patients with congestive heart failure, coronary disease or significant renal impairment are typically much more limited [2]. Specifics of individual antiarrhythmic drugs are described in detail in another chapter of this book.

The majority of AF patients treated with antiarrhythmic drugs take these agents on a daily basis to prevent recurrences of AF. For some patients with rare episodes of AF, however, a "pill in the pocket" approach, in which the drug is taken at the onset of symptomatic AF in an attempt to terminate the episode within a short period of time, may be a practical and effective strategy. Most commonly this is done with the class IC agents, flecainide or propafenone, as their positive use dependent (greater drug effect at higher atrial rates) makes them more effective than most class III agents including amiodarone for acute conversion of AF. The use of class IC agents does carry the risk of organization of atrial fibrillation to atrial flutter, which can in some cases result in 1:1 conduction to the ventricles. For this reason, an AV nodal blocking agent (beta blocker or calcium channel blocker) is typically given in conjunction with the class IC agent.

In recent years, catheter and surgical ablation for AF have assumed an increasingly prominent role in the rhythm control approach to AF. As with ablative therapies for many other arrhythmias, the original approach to AF involved open cardiac surgical procedures (termed Maze procedures), but the discovery of triggering of AF from the pulmonary veins created a rational scientific basis for a catheter-based approach to ablation of AF [21]. Pulmonary vein isolation remains the cornerstone of most catheter-based AF ablation procedures (Fig. 15.1), although substrate-based ablation performed in addition to pulmonary vein isolation may improve the success of AF ablation, particularly for patients with persistent and long-standing persistent AF [2]. Strategies for AF ablation are described in detail in another chapter in this book and will not be repeated here.

Most randomized studies comparing catheter ablation to antiarrhythmic drug therapy have demonstrated significantly greater efficacy for ablation in the prevention of recurrent symptomatic AF. AF ablation carries procedural risks, however, and consensus guidelines suggest that therapy with at least one antiarrhythmic drug be attempted before proceeding to AF ablation for most patients [2]. However, AF ablation as first-line therapy is gaining increasing acceptance for some highly selected patients, particularly young patients with structurally normal hearts and highly symptomatic paroxysmal AF who are at low risk for procedural complications. If an antiarrhythmic drug is not effective or not tolerated, then AF ablation is a reasonable option, although some patients may prefer to try another antiarrhythmic drug or to transition to a rate control strategy rather than to undergo an ablation procedure. Although ablation is more effective than antiarrhythmic drug therapy, ablation efficacy for persistent, and especially for long-standing persistent AF, remains moderate when outcomes are analyzed over several years, and the need for repeat ablation procedures in these patients is relatively common [3]. Catheter or surgical ablation for AF should generally not be offered with the primary goal of eliminating the need for anticoagulation, particularly in patients who are at high risk for stroke. While the safety of stopping anticoagulants in intermediate risk patients with no prior history of stroke after apparently successful ablation

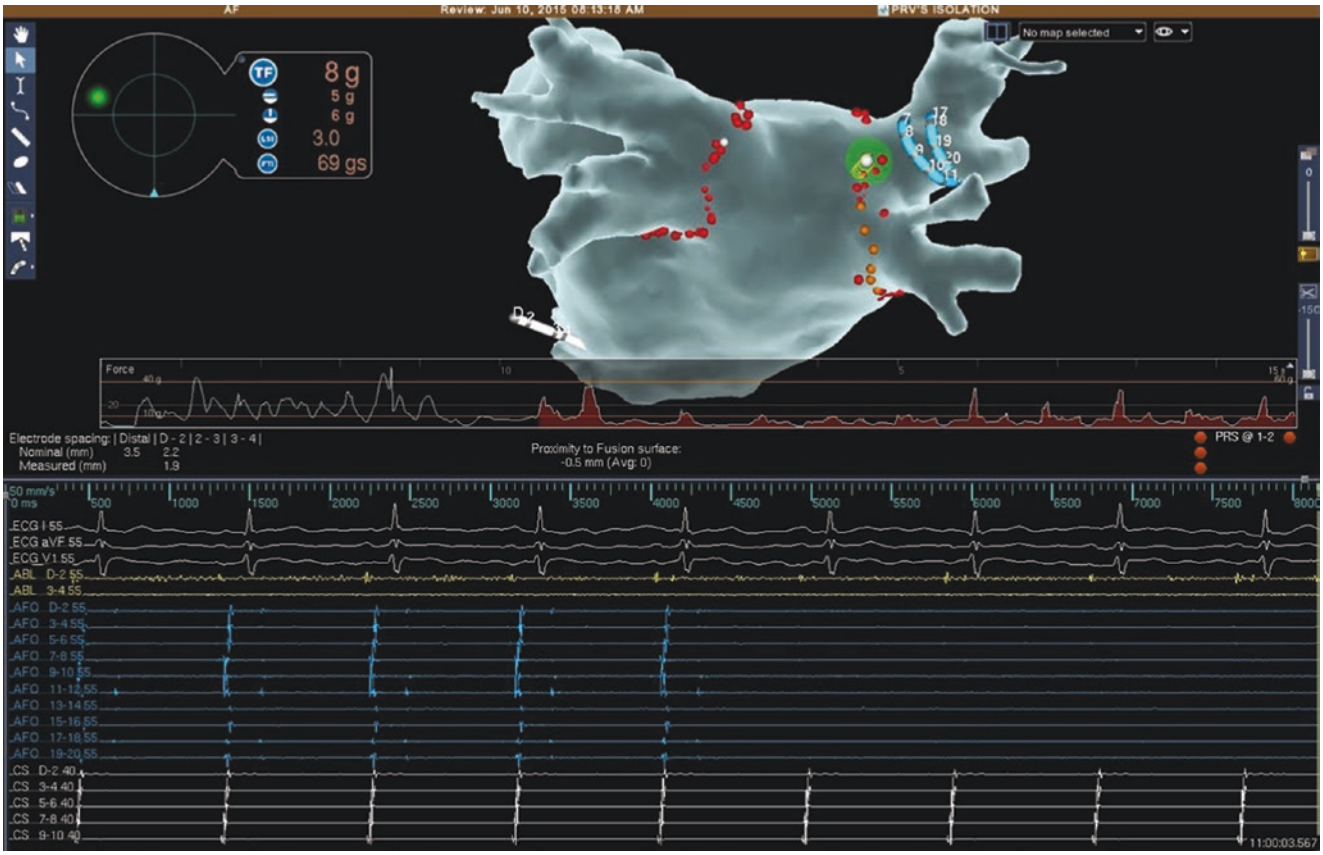


Fig. 15.1 Catheter ablation procedure for atrial fibrillation (pulmonary vein isolation). The top portion of the figure shows a posterior-anterior projection of the left atrium. A lesion set (*red dots*) has been completed encircling and isolating the left pulmonary veins, and is nearly complete around the right pulmonary veins. The force-sensing radiofrequency ablation catheter is evident (*yellow/green dot*) at the posterior antrum of the right superior pulmonary vein. The lower portion of the figure shows surface and intracardiac electrograms, with right pulmonary vein isolation occurring in the middle of the tracings (right pulmonary vein electrograms are marked AFO D-2 through AFO 19–20)

procedures has not been established by randomized control trials, observational data from some investigators has provided suggestive evidence that this can be done with low risk of stroke over 1–2 years in carefully selected and monitored patients. No data exist over longer durations of follow up and it is important to emphasize that recurrences of AF can occur at any time post-ablation. These factors should be discussed in detail with each patient before a decision is made about whether or not to undergo ablation.

AF ablation can be performed using either catheter-based or surgical techniques. Modern surgical approaches to AF ablation, when performed as a stand-alone procedure, can often be performed with minimally invasive surgical techniques (mini-thoracotomy or thorascopic approach). Even with minimally invasive techniques, surgical ablation of AF is a much more invasive procedure than catheter ablation, with longer hospital stays and recovery periods. There are relatively few randomized data comparing surgical vs. catheter ablation of AF, but one small randomized study demonstrated greater efficacy, and greater complication rates, with surgical vs. catheter-based AF ablation [22]. For patients who require cardiac surgery for another reason (e.g. valve repair or replacement) and who also have AF and desire a rhythm control approach, surgical AF ablation at the time of the cardiac surgery should be performed. For most patients who do not require cardiac surgery for other reasons, the lower morbidity of catheter ablation make this the preferred approach to AF ablation, particularly in the absence of robust evidence that one approach is more effective than the other. For patients with AF who are interested in ablation but likely to have a low success rate with catheter ablation (most commonly long-standing persistent AF with marked atrial enlargement), stand-alone surgical ablation may be a reasonable option, although the long term success of surgical ablation in this population is not well defined. "Hybrid" AF ablation procedures involving both catheter and minimally invasive surgical approaches have been described, although these do carry the additional morbidity of surgical access [23]. One advantage of surgical ablation compared to traditional catheter-based ablation procedures is the ability to surgically excise the left atrial appendage (LAA), which may both

reduce the risk of recurrent AF related to the LAA as an arrhythmic trigger, and potentially reduce the risk of stroke related to LAA thrombus.

Approach to Stroke Prevention

Stroke is among the most feared complications of AF, and is the major cause of morbidity and mortality resulting from AF. The risk of AF-related stroke is independent of AF symptoms, and stroke prevention strategies must be applied to patients with all types of AF regardless of the presence or absence of associated symptoms. In some cases of cryptogenic stroke, AF is subsequently identified as the cause, increasingly with the use of long-term ECG monitoring. The risk of stroke is elevated in both paroxysmal as well as persistent AF, although the AF burden that is required to elevate the risk of stroke has not been precisely defined. This is at least in part related to the difficulty in determining AF burden in most patients over long periods of time in the absence of implanted monitors. One study of patients with pacemakers, which can precisely determine AF onset, offset and burden, detected a significant increase in stroke risk using a pre-specified cutoff of 6 min of atrial tachycarrhythmia [24].

AF-related cardioembolic stroke is believed to arise from thrombus in the LAA in large majority of patients. The risk of stroke in patients with AF can be estimated using the CHADS2 score (1 point each for congestive heart failure, hypertension, age ≥75, diabetes, and 2 points for prior stroke or transient ischemic attack). Because of its better performance as a predictor of stroke risk in AF, the CHADS2 score has been widely replaced by the CHADS2-VASc score (1 additional point for vascular disease, age 65–75, and female gender) [2]. For patients with AF but without other stroke risk factors (particularly for those with a CHADS2-VASc score of 0 or 1), the risk of AF-related stroke may be sufficiently low that the benefits of anticoagulation may be outweighed by bleeding risk, and no anti-coagulation or aspirin may be reasonable options [25].

Anticoagulation with warfarin has formed the basis for stroke prevention in AF patients for decades, with overwhelming data to support its use. Antiplatelet therapy with aspirin and/or clopidogrel is significantly less effective than warfarin for this purpose, and should not be considered an acceptable alternative for patients with AF and risk factors for stroke [26]. Warfarin is a challenging drug to manage, with a narrow therapeutic index and substantial food and drug interactions. In recent years, novel oral anticoagulants (NOACs) have been developed, including the factor Xa inhibitors rivaroxaban, apixaban and edoxaban, and the direct thrombin inhibitor dabigatran. These drugs have much more convenient dosing without the need for frequent blood monitoring and dietary restrictions required with warfarin, and have shown equivalent and in some cases superior efficacy and overall safety compared to warfarin in large randomized trials [27]. This has led to approval of these agents by the U.S. Food and Drug Administration. A more detailed description of these agents and the data supporting their use is contained in the chapter on anticoagulants in this book.

For most patients with a diagnosis of AF, anticoagulation with either warfarin or a NOAC should be initiated as soon as possible, regardless of whether an initial rate or rhythm control strategy is chosen. The choice of the individual agent should be a shared decision between the patient and clinician, taking into account safety and efficacy, patient preference and convenience, and cost. For patients with AF who are at very low (0.2–0.6%) risk for stroke (CHADS2-VASc score of 0 or 1), aspirin or no anticoagulation may be reasonable options. Since the predictive value of current risk scores is not optimal, some patients with a CHADS2-VASc score of 1 may be considered for anticoagulation, particularly in the presence of other risk factors such as marked left atrial enlargement, fibrotic atrial cardiomyopathy or renal dysfunction. Data from large trials of rate vs. rhythm control such as AFFIRM have demonstrated that apparent efficacy of antiarrhythmic drugs based on occasional ECGs does not allow for safe discontinuation of anticoagulation, likely related to the occurrence of undetected asymptomatic AF in these patients [5]. Some large registries of patients undergoing catheter ablation for AF have suggested a very low stroke risk after successful AF ablation (as documented by outpatient monitoring) when anticoagulation is discontinued [28, 29]. However, there are at the present time no randomized trial data to support this practice, and recurrence of AF many years after initially successful AF ablation is not uncommon.

Since the left atrial appendage (LAA) is the source of most cardioembolic events related to AF, closure or excision of the LAA has been targeted as an alternative strategy to anticoagulation for stroke prevention. Closure of the LAA as a stroke reduction strategy has been supported by data from randomized controlled trials including the PROTECT-AF and PREVAIL studies of a percutaneous, catheter-delivered LAA closure device. In these studies, patients randomized to LAA closure had comparable risk of all cause (ischemic and hemorrhagic) stroke compared to patients randomized to warfarin over several years of follow-up [30]. The risk of procedural complications related to device placement was counterbalanced by a higher bleeding risk during follow-up in the warfarin group. This device was approved by FDA for clinical use in 2015, and multiple other percutaneous LAA closure devices are currently in clinical development. At the present time, the major advantage of mechanical LAA closure appears to be in patients who are very high risk for major or life threatening bleeding on anticoagulant therapy.

Conclusions

The treatment of patients with atrial fibrillation requires careful decision making in multiple domains including: an assessment of the risk of and the need for prophylaxis against thromboembolic stroke; a detailed assessment of AF-related symptoms and an understanding of the substrate in which AF is occurring [31]. A thorough knowledge of the benefits, risks and limitations of all available treatment strategies allows the clinician and the patient to select an approach that is tailored to best address each patient's individual needs and preferences.

References

1. Glotzer TV, Ziegler PD. Cryptogenic stroke: is silent atrial fibrillation the culprit? Heart Rhythm. 2015;12(1):234–41.
2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1–76.
3. Lim HS, Derval N, Komatsu Y, Zellerhoff S, Denis A, Shah AJ, et al. Is ablation to termination the best strategy for ablation of persistent atrial fibrillation? Persistent atrial fibrillation is best ablated by a strategy that terminates the arrhythmia: procedural termination is associated with improved long-term outcomes. Circ Arrhythm Electrophysiol. 2015;8(4):963–71.
4. Gupta S, Figueredo VM. Tachycardia mediated cardiomyopathy: pathophysiology, mechanisms, clinical features and management. Int J Cardiol. 2014;172(1):40–6.
5. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347(23):1825–33.
6. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347(23):1834–40.
7. Guglin M, Chen R, Curtis AB. Sinus rhythm is associated with fewer heart failure symptoms: insights from the AFFIRM trial. Heart Rhythm. 2010;7(5):596–601.
8. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation. 2004;109(12):1509–13.
9. Moreno J, Zamorano JL. The CABANA trial. Eur Heart J. 2014; 35(29):1908–9.
10. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med. 2010;362(15):1363–73.
11. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. 2010;376(9744):886–94.
12. Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. Eur Heart J. 2015;36(28):1831–8.
13. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? J Am Coll Cardiol. 2003;42(11):1944–51.
14. Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. Am J Cardiol. 1998;81(5):594–8.
15. Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, et al. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. N Engl J Med. 2001;344(14):1043–51.
16. Nowinski K, Gadler F, Jensen-Urstad M, Bergfeldt L. Transient proarrhythmic state following atrioventricular junctional radiofrequency ablation. Pacing Clin Electrophysiol. 2002; 25(3):291–9.
17. Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol. 2005;16(11):1160–5.
18. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol. 2014;64(21):2222–31.
19. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med. 2005;352(18):1861–72.
20. Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. J Cardiovasc Electrophysiol. 2010;21(6):597–605.
21. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659–66.
22. Boersma LV, Castella M, van Boven W, Berruezo A, Yilmaz A, Nadal M, et al. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. Circulation. 2012;125(1):23–30.
23. Pison L, La Meir M, van Opstal J, Blaauw Y, Maessen J, Crijns HJ. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. J Am Coll Cardiol. 2012;60(1):54–61.
24. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366(2):120–9.
25. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. J Am Coll Cardiol. 2015;65(3):225–32.
26. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367(9526):1903–12.
27. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62.
28. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J Am Coll Cardiol. 2010;55(8):735–43.
29. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, et al. Warfarin is not needed in low-risk patients following atrial fibrillation ablation procedures. J Cardiovasc Electrophysiol. 2009;20(9):988–93.
30. Holmes DR, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis. J Am Coll Cardiol. 2015;65(24):2614–23.
31. Kirchhof P, Breithardt G, Aliot E, Al Khatib S, Apostolakis S, Auricchio A, et al. Personalized management of atrial fibrillation: proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference. Europace. 2013;15(11):1540–56.

Ventricular Tachycardia and Fibrillation in Patients with Structural Heart Disease

16

Raul D. Mitrani and Robert J. Myerburg

Abstract

Ventricular tachyarrhythmias are common in patients with structural heart disease and cause syncope and/or sudden cardiac death. Sudden cardiac death may represent the initial manifestation of structural heart disease in patients with ischemic or nonischemic cardiomyopathy. In patients with ischemic cardiomyopathy due to coronary artery disease, ventricular tachycardia often results from reentry involving areas of scar and peri-infarct myocardium. Similarly, reentry may occur in patients with nonischemic cardiomyopathy, involving areas of patchy fibrosis. During ischemia, or during the early phases of acute myocardial infarction, other mechanisms may play a role in promoting ventricular tachyarrhythmias. The combination of electrophysiology testing, electro-anatomic mapping, and magnetic resonance imaging, have expanded our knowledge of the substrate and mechanism of ventricular arrhythmias in patients with structural heart disease. Prevention and treatment of ventricular tachyarrhythmias is based on firm understanding of the pathophysiology, and epidemiology of ventricular tachyarrhythmias in patients with structural heart disease.

Keywords

Ventricular tachycardia • Ventricular fibrillation • Sudden cardiac death • Ischemic cardiomyopathy • Nonischemic cardiomyopathy

Abbreviations

CAD	Coronary artery disease
DAD	Delayed after depolarization
EAD	Early after depolarization
EF	Ejection fraction
ICD	Implantable cardioverter defibrillator
OHCA	Out of hospital cardiac arrest
PVC	Premature ventricular complex
SCD	Sudden cardiac death
VF	Ventricular fibrillation
VT	Ventricular tachycardia

R.D. Mitrani, M.D. (✉) • R.J. Myerburg, M.D.
Division of Cardiology, Department of Medicine,
University of Miami, Miller School of Medicine,
1400 NW 12th Ave; Suite 4062,
Miami, FL 33136, USA
e-mail: rmitrani@miami.edu; rmyerbur@med.miami.edu

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_16

Epidemiology

The epidemiology of ventricular tachycardia (VT) and ventricular fibrillation (VF) has been intertwined with epidemiology of sudden cardiac death (SCD). Epidemiologic studies of SCD are difficult to interpret due to differing definitions, adjudication of SCD, indeterminate pathophysiologic mechanisms, and making distinctions between population risk and individual risk [1]. Furthermore, approximately half of all cases of SCD represent the initial presentation of ischemic or non-ischemic cardiomyopathy.

It is estimated that 350,000 out-of-hospital SCD's occur each year in the United States, with approximately 250,000 of these occurring in patients with coronary heart disease [2]. The second most frequent etiology associated with SCD includes patients with known or previously undiagnosed cardiomyopathies (hypertrophic or dilated). The precise epidemiology of SCD is difficult to determine because of the non-uniformity of various registries and definitions, and the absence of a national reporting system for collecting out-of-hospital cardiac arrest (OHCA) data [3]. Data from EMS attended out of hospital cardiac arrest may underestimate incidence of SCD while data from death certificates may overestimate it [4].

Additionally, it is difficult to quantify the incidence of VT not associated with cardiac arrest. Many patients with syncope and structural heart disease may be presumed to have had a VT event based on clinical evaluation and/or electrophysiologic testing. Patients may present with hypotensive VT and successfully cardioverted. These patients are not included in statistics of OHCA.

Patients with implantable defibrillators (ICD) have appropriate shocks or antitachycardia-pacing therapies for VT or VF and the annual incidence is difficult to quantify. In one meta-analysis, the incidence of appropriate ICD therapies in patients with ischemic cardiomyopathy who received ICDs for primary prevention indications ranged from 17 to 31% over mean follow-up of 22 months [5].

Appropriate ICD therapies may actually overestimate the incidence of sustained VT/VF since traditional detection algorithms responded within 5–15 s to an episode of VT or VF. Studies using delayed detection algorithms have shown decrease frequency of appropriate ICD therapies suggesting that traditional ICD detect/treatment parameters may have prematurely treated episodes of VT/VF that may have otherwise spontaneously terminated had the detection algorithm delayed therapies for a few more seconds [6].

VT/VF as the Mechanism of SCD

Overall survival rates are low for patients with out of hospital cardiac arrest; however survival rates are higher for patients presenting with VT/VF [1]. While VT/VF used to account for the majority of SCD events, recent data suggests that pulseless electrical activity and asystole account for an increasing proportion of SCD cases [7] (Table 16.1). Furthermore, the Resuscitation Outcomes Consortium has demonstrated that while the majority of out of hospital cardiac arrests occur at home, the proportion of initial VF or pulseless VT was greater if the first responder contact occurred in a public venue [8] (Fig. 16.1).

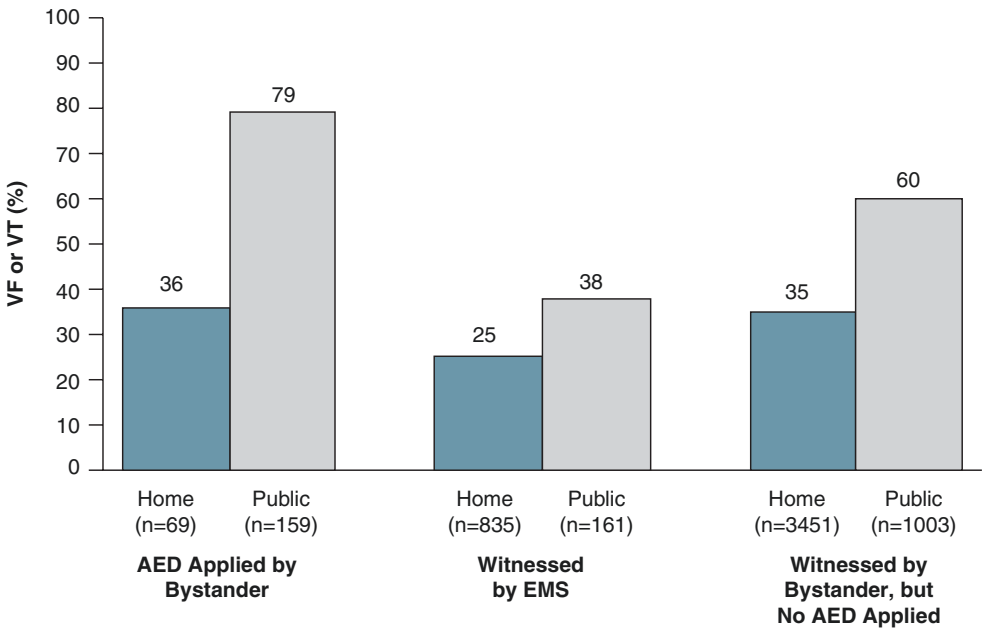


Fig. 16.1 This figure shows that the proportion of initial VF or pulseless VT as a cause of cardiac arrest was greater if the event occurred in a public venue. Reproduced with Permission from Weisfeldt et al. Resuscitation Outcomes Consortium I. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. *N Engl J Med*. 2011;364:313–21

Table 16.1 VT/VF in patients with structural heart disease

Clinical context	Incidence
Associated with out of hospital cardiac arrest	Approximately 25% of 250,000–4,000,000
Associated with in-hospital cardiac arrests	Approximately 40–50%
Associated with syncope	Unknown
Hypotensive VT not associated with cardiac arrest	Unknown
VT/VF resulting in appropriate ICD shocks	Approximately 6%/year of primary prevention (SCD-HeFT)

Coronary Heart Disease

SCD is associated with coronary heart disease in the acute, subacute and chronic phases of the disease. The presence of acute ischemia during an acute myocardial infarction has been reported to be associated with VT and/or VF in up to 4.5% of infarcts [9]. Approximately 15–25% of all unexplained SCD events are associated with an acute myocardial infarction.

After an acute myocardial infarction, the risk of SCD increases with a rate of 1.2–1.4% within the first 30 days post infarct [10, 11]. The risk is even higher in patients with congestive heart failure or depressed ejection fraction (EF). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT) [11], after the first months following MI, the risk of SCD progressively declined to approximately 1–2%/year. Other studies confirm an incidence of SCD of approximately 1.2%/year after myocardial infarction lasting until approximately 5 years [10].

Pathophysiology: Acute Ischemia

The pathophysiology and electrophysiological expressions of ventricular tachyarrhythmias during acute myocardial ischemia and the early evolution of myocardial infarction are complex and dynamic. The mechanisms that wax and wane during the first 24–48 h after the onset of ischemia (transient, or onset and progression of myocardial infarction) (Fig. 16.2), include re-entry, enhanced automaticity, and likely triggered activity [12] which can manifest as either monomorphic or polymorphic VT, accelerated ventricular rhythms, or ventricular fibrillation. Generally, arrhythmias occurring during this early phase of an ischemic event are not predictive of future recurrences. However, the subgroup that evolves into a completed infarction with a permanent and significant left ventricular dysfunction has a significant risk of VT/VF in the future, as opposed to the acute event. Recently described familial clustering of cardiac arrest as the initial manifestation of an acute coronary syndrome [13], suggests that there is a genetic contribution to ischemia-based arrhythmia risk. It also raises the yet unanswered question whether such events are predictive of the recurrence of VT/VF at the onset of a later recurrent ischemic event.

Transient Ischemia and the Onset on Myocardial Infarction

A few minutes of ischemia, whether transient or the initial part of the process heralding acute myocardial infarction, can create intense cellular electrophysiological changes in the

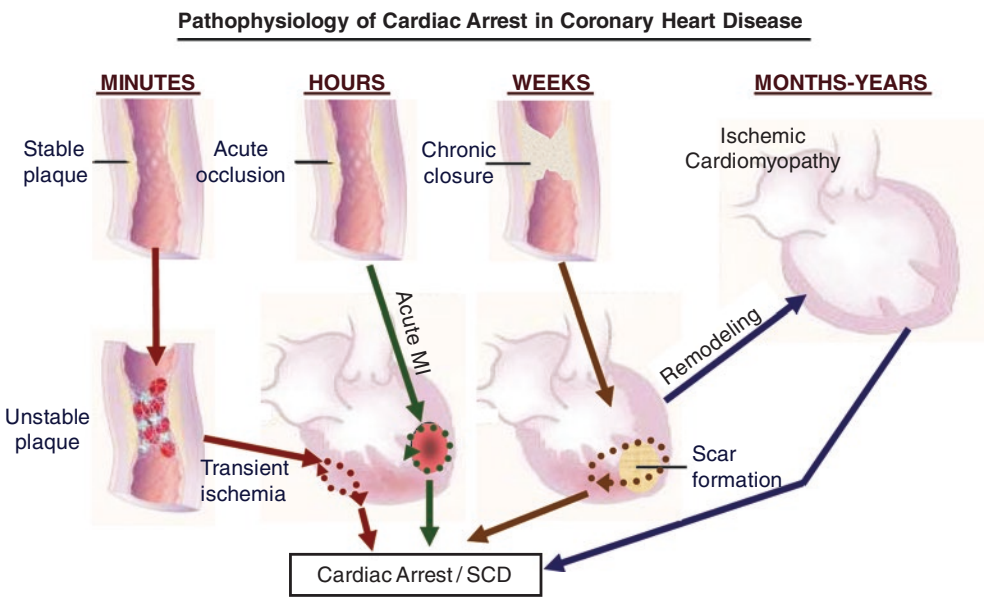


Fig. 16.2 This schematic shows dynamic changes from acute ischemia to chronic ischemic cardiomyopathy that can lead to VT/VF and SCD at any stage

region of ischemia. These include both slowing of the rate of depolarization and accelerated repolarization, the former slowing conduction velocity in the ischemic zone and the latter creating boundaries of heterogeneous recovery of excitability during the repolarization process. The combination of regions of slow conduction and non-uniform recovery of excitability provide the substrate for re-entrant arrhythmias, leading to the potential for the onset of VT or VF. During this very early phase of ischemia, this mechanism is transient but intense, and contributes to the relatively high risk of fatal ventricular tachyarrhythmias during this phase.

Reperfusion After Transient Ischemia

When myocardium is reperfused after a period of approximately 5–30 min of ischemia, whether due to reversal of coronary artery spasm or vasodilatation of a partially thrombosed lesion, another potential mechanism of arrhythmogenesis is initiated. There are substantial data demonstrating that reperfusion after short episodes of ischemia delays the time course of repolarization in the affected region, likely due to blunting of transmembrane potassium currents, in contrast to the acceleration of repolarization during acute ischemia. This sets the stage for Ca^{2+}-mediated afterdepolarizations that lead to triggered activity, which in turn can initiate VT, polymorphic ventricular tachycardia and the potential for initiation of VF. This phenomenon is time-sensitive in respect to the duration of ischemia before reperfusion and the short time that this mechanism persists. Specifically, experimental data suggests that this mechanism does not appear to be operative before 5 min of ischemia has elapsed and does not occur after approximately 30 min of ischemia [14, 15]. Thus, during reperfusion as a consequence of PCI 60–120 min after onset of myocardial infarction, this form of reperfusion-associated ventricular

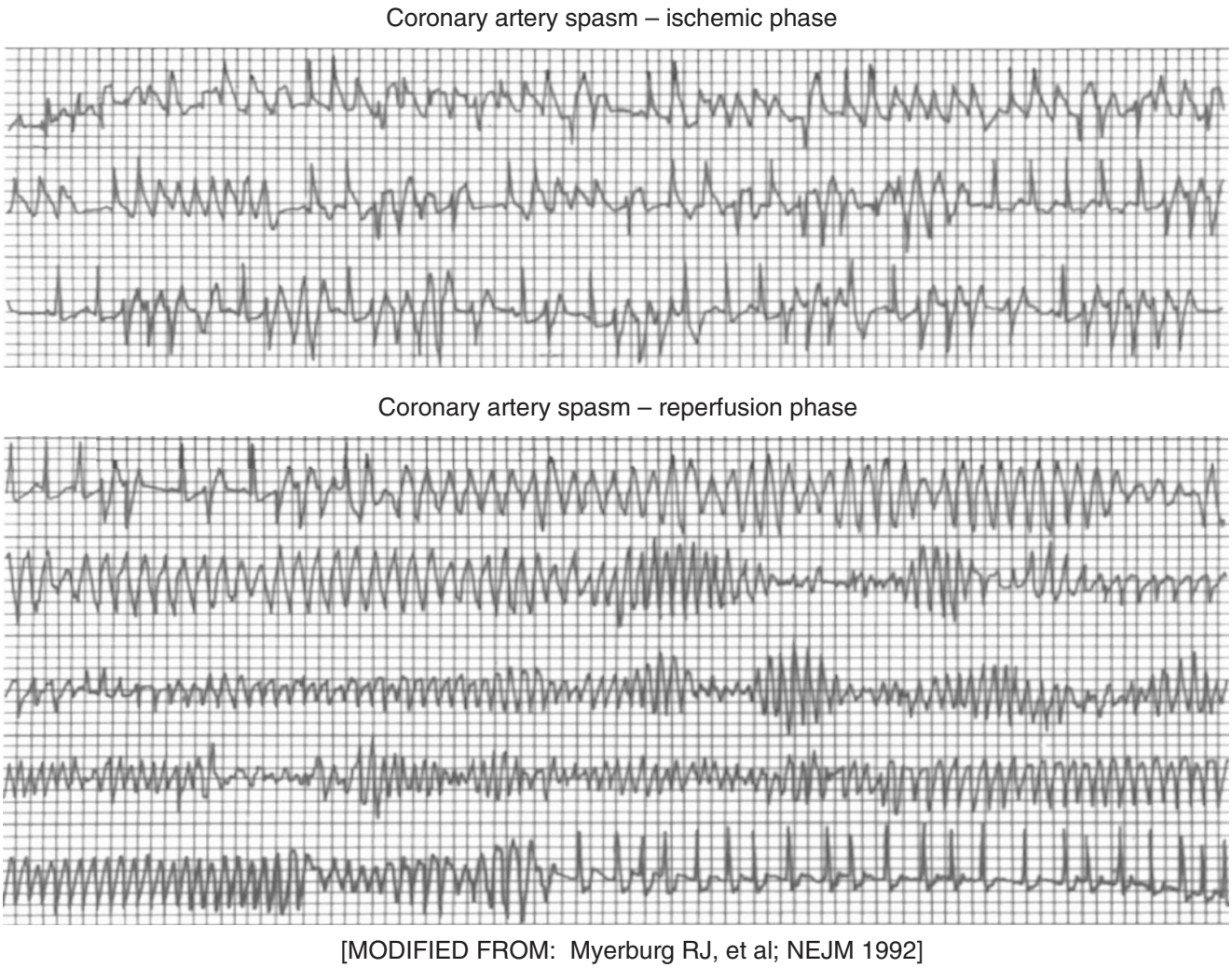


Fig. 16.3 This is an example of coronary spasm causing salvos of VT, which degenerates into VF. The patient had spontaneous conversion and thus did not have a SCD event. Modified from Myerburg RJ et al. NEJM 1992

tachyarrhythmia is not likely. In contrast, ischemia-reperfusion sequences associated with transient coronary artery spasm may trigger such events (see Fig. 16.3).

Enhanced Automaticity and Accelerated Ventricular Rhythms Shortly After Onset of Myocardial Infarction

Tissues capable of generating spontaneous phase 4 depolarization as a mechanism for normal automaticity, especially the specialized conduction tissue in the His-Purkinje system, are subject to enhanced impulse formation during ischemic injury. These tissues normally serve a backup subordinate to the normal sinus node rate. During an early phase of an ischemic event, particularly in the region of the inferior wall, these cells with subordinate pacemaker function may develop enhanced automaticity and usurp pacemaker function or an escape function interacting with sinus bradycardia due to an ischemia-mediated vagal reflex. When the latter occurs at a rate range of 60 to <100 per minute, it is termed an accelerated ventricular rhythm. At a rate exceeding 100 per minute, they are labeled a ventricular tachycardia due to increased automaticity. In the setting of inferior wall ischemia or the onset of infarction, these rhythms generally present within the first 12 h and abate spontaneously within 24–36 h. Unless very rapid and/or associated with hemodynamic consequences, they are best left untreated.

VT/VF During the First 48 h After the Onset of Myocardial Infarction

The acute phase of myocardial infarction is usually defined from the onset of symptoms through the first 48 h. This time period is pathophysiologically dynamic, in that the ischemic substrate is changing. The patterns associated with the onset of ischemia through the first 12 h have been discussed above in the context of transient ischemia. In reality, it is a challenge to distinguish transient ischemia from the initial minutes of a true myocardial infarction. However, VT/VF that occurs after the first few minutes, up to 48 h, is largely associated with slow conduction in the infarct zone, regional differences in repolarization, and variations in conduction patterns in and around the infarct. This substrate is the basis for re-entrant mechanisms of initiation of VT/VF. As is the case for spontaneous VT/VF during the first 48 h of a myocardial infarction, inducible VT during this period is not considered a reliable indicator of risk for VT/VF during the later healed or chronic phase of myocardial infarction (see below). If fact, lack of reliability of risk prediction of inducible VT after myocardial infarction may extend as far as 96 h after the onset [16, 17].

Cardiac Arrest During Early Convalescence

The early convalescent phase after myocardial infarction refers to the period from the end of the 48-h acute phase, through the weeks during which healing and scar formation is evolving. Beyond the first 4–6 weeks, the late convalescent phase merges into the chronic state. It has long been suggested that ventricular arrhythmias occurring during the convalescent phase predict the risk of SCD over time, in contrast to arrhythmias during the acute phase. The magnitude of arrhythmia-associated risk is greater when substantial myocardial damage has occurred, as reflected by the left ventricular EF. Studies from the early years of post–myocardial infarction risk assessment suggested that large anterior infarcts with low ejection fractions and new right bundle branch block indicated a 35% risk of SCD in 6 months. A more recent study has indicated that, despite modern therapies, a high risk remains over time, although its incidence is likely lower because of percutaneous interventions during the early acute phase of myocardial infarction. It also appears that the early convalescent phase (i.e., the first 3 months) is a higher-risk period in susceptible individuals. Data from VALIANT [11] demonstrated that a large proportion of post–myocardial infarction SCDs occur during this period, and the expression of risk is associated with a number of variables, including the size of the myocardial infarction and the ejection fraction. Even though the increased mortality during the early convalescent phase includes substantial risk of SCD, two studies have failed to demonstrate all-cause survival benefit attributable to ICDs when prescribed during the earlier convalescent phase [18, 19]. However, there was a subgroup benefit for arrhythmic deaths. The increase in non-arrhythmic deaths in the ICD recipients, compared with the conventional therapy group, remains unexplained.

Electrophysiologic Mechanisms

In patients with chronic CAD, the mechanisms for VT may involve reentry, triggered activity or enhanced depolarization. Patients with chronic CAD have areas of scar, and dysfunctional myocardium, which can lead to heterogeneous conduction and regions of slow conduction. Patients with greater degrees of left ventricular dysfunction and depressed EF are more likely to have greater scar burden and hence be at greater risk for VT/VF. Scarred myocardium intermingled with surviving cardiomyocytes leads to areas of anisotropic (nonuniform) conduction and dispersion of refractoriness. This leads to the substrate for reentry VT, which is the most common mechanism for VT.

In addition, other mechanisms come into play to promote VT. Enhanced sympathetic tone, regional sympathetic denervation, recurrent transient ischemia, and electrolyte abnormalities from pharmacologic therapy, all can interact with the diseased substrate to promote VT.

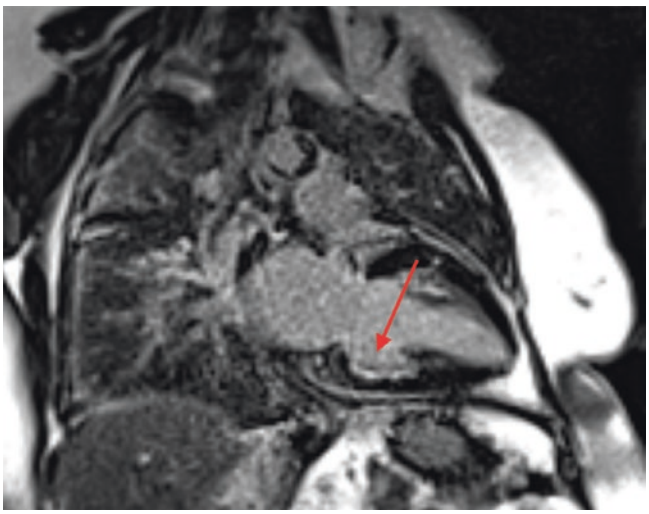


Fig. 16.4 This is an MRI coronal view with delayed enhancement using gadolinium contrast. It shows a subendocardial basal inferior scar. Courtesy, Dr. Joel Fishman, University of Miami, Miller School of Medicine

Table 16.2 Mechanisms of VT

	Reentry	Triggered activity	Enhanced automaticity
Manifest entrainment	Yes	No	No
Concealed entrainment	Yes	No	No
Reproducible induction by PES	Yes	Yes[a]	No
Inverse relationship of coupling interval to the interval preceding tachycardia	Yes	No	Not applicable
Bradycardia dependent	No	Yes	No
Warm up phenomena	No	Yes	Yes

[a]Triggered activity has two components: that related to repetitive responses/polymorphic VT which is a triggering event, and that which is related to re-entry which is often the mechanism for a persistent tachycardia. Either or neither may be inducible in the EP laboratory

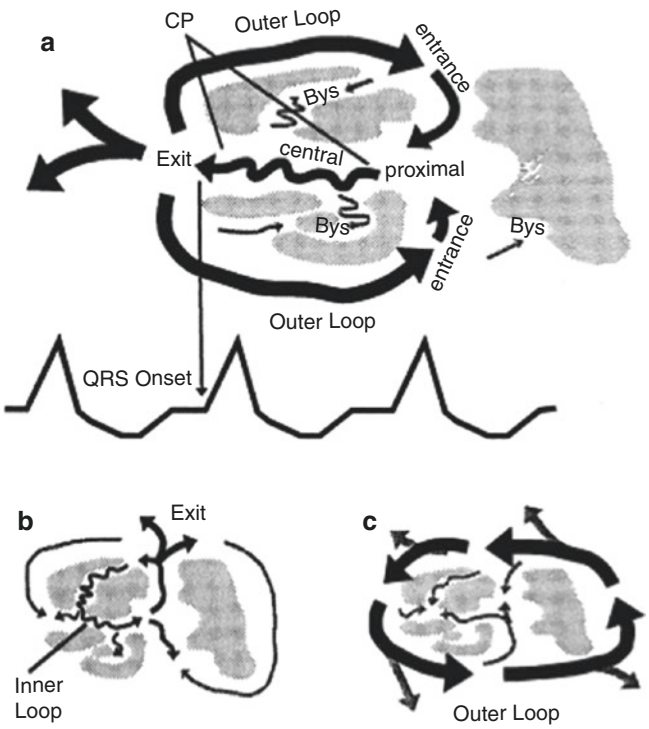


Fig. 16.5 Three theoretic reentry circuits depicted. In each panel, the reentry circuit is indicated by the **black arrows**. **Gray stippled areas** are inexcitable regions in the chronic infarct. Panel (**a**) shows a critical isthmus of tissue within the scar that exits the scar and forms a figure of 8 reentry using outer loop. There are channels of conduction within the scar labeled as bystander (Bys). Panels B and C show reentry loops contained wholly within areas of scar (**b**) or entirely external to the scar (**c**). The presence of channels within the scar that may or may not be critical to reentry adds to the complexity of these reentry circuits in patients with ischemic cardiomyopathy. Reproduced with permission from Stevenson WG et al. Exploring Postinfarction Reentrant Ventricular Tachycardia with Entrainment Mapping. J Am Coll Cardiol 1997; 29:1180–9

The incidence of sustained monomorphic VT following myocardial infarction has been substantially reduced due to therapeutic advances in coronary intervention and pharmacologic therapy. Nevertheless, the growing survival rates of patients after MI signifies that there is still a large population at risk. For those patients who develop sustained monomorphic VT following MI, the VT event may occur from weeks to years after the index infarction.

The anatomic basis for VT in patients with chronic ischemic cardiomyopathy has been demonstrated with imaging studies as well as electroanatomic mapping. Echocardiograms and CT scans demonstrate areas of myocardial thinning, and akinesis consistent with scar. MRI scan can delineate areas of scar with excellent spatial resolution (Fig. 16.4). Electroanatomic studies in humans have shown that areas of scar can be represented to correlate with endocardial bipolar voltages <0.5 mV whereas healthy tissue has bipolar voltages >1.5 mV. High-density electroanatomic mapping can uncover potential channels through or around areas of scar that can serve as substrate for reentry. Targeting these channels during catheter ablation procedures has been shown to reduce the risk of recurrent VT.

Electrophysiology testing is often helpful in confirming the mechanism of VT [12] (Table 16.2). Reproducible induction of VT using programmed electrical stimulation is the hallmark of reentrant VT. The reentry circuits can be quite complex and can involve multiple loops within broad areas of scar and diseased myocardium (Fig. 16.5). Electrograms from these areas usually show low amplitude fractionated potentials. During normal sinus rhythm, there may be delayed activation of local tissue and these late ventricular electrograms are not visible on standard ECG. However, during sinus rhythm, these late potentials form the basis for the use of Signal Average ECG, which can detect low amplitude late potentials.

The use of entrainment can be very useful in defining reentry mechanism of VT and also to guide catheter ablation [20, 21]. As shown in Fig. 16.5, the areas of scar, injured myocardium can be quite complex. Entrainment is a term that applies when there is external pacing during VT, which not only captures the ventricle, but also preserves conduction through the reentry circuit, and does not terminate VT. If pacing is done external to the reentry circuit, it is termed Manifest Entrainment, and the QRS complex would differ from the VT QRS complex morphology. If pacing is done within an area of slow conduction within the reentry circuit, it is termed Concealed Entrainment and the paced-QRS complex matches the VT QRS complex morphology. The use of concealed entrainment, in particular, can be used to guide catheter ablation of reentry VT.

Diseased myocardium can cause abnormal functioning of ion channels leading to other mechanisms of VT. Abnormal automaticity may arise from border zones during acute ischemia. Abnormal metabolism and increased oxidative stress can result in alterations of ion channels and be proarrhythmic. Additionally, the same abnormal metabolism and oxidative stress can affect vascular tone, and the autonomic nervous system which can interact with diseased myocardium to produce an arrhythmogenic state [22].

VT due to triggered activity may also be induced by programmed extrastimuli, rapid pacing, or infusion of catecholamines. However, on occasion trigged VT cannot be induced at all in the EP laboratory, particularly if patients are sedated. Triggered VT, like atrial tachycardia, generally demonstrates a 'warm-up' phenomenon. Additionally, there is a different response of triggered VT vs. reentry VT to differing coupling intervals during programmed extrastimuli [12] (Table 16.2). Triggered VT is described as a "focal" arrhythmia as opposed to the reentrant nature of scar-mediated VT.

After-depolarizations occur in calcium overload states, particularly in the case of delayed after-depolarization (DAD). Rapid rates exacerbate DADs, which can trigger VT. Early after-depolarization (EADs) have been linked with multiple channel abnormalities including L-type calcium, potassium rectifier currents and late sodium current as well as the Ca-Na exchange. EADs also may be bradycardia dependent (Table 16.2).

Action potential prolongation is a mechanism associated with initiation of life-threatening arrhythmias and cardiac arrest due to VT/VF in patients with heart failure from any etiology [23]. Reductions in potassium currents can lead to the prolonged action potential duration and be arrhythmogenic. Dispersion of refractoriness on a temporal and spatial basis may form the basis of arrhythmias. Alteration of calcium homeostasis has been described in heart failure. Calcium overload states, coupled with other electrophysiologic abnormalities can predispose to ventricular arrhythmias, particularly EADs.

The I_{Na} current is also disrupted in heart failure and may predispose to arrhythmias. It is known that patients with more advanced heart disease have abnormalities in conduction manifested by widened QRS complex. This may be a manifestation of delayed conduction due to alterations in I_{Na} current.

Myocardial infarction may cause areas of regional sympathetic denervation resulting in denervated myocardium that may be supersensitive to catecholamines [24]. Sympathetic nerve sprouting and reinnervation occur after myocardial infarction. Moreover, hyperinnervation has been also shown to be linked with increased propensity for VT/VF [25].

Augmented adrenergic tone has been well described in coronary artery disease, particularly in patients with systolic dysfunction. Markers of enhanced sympathetic tone, such as reduced heart rate variability has been associated with increased risk for VT/VF [26]. Increase in adrenergic tone and circulating catecholamines may interact an infarcted heart with regional heterogeneity of sympathetic innervation/denervation. The denervated myocardium responds to enhanced sympathetic tone and catecholamines with exaggerated shortening of refractory periods leading to disparity of refractory periods across myocardial tissue. Furthermore, such tissue is susceptible to lower threshold for VF induction. Consistent with this notion was the finding that there were more ICD shocks for VT/VF after the 9/11/2001 attacks; a time of heightened stress among the subjects studied [27].

Many therapies aimed at preventing VT/VF are based on reducing adrenergic tone supplied to and within the ventricles. Beta blockers have been shown in multiple studies to reduce VT/VF and SCD [28]. There is growing evidence that vagal stimulation is antiarrhythmic [29] although the precise role for muscarinic stimulation and mechanisms of action remain unclear. Lastly, bilateral sympathetic denervation has been shown to be effective in patients with VT storm refractory to pharmacologic and/or catheter ablation therapy [30].

Onset of VT/VF

In patients with structural heart disease, the onset of VT generally requires premature ventricular complexes (PVCs). The PVCs often are due to triggered activity or abnormal automaticity and fall outside the area of the reentrant arrhythmias. Sustained repetitive PVCs can lead to heterogeneous conduction and formation of reentrant circuits.

It is not uncommon for VT to degenerate to VF, particularly with rapid monomorphic VTs or polymorphic VTs. Rapid rates can lead to wide dispersion of refractoriness, which in turn may cause formation of other reentry circuits and consequently VF. Ischemia, especially when nonuniform, often plays a central role in the initiation of VT or its transition to VF. The role of ischemia can work in two ways. Transient ischemia altering the electrophysiological state of a vulnerable scarred area can be responsible for the initiation of

monomorphic or polymorphic VT, or VF. Conversely, the encroachment on diastolic flow in a diseased coronary artery during a tachycardia can induce sufficient ischemia to transition a VT to VF, or initiate VT de novo. The initiation of ischemia during VT and particularly during VF enhances this transformation to VF. Other mechanisms such as dynamic wavelet reentry, rotor waves and Purkinje system activation likely play a role in the maintenance of VF [31].

Treatment of VT

Treatment and prevention of VT in patients with ischemic cardiomyopathy should include optimal medical therapy and revascularization of the underlying coronary artery disease and left ventricular dysfunction, if present. Specific therapies for patients who have VT include antiarrhythmic drugs (see Chap. 8), implantable cardioverter defibrillator (Chap. 11), and/or catheter ablation (Chap. 12) [32, 33]. In general, the occurrence of VT and/or VF in patients with ischemic cardiomyopathy in the absence of reversible causes is an indication for an implantable cardioverter defibrillator (ICD) [34, 35]. Furthermore, many patients with low ejection fraction despite optimal pharmacologic therapy fulfill criteria for ICD [33, 34]. However, additional therapy may be indicated to prevent episodes of VT/VF that may cause the patient syncope, ICD shocks or other symptoms.

The use of antiarrhythmic drugs is generally guided by the underlying heart disease and LV function. Since many of these patients have LV dysfunction and concomitant CHF, amiodarone is commonly used. Other potassium channel blocker such as sotalol or dofetilide may be considered if there exists contraindication, high risk or manifest side effects of amiodarone, or reluctance to initiate amiodarone. Although sotalol may not have the same level of efficacy as amiodarone for ambient arrhythmia or ICD therapy reductions, it does not share the same long term organ toxicity profile, and may be equivalent or preferred therapy for patients with low EFs without heart failure. When selecting a class III antiarrhythmic medication in patients with SHD, it is crtically important to ensure normal renal function in order to minimize the risk of torsades. The Class Ic drugs are contraindicated in patients with coronary artery disease as their use lead to increased mortality in the CAST trial [36]. However, class Ib agents like mexiletine, while not commonly used, may be combined with amiodarone to control patients with multiple recurrences of VT and/or VF. Nevertheless, the currently available antiarrhythmic drugs have not been shown to prolong survival or reduce mortality in multiple randomized controlled trials [33]. Therefore, the use of these drugs is generally intended to reduce ventricular arrhythmia burden, which may be causing symptoms and/or ICD therapies.

Catheter ablation for VT plays a useful role in treatment of VT in patients with ischemic cardiomyopathy [32]. Prospective studies have shown reduction of ICD shocks and ICD therapies in patients with history of myocardial infarction who had received ICDs for secondary prevention [37, 38]. For patients with drug-refractory ventricular tachycardia in the presence of coronary artery disease, the use of catheter ablation may eliminate or modify inducible VT in up to 80% of patients and eliminate VT during intermediate follow-up (approx. 3 years) in up to 60% of patients [39]. However, in one single site study, complication rates were noted to be 5.6% in patients >75 years and 2.3% in patients younger than 75 years [39].

VT/VF in Patients with Nonischemic Cardiomyopathy

Nonischemic cardiomyopathy (NICM) comprises a broad spectrum of disorders, accounting for up to 15–20% of SCDs. Some of the disorders such as arrhythmogenic right ventricular dysplasia/cardiomyopathy (Chap. 20) or hypertrophic cardiomyopathy (Chap. 20) are covered elsewhere. There are some similarities in diagnosis, pathophysiology, mechanism of VT and treatment between patients with history of CAD and those with nonischemic cardiomyopathy. Depending on the etiology of the NICM, patients may present at a younger age than those with ischemic heart disease as the basis of the VT/VF. Different terms, such as idiopathic dilated cardiomyopathy, NICM, dilated cardiomyopathy (DCM) have overlapping definitions. For example, a patient with DCM presumed secondary to alcohol abuse may be characterized as having NICM or DCM but would not be characterized as having idiopathic DCM. Thus the use of different terms and definitions needs to be accounted when examining statistics and epidemiology within the spectrum of DCM.

Dilated Cardiomyopathy

DCM is notable for areas of patchy fibrosis, hypertrophy and myocyte necrosis, which can lead to an arrhythmia substrate [40]. Unlike fibrosis patterns in ischemic cardiomyopathy, which tend to be large and follow anatomic areas from coronary occlusion, fibrosis in DCM tends to be characterized by patchy areas of fibrosis, that are generally not as large as that seen in ischemic cardiomyopathy. These regions of scarring are often clustered at the annuli, mid-myocardial, and epicardial myocardium. The tendency for more mid-myocardial and/or epicardial scarring has implications for ablation

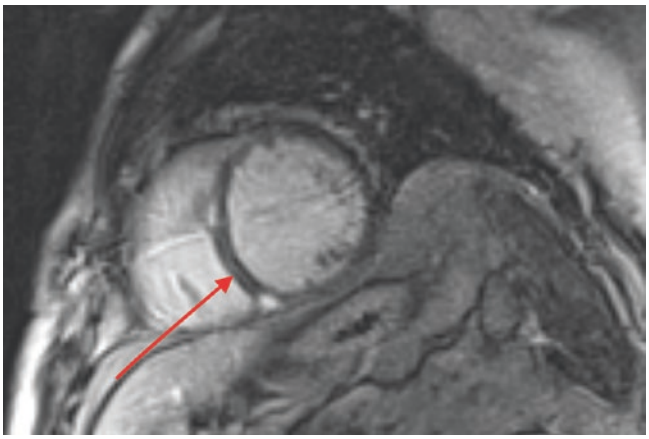


Fig. 16.6 This is an MRI coronal view with delayed enhancement using gadolinium contrast. It shows a thin line of delayed enhancement typical midwall septal enhancement of NICM as well as enhancement at the inferior right ventricular-septal insertion point which can also be present in NICM (as well as elevated R side pressures). Courtesy, Dr. Joel Fishman, University of Miami, Miller School of Medicine

therapy (Fig. 16.6). Additionally, fibrosis tends to be progressive in patients with DCM. Greater amounts of myocardial fibrosis may be predictive of ventricular arrhythmias independent of LVEF [41, 42]. Thus, increasing myocardial burden of patchy fibrosis sets up the substrate for ventricular arrhythmias.

Patients who present with left ventricular dilatation in the absence of any other causes (i.e. valvular heart disease, known infiltrative heart disease) have been labeled as having idiopathic dilated cardiomyopathy (IDCM). In up to 50% of these patients, a familial component has been identified [43]. The prevalence of familial DCM is approximately 1:2000 in the US. Recent guidelines have recommended comprehensive or targeted genetic testing of LMNA and SCN5A in patients with a familial pattern of DCM and conduction system disorder, or a family history of sudden cardiac death [43]. Variants have been identified in >50 genes [44], and the identification of genetic mutations in patients with IDCM continues to grow. Thus, genetic testing in any patient with familial DCM should be considered. Because it is common to identify a variant of uncertain or unknown significance, suggesting a previously unreported variant in a relevant gene, interpretation of these findings can be challenging unless multiple family members carry the variant *and* are affected clinically.

The use of genetic testing has not advanced sufficiently to reliably identify those patients at high or conversely low risk for VT/VF. Nevertheless, mutations in the LMNA has been linked with electrical instability and conduction system disease such that patients may be at risk for SCD prior to the onset of heart failure [44].

Pathophysiology

The pathophysiology of VT/VF in patients with DCM is similar to that in patients with ischemic heart disease. MRI may demonstrate patchy areas of scar that do not follow a typical distribution for coronary artery disease. Furthermore, patients with DCM are more likely to have areas of epicardial and/or mid-myocardial scar as compared with patients with ischemic cardiomyopathy. Electroanatomic mapping may show corresponding areas of scar manifested by low voltage on the endocardial and epicardial surface of the heart. The presence of myocardial scar intermingled with areas of diseased myocardium set up the substrate for reentry. Because of this anatomic distribution of scar and fibrosis, patients with VT in the setting of DCM may be more likely to require an epicardial approach during catheter ablation.

Bundle branch reentry VT (BBR-VT) is a macroreentrant VT utilizing the His Purkinje system. This is also more common in patients with DCM. Typically, the patients with BBR-VT have reentry with antegrade conduction through the right bundle, and retrograde conduction through the left bundle with completion of the circuit in the His Bundle. Patients with BBR-VT typically present with left bundle branch block or nonspecific intraventricular conduction delay at baseline. During invasive EPS, the HV interval is prolonged. The use of entrainment and other techniques confirm the diagnosis. The confirmation of this type of VT in patients is important, as the therapy would be ablation of the right bundle branch [45].

The most common mechanism for VT in patients with DCM is reentry in and around the areas of scar and fibrosis. Electroanatomic mapping has demonstrated areas of low voltage and/or abnormal local electrograms in areas where VT was mapped and ultimately ablated [40, 46].

Similar to patients with ischemic cardiomyopathy, other mechanisms may play a role in VT in patients with DCM including enhanced automaticity and triggered activity. Regional cardiac sympathetic denervation has been described in patients with DCM with mismatches between I-123 MIBG scans and corresponding Thallium scans [47]. Thus areas of denervated myocardium may be supersensitive to circulating catecholamines resulting in heterogeneous repolarization.

Predictors of VT/VF and SCD in Patients with DCM

As compared with patients with ischemic cardiomyopathy, there are some similarities and differences in terms of predictors of VT/VF and SCD. Similar to patients with ICM, left ventricular ejection fraction (LVEF) inversely correlates

with overall survival. Clinical indicators, such as heart failure and its severity and increased pulmonary pressure, also are predictive of SCD [48]. Development of atrial fibrillation has also been correlated with lower survival [49] among patients with DCM.

The presence of left bundle branch block (LBBB) is particularly ominous in patients with DCM. In one series, the presence of LBBB in patients with DCM identified a cohort with lower LVEF, and higher incidence of syncope, although the risk of spontaneous or induced VT was not increased [50].

Programmed ventricular stimulation, to induce VT, has not been shown to be as reliable or reproducible in patients with DCM as compared with patients with ischemic cardiomyopathy [51]. Programmed ventricular stimulation is not sufficiently accurate in predicting future VT/VF events in patients with DCM to be incorporated into guidelines recommending its use for risk stratification in these patients. The induction of polymorphic VT or VF may represent a nonspecific response. However, in patients with DCM presenting with wide QRS complex tachycardia, an electrophysiology study would be reasonable to elucidate the mechanism of the tachycardia.

A meta-analysis of 45 studies involving 6088 patients with DCM was performed to examine association between predictive tests and ventricular arrhythmia outcomes [52]. In this study, the odds of future SCD was greatest in the presence of fragmented QRS complexes and positive T wave alternans while none of the autonomic tests were significant predictors. Interestingly, the finding of LBBB or wide QRS complex was not a significant predictor in this meta-analysis.

Therapy to Prevent and Treat VT/VF in Patients with DCM

Standard guideline directed therapy is quite effective in patients with DCM [33, 34, 53, 54]. The use of beta-blockers is recommended in all patients with DCM to reduce the risk of ventricular arrhythmia, SCD, and progression of heart failure.

The use of ICDs, should be considered for patients who fulfill criteria. Multiple studies have confirmed that patients with DCM derive similar benefit from ICD therapy, compared with patients with ischemic cardiomyopathy. For patients who have had a VT/VF event, in the absence of reversible cause, an ICD is a Class 1 indication. Similarly, for patients with DCM and reduced LVEF, and syncope thought to be due to ventricular arrhythmia, ICD implantation is also reasonable. Additionally, based on the SCD-HeFT [55], and other earlier trials, patients with DCM and LVEF $\leq$ 35%, despite optimal pharmacologic therapy benefit from primary prevention ICD. However, the recently published DANISH trial raised questions as to the survival benefit of primary prevention ICDs in patients with DCM, primarily idiopathic DCM, and low EF [56]. Although SCD rate was reduced by 50% in the ICD arm, there was no significant mortality reduction over a mean of 6.7 years. A subgroup of patients younger than 68 years did demonstrate survival benefit.

Patients with genetic abnormalities such as Lamin A/C mutations or patients with LV noncompaction, carry a sufficiently high risk that ICD may be warranted.

Cardiac resynchronization therapy has been shown to be quite effective for reducing overall mortality and CHF symptoms in appropriately selected patients with wide QRS complex, generally LBBB, and cardiomyopathy from any etiology [34, 53, 57]. The effect of CRT on ventricular tachyarrhythmias is less certain. In a sub-study from the MADIT-CRT Trial, it was noted that normalization of LVEF was associated with a very low absolute and relative risk for VT/VF [58]. In this sub-study, the presence of NICM was one of the factors on multivariate analysis that predicted normalization of LVEF and consequently marked reduction of VT/VF. Other factors included LBBB, female gender, LVEF > 30% and absence of severe left ventricular or left atrial enlargement [58]. A recent meta-analysis of six studies including data on patients who underwent CRT therapy suggested that improvement of LVEF was associated with lower risk for appropriate ICD therapies for VT/VF [59]. Approximately half the patients in this meta-analysis had NICM.

Special Populations

Alcoholic Cardiomyopathy

Heavy and regular alcohol consumption is a known cause of nonischemic DCM [60]. In particular, daily and chronic consumption of over 90 g of alcohol can lead to a DCM. Alcoholic cardiomyopathy may account for up to 35% of all cases of nonischemic DCM in Western countries [60]. Acute and chronic alcohol use and abuse has been associated with atrial arrhythmias, particularly atrial fibrillation. However, there is growing evidence that patients with alcoholic DCM are susceptible to ventricular arrhythmias. In one study comparing patients with alcoholic DCM vs. those with idiopathic DCM, only the presence of LBBB and alcohol mediated DCM were associated with malignant ventricular arrhythmias [61].

Left Ventricular Non-compaction (LVNC)

LVNC is a cardiomyopathy thought to result from lack of normal compaction process of myocardial fibers in utero. The clinical manifestations from LVNC include CHF,

thromboembolism, VT, VF, and SCD [62]. From a pathophysiologic standpoint, the myocardium is characterized by a spongy morphologic appearance. There are deep intertrabecular recesses within the hypertrophied myocardium, which can serve as a substrate for macro or micro-reentrant VT. LVNC may comprise up to 9% of all newly diagnosed cardiomyopathies [63].

There are a number of mutations identified in LVNC [43, 62, 63]. There have been reports of X-linked recessive gene inheritance, autosomal dominant, autosomal recessive, and mitochondrial inheritance patterns, although sporadic cases seem to predominate. Abnormalities have been identified in cytoskeletal, sarcomeric and ion channel genes. Despite the multiple possible abnormal mutations, genetic testing has not been shown to be useful in terms of individual risk prediction or to guide therapy.

Ventricular arrhythmias are prevalent in patients with LVNC, expressing in 0 -47% of affected patients in published series [63]. SCD may account for over 50% of the total mortality. Therefore, there is heightened concern that patients with LVNC may be at risk for ventricular arrhythmias and thus require an ICD. There are no uniform guidelines for risk factors for VT/VF in patients with LVNC. Indications for an ICD are similar to other patients with dilated cardiomyopathy. The presence of syncope or VT would identify a higher risk cohort [62].

Amyloid

Cardiac amyloidosis belongs to the category of infiltrative cardiomyopathies resulting from deposition of proteinaceous material in the heart [64, 65]. The most common types of amyloid include AL amyloidosis resulting from abnormal light changes produced by plasma cell dyscrasia, familial amyloidosis due to mutation in the transthyretin (TTR) gene, or wild type TTR that results in senile systemic amyloidosis. Amyloid cardiomyopathy associated with a TTR variant is generally a late-onset phenomenon—age generally >50 years—in contrast to those associated with proteinopathies. Amyloid can cause atrial and ventricular tachyarrhythmias and there exists increased risk for SCD. Traditionally, the prognosis for patients with cardiac amyloid has been poor, especially once heart failure has occurred. Furthermore, the mode of SCD was thought to be due to non VT-VF rhythms (atrioventricular block, asystole, and electro-mechanical dissociation). Therefore, there was limited rationale for implantable cardioverter defibrillators [65]. However, a recent study from the Mayo Clinic showed 32% appropriate ICD therapies in the first year of after implant (2000–2009) in patients with amyloid, most notably in the patients with AL amyloid and in those with prior ventricular tachyarrhythmias [66]. However, despite the high rate of appropriate ICD therapies, there was no apparent survival benefit associated with ICD implantation. More recently, the overall treatment of amyloid has advanced with specific treatments geared towards the different amyloid subtypes [67]. This has resulted in longer survival. Furthermore, in a study from Stanford University, it was noted that patients with amyloid have a high prevalence of nonsustained VT (74%) as well as sustained VT/VF (19%) [68]. Based on their findings they proposed that patients with amyloidosis who do not have Class IV CHF and have >1 year expected survival should be considered for ICD if they have syncope or if they have findings of nonsustained VT on ambulatory monitoring [68].

Sarcoid Cardiomyopathy

Sarcoid cardiomyopathy is a disorder of unknown etiology with pathologic findings of non-caseating granulomas in the myocardium. This disorder is seen more often in women and in African Americans. Although there is typically other organ involvement, particularly the lungs, isolated cardiac Sarcoid is not rare. The hallmark of cardiac Sarcoid is conduction abnormalities, ventricular dysrhythmias and heart failure [69, 70]. LV dysfunction is also a prominent feature of this disease. Diagnosis of cardiac Sarcoid may be difficult. Cardiac biopsies, although highly specific, have a low yield secondary to the patchy distribution of the granulomas. Imaging with MRI or PET may be helpful [69, 70]. Patients with Sarcoid cardiomyopathy should receive standard therapy for cardiomyopathy, particularly for LV dysfunction, if present. Furthermore, patients with Sarcoid generally are treated with immunosuppressive therapy.

Involvement of the cardiac conduction system can cause AV block. In fact, young patients (<60 years of age) with unexplained or high degree AV block should be worked up for cardiac Sarcoid [69]. Retrospective studies have suggested that Cardiac Sarcoid may be diagnosed in 19–34% of such patients [70]. In patients with cardiac sarcoid and AV Block, consideration should be given to implant of a combined dual chamber pacing-ICD device rather than a standard dual chamber pacemaker [69, 71].

Granulomas in either ventricle may make the patient susceptible to ventricular tachyarrhythmias Ventricular arrhythmias are related to scar formation, and reentry is likely the most common mechanism [69–72]. The management of ventricular arrhythmias in patients with Cardiac Sarcoid is similar to that of patients with structural heart disease [32, 73]. The treatment of ventricular arrhythmias in patients with Cardiac Sarcoid include antiarrhythmic drugs, ICD and/or catheter ablation [32, 69, 72, 73]. In addition, for patients in whom myocardial inflammation is documented with FDG-PET, immunosuppression can be useful to manage the ventricular arrhythmias [69].

ICD would be recommended for patients with prior sustained ventricular arrhythmias or aborted SCD [69].

Recommendations for risk stratification in patients with Cardiac Sarcoid should follow general recommendations for patients with NICM [35, 74]. However, in contrast to patients with other NICMs, there may be a role for programmed ventricular stimulation to assist in risk stratification [69, 71], particularly in patients who are perceived to be at increased risk for ventricular arrhythmias who do not meet standard criteria. An example would be a patient presenting with syncope who has Cardiac Sarcoid and EF greater than 35%. A specific Class IIb recommendation for ICD unique to patients with Cardiac Sarcoid would include those patients with EF 35–49% who have right ventricular dysfunction with RVEF < 40% [69].

Conclusion

Patients with ischemic or nonischemic cardiomyopathy are prone to malignant ventricular tachyarrhythmias. There are diverse etiologies to cardiomyopathy. However, the pathophysiology of VT is similar. For many patients, there may be reentry in ventricular myocardium around areas of scar that can lead to VT. Furthermore, other mechanisms may also play a role such as triggered activity or enhanced automaticity. There has been advances in cardiac imaging with use of MRI scan and use of three dimensional electro-anatomical mapping that have increased our understanding of the mechanisms of VT as well as provide guide for catheter ablation. Genetic testing is currently used to identify and categorize patients with nonischemic cardiomyopathy. In the future, genetic testing may enable us to provide patients with a more personalized approach in terms of risk prediction of VT/VF and therapeutic options. For now, there is no question that Guideline-directed therapy for patients with cardiomyopathy can prolong survival and reduce risk of sudden cardiac death. Other therapies such as antiarrhythmic drugs and implantable defibrillators play a crucial role in prevention and treatment of VT/VF.

References

1. Mitrani RD, Myerburg RJ. Ten advances defining sudden cardiac death. Trends Cardiovasc Med. 2016;26(1):23–33.
2. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. Circulation. 2012;125(8):1043–52.
3. Arrest CotToC. Strategies to improve cardiac arrest survival: a time to act. Washington, DC: Institute of Medicine of the National Academies; 2015. Report No
4. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. Circ Res. 2015;116(12):1887–906.
5. Gracieux J, Sanders GD, Pokorney SD, Lopes RD, Thomas K, Al-Khatib SM. Incidence and predictors of appropriate therapies delivered by the implantable cardioverter defibrillator in patients with ischemic cardiomyopathy: a systematic review. Int J Cardiol. 2014;177(3):990–4.
6. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med. 2012;367(24):2275–83.
7. Myerburg RJ, Halperin H, Egan DA, Zipes DP. Pulseless electric activity. Definition, causes, mechanisms, management and research priorities for the next decade: report from a NHLBI Workshop. Circulation. 2013;128(23):2532–41.
8. Weisfeldt ML, Everson-Stewart S, Sitlani C, Rea T, Aufderheide TP, Atkins DL, et al. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. N Engl J Med. 2011;364(4):313–21.
9. Thompson CA, Yarzebski J, Goldberg RJ, Lessard D, Gore JM, Dalen JE. Changes over time in the incidence and case-fatality rates of primary ventricular fibrillation complicating acute myocardial infarction: perspectives from the Worcester Heart Attack Study. American Heart J. 2000;139:1014–21.
10. Adabag AS, Therneau TM, Gersh BJ, Weston SA, Roger VL. Sudden death after myocardial infarction. JAMA. 2008;300(17):2022–9.
11. Solomon SD, Zelenkofske S, McMurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfuntion, heart failure or both. N Engl J Med. 2005;352:2581–8.
12. Anter Elad JM. Ischemic heart disease. In: Zipes DP, Jalife J, editors. Cardiac electrophysiology: from cell to bedside. Philadelphia: Elsevier; 2014. p. 849–58.
13. Dekker LR, Bezzina CR, Henriques JP, Tanck MW, Koch KT, Alings MW, Arnold AE, de Boer MJ, Gorgels AP, Michels HR, Verkerk A, Verheugt FW, Zijlstra F, Wilde AA. Familial sudden death is an important risk factor for primary ventricular fibrillation. Circulation. 2006;114:1140–5.
14. Coronel R, Wilms-Schopman FJ, Opthof T, Cinca J, Fiolet JW, Janse MJ. Reperfusion arrhythmias in isolated perfused pig hearts: inhomogeneities in extracellular potassium, ST and TQ potentials, and transmembrane action potentials. Circ Res. 1992;71:1131–42.
15. Kimura S, Cameron JS, Kozlovskis PL, Bassett AL, Myerburg RJ. Delayed afterdepolarizations and triggered activity induced in feline Purkinje fibers by α-adrenergic stimulation in the presence of elevated calcium levels. Circulation. 1984;70:1074–82.
16. Piccini JP, White JA, Mehta RH, Lokhnygina Y, Al-Khatib SM, Tricoci P, Pollack CV, Montalescot G, Van de Werf F, Gibson CM, Giugliano RP, Califf RM, Harrington RA, Newby LK. Sustained ventricular tachuycardia and ventricular fibrillation complicating non-ST segment elevation acute coronary syndromes. Circulation. 2012;126:41–9.
17. Avezum A, Piegas LS, Goldberg RJ, Brieger D, Stiles MK, Paolini R, Huang W, Gore JM. Magnitude and prognosis associated with ventricular arrhythmias in patients hospitalized with acute coronary syndromes (GRACE Registry). Am J Cardiol. 2008;102:1577–82.
18. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ, DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004;351(24):2481–8.
19. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, Kornacewicz-Jach Z, Sredniawa B, Lupkovics G, Hofgartner F, Lubinski A, Rosenqvist M, Habets A, Wegscheider K, Senges J, IRIS Investigators, Defibrillator implantation early after myocardial infarction. N Engl J Med. 2009;361(15):1427–36.
20. Stevenson WG FP, Sager PT, Saxon LA, Kocovic D, Harada T, Wiener I, Khan H. Coll Cardiol. 1997;29(6):1180–9.
21. Waldo AL. From bedside to bench: entrainment and other stories. Heart Rhythm. 2004;1(1):94–106.
22. Yang KC, Kyle JW, Makielski JC, Dudley SC Jr. Mechanisms of sudden cardiac death oxidants and metabolism. Circ Res. 2015;116:1937–55.
23. Tomaselli G, Zipes DP. What causes sudden death in heart failure? Circ Res. 2004;95:754–63.

24. Inoue H, Zipes DP. Results of sympathetic denervation in the canine heart: supersensitivity that may be arrhythmogenic. Circulation. 1987;75(4):877–87.
25. Ogawa M, Zhou S, Tan AY, Fishbein MC, Lin SF, Chen LS, et al. What have we learned about the contribution of autonomic nervous system to human arrhythmia? Heart Rhythm. 2009;6(8 Suppl):S8–11.
26. Huikuri HV, Stein PK. Heart rate variability in risk stratification of cardiac patients. Progr Cardiovasc Dis. 2013;56(2):153–9.
27. Steinberg JS, Arshad A, Kowalski M, Kukar A, Suma V, Vloka M, et al. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. J Am Coll Cardiol. 2004;44(6):1261–4.
28. Al-Gobari M, El Khatib C, Pillon F, Gueyffier F. β-Blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2013;13:52.
29. Brack KE, Winter J, Ng GA. Mechanisms underlying the autonomic modulation of ventricular fibrillation initiation--tentative prophylactic properties of vagus nerve stimulation on malignant arrhythmias in heart failure. Heart Fail Rev. 2013;18(4):389–408.
30. Vaseghi M, Gima J, Kanaan C, Ajijola OA, Marmureanu A, Mahajan A, et al. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: intermediate and long-term follow-up. Heart Rhythm. 2014;11(3):360–6.
31. Dosdall DJ. Mechanisms of ventricular tachycardia and fibrillation. In: Zipes DP, Jalife J, editors. Cardiac electrophysiology: from cell to bedside. Philadelphia: Elsevier; 2014. p. 475–82.
32. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E, et al. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart Rhythm. 2009;6(6):886–933.
33. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36(41):2793–867.
34. Russo AMSR, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 Appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy. J Am Coll Cardiol. 2013;61(12):1323–73.
35. Tracy CM, Epstein AE, Darbar D, Dimarco JP, Dunbar SB, Estes NA III, et al. 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Heart Rhythm. 2012;9(10):1737–53.
36. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo. The cardiac arrhythmia supprsion trial. N Engl J Med. 1991;324:781–8.
37. Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K, Kralovec S, Sediva L, Ruskin JN, Josephson ME. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med. 2007;357:2657–65.
38. Kuck KH, Schaumann A, Eckardt L, Willems S, Ventura R, Delacretaz E, Pitschner HF, Kautzner J, Schumacher B, Hansen PS, VTACH study group. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. Lancet. 2010;375:31–40.
39. Inada K, Roberts-Thomson KC, Seiler J, Steven D, Tedrow UB, Koplan BA, et al. Mortality and safety of catheter ablation for antiarrhythmic drug-refractory ventricular tachycardia in elderly patients with coronary artery disease. Heart Rhythm. 2010;7(6):740–4.
40. Kumar S, Stevenson WG, John RM. Arrhythmias in dilated cardiomyopathy. Card Electrophysiol Clin. 2015;7:221–33.
41. Gulati A, Jabbour A, Ismail TF, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA. 2013;309(9):896–908.
42. Iles L, Pfluger H, Lefkovits L, Butler MJ, Kistler PM, Kaye DM, et al. Myocardial fibrosis predicts appropriate device therapy in patients with implantable cardioverter-defibrillators for primary prevention of sudden cardiac death. J Am Coll Cardiol. 2011;57(7):821–8.
43. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8(8):1308–39.
44. Refaat MM, Hotait M, London B. Genetics of sudden cardiac death. Curr Cardiol Rep. 2015;17(7):606.
45. Balasundaram R, Rao HB, Kalavakolanu S, Narasimhan C. Catheter ablation of bundle branch reentrant ventricular tachycardia. Heart Rhythm. 2008;5(6 Suppl):S68–72.
46. Soejima K, Stevenson WG, Sapp JL, Selwyn AP, Couper G, Epstein LM. Endocardial and epicardial radiofrequency ablation of ventricular tachycardia associated with dilated cardiomyopathy: the importance of low-voltage scars. J Am Coll Cardiol. 2004;43(10):1834–42.
47. Mitrani RD, Klein LS, Miles WM, Hackett FK, Burt RW, Wellman HN, Zipes DP. Regional cardiac sympathetic denervation in patients with ventricular tachycardia in the absence of coronary artery disease. J Am Coll Cardiol. 1993;22:1344–53.
48. Tamburro P, Wilber D. Sudden death in idiopathic dilated cardiomyopathy. Am Heart J. 1992;124:1035–45.
49. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. Circulation. 1991;84:40–8.
50. Brembilla-Perrot B, Alla F, Suty-Selton C, Huttin O, Blangey H, Sadoul N, et al. Nonischemic dilated cardiomyopathy: results of noninvasive and invasive evaluation in 310 patients and clinical significance of bundle branch block. PACE. 2008;31:1383–90.
51. Grimm WHJ, Menz V, Luck K, Maisch B. Programmed ventricular stimulation for arrhythmia risk prediction in patients with idiopathic dilated cardiomyopathy and nonsustained ventricular tachycardia. J Am Coll Cardiol. 1998;32:739–45.
52. Goldberger JJ, Subacius H, Patel T, Cunnane R, Kadish AH. Sudden cardiac death risk stratification in patients with nonischemic dilated cardiomyopathy. J Am Coll Cardiol. 2014;63(18):1879–89.
53. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013;34(29):2281–329.
54. European Heart Rhythm Association, European Society of Cardiology, Heart Rhythm Society, Heart Failure Society of America, American Society of Echocardiography, American Heart Association, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Heart Rhythm. 2012;9(9):1524–76.
55. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225–37.

56. Køber LTJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016;375:1221–30.
57. Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med. 2014;370(18):1694–701.
58. Ruwald MH, Solomon SD, Foster E, Kutyifa V, Ruwald AC, Sherazi S, et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial. Circulation. 2014;130(25):2278–86.
59. Chatterjee NA, Roka A, Lubitz SA, Gold MR, Daubert C, Linde C, et al. Reduced appropriate implantable cardioverter-defibrillator therapy after cardiac resynchronization therapy-induced left ventricular function recovery: a meta-analysis and systematic review. Eur Heart J. 2015;36(41):2780–9.
60. Laonigro I, Correale M, Di Biase M, Altomare E. Alcohol abuse and heart failure. Eur J Heart Fail. 2009;11:453–62.
61. Guzzo-Merello G, Dominguez F, Gonzalez-Lopez E, Cobo-Marcos M, Gomez-Bueno M, Fernandez-Lozano I, et al. Malignant ventricular arrhythmias in alcoholic cardiomyopathy. Int J Cardiol. 2015;199:99–105.
62. Hussein A, Karimianpour A, Collier P, Krasuski RA. Isolated noncompaction of the left ventricle in adults. J Am Coll Cardiol. 2015;66(5):578–85.
63. Miyake CY, Kim JJ. Arrhythmias in left ventricular noncompaction. Card Electrophysiol Clin. 2015;7(2):319–30.
64. Mohty D, Damy T, Cosnay P, Echahidi N, Casset-Senon D, Virot P, et al. Cardiac amyloidosis: updates in diagnosis and management. Arch Cardiovasc Dis. 2013;106(10):528–40.
65. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation. 2005;112:2047–60.
66. Lin G, Dispenzieri A, Kyle R, Grogan M, Brady PA. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. J Cardiovasc Electrophysiol. 2013;24(7):793–8.
67. Sharma N, Howlett J. Current state of cardiac amyloidosis. Curr Opin Cardiol. 2013;28:242–8.
68. Varr BC, Zarafshar S, Coakley T, Liedtke M, Lafayette RA, Arai S, et al. Implantable cardioverter-defibrillator placement in patients with cardiac amyloidosis. Heart Rhythm. 2014;11(1):158–62.
69. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014;11(7):1305–23.
70. Hamzeh N, Steckman DA, Sauer WH, Judson MA. Pathophysiology and clinical management of cardiac sarcoidosis. Nat Rev Cardiol. 2015;12:278–88.
71. Kim JS, Judson MA, Donnino R, Gold M, Cooper LT Jr, Prystowsky EN, et al. Cardiac sarcoidosis. Am Heart J. 2009;157(1):9–21.
72. Koplan BA, Soejima K, Baughman K, Epstein LM, Stevenson WG. Refractory ventricular tachycardia secondary to cardiac sarcoid: Electrophysiologic characteristics, mapping, and ablation. Heart Rhythm. 2006;3:924–9.
73. European Heart Rhythm Association, Heart Rhythm Society, Zipes DP, Camm AJ, Borggrefe M, Buxton AE, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48(5):e247–346.
74. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Circulation. 2008;117(21):e350–408.

Ventricular Arrhythmias in the Absence of Structural Heart Disease

17

Juan Acosta and Josep Brugada

Abstract

Ventricular arrhythmia (VA) in structurally normal hearts can be classified as monomorphic or polymorphic. Monomorphic VA is common and generally carries an excellent prognosis. However, rare sudden cardiac death events have been reported. Very frequent ventricular ectopic beats may also result in a cardiomyopathy in a minority of patients. Suppression of VA may be achieved using calcium-channel blockers, beta-adrenergic blockers, and class I or III antiarrhythmic drugs. Radiofrequency ablation has emerged as an excellent option to eliminate these arrhythmias. Polymorphic ventricular tachycardia (VT) generally occurs in patients with genetic ion channel disorders including long QT syndrome, Brugada syndrome and catecholaminergic polymorphic VT. These arrhythmic syndromes are associated with sudden cardiac death. While the cardiac gross morphology is normal, suggesting a structurally normal heart, abnormalities exist at the molecular level and predispose them to arrhythmias. Finally, the early repolarization syndrome is associated with ventricular fibrillation episodes in the absence of structural heart disease or known channelopathies, and is characterised by the presence of J waves and ST-segment elevation in inferolateral leads.

Keywords

Idiopathic ventricular tachycardia • Idiopathic ventricular fibrillation • Outflow tract ventricular arrhythmias • Long QT syndrome • Brugada syndrome

Introduction

The evaluation and management of ventricular tachyarrhythmias are uniquely challenging due to the unpredictable and potentially lethal nature of the events. Malignant arrhythmias usually occur in the presence of significant structural heart disease (SHD). In this setting, ventricular arrhythmias carry a high risk of sudden cardiac death (SCD).

J. Acosta, M.D. • J. Brugada, M.D., Ph.D. (✉)
Arrhythmia Section, Cardiology Department,
Thorax Institute, Hospital Clínic, University of Barcelona,
C/ Villarroel 170, Barcelona, Catalonia, Spain
e-mail: juacosta@clinic.ub.es; jbrugada@clinic.ub.es

Less commonly, ventricular tachycardia (VT) and ventricular fibrillation (VF) occur in hearts that appear normal. In many such cases, however, the heart is in fact not normal, but rather has less visible abnormalities including derangements of cardiac ion channels or structural proteins. In these patients, ventricular arrhythmias also carry a high risk of SCD. Thus, a significant majority of patients with VT or VF have some form of underlying cardiac disease, are at increased risk for SCD, and require a thorough cardiac evaluation to exclude structural abnormalities and nonstructural disorders.

Although the term idiopathic VT/VF is widely used for the VT/VF syndromes described in this chapter, use of "idiopathic" can be misleading. Historically, both VT and VF that occur in the absence of apparent heart disease have been referred to as idiopathic. However, with continual

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_17

improvements in both the understanding of arrhythmia mechanisms and diagnostic methods, an increasing percentage of patients are now given a diagnosis (e.g., Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and catecholaminergic polymorphic VT). The diagnosis, characterization, and management of these VT/VF syndromes in the absence of SHD will be reviewed in this chapter.

Monomorphic VT in the Absence of Apparent SHD

Classification

Terminology and classifications vary, but most investigators acknowledge the existence of at least three syndromes of idiopathic monomorphic VT:

- Repetitive monomorphic VT, also called right ventricular (RV) outflow tract (OT) VT, is a triggered arrhythmia that is characterized by frequent short "salvos" of nonsustained VT. Less commonly, arrhythmias with similar characteristics and mechanisms originate from the LVOT, and these are considered a variant of RVOT.
- Paroxysmal sustained VT, which also arises from the RV, and is sometimes considered a sustained variant of repetitive monomorphic VT.
- Idiopathic left ventricular tachycardia, which differs from the LVOT variant of RVOT VT in both the mechanism (reentry) and site of origin (inferoapex or midseptum).

These three syndromes effectively characterize the majority of patients with idiopathic monomorphic VT and often unite clinical presentation, ECG morphology, and anatomic location into recognizable syndromes [1, 2].

Idiopathic VT has accounted for approximately 10% of all patients referred for evaluation of VT [1]. The mean age of patients with idiopathic VT is less than that of patients with VT secondary to underlying heart disease. It is important to recognize that not all VT that occurs in the apparent absence of structural heart disease is idiopathic VT. Distinguishing idiopathic VT from other monomorphic VT syndromes is important for several reasons:

- Idiopathic VT is generally considered to have an excellent prognosis in terms of freedom from both the development of structural heart disease and arrhythmic death [3–9]. There are several exceptions to this generalization, however, and episodes of SCD can occur.
- Idiopathic VT often responds to antiarrhythmic drugs that would be unhelpful or even contraindicated in VT occurring in the setting of coronary heart disease.
- Most idiopathic VT syndromes are now amenable to cure with catheter ablation techniques.

Diagnostic Evaluation

By definition, patients with idiopathic monomorphic VT have no detectable structural heart disease. Thus, the assessment of these patients focuses upon establishing the presence of a normal heart.

General Approach

- The resting ECG is typically normal between arrhythmia episodes, although some patients have temporary ECG repolarization abnormalities immediately after VT termination.
- The signal averaged ECG recorded during sinus rhythm is usually normal [5, 10].
- Functional studies of left ventricular (LV) and RV performance during sinus rhythm are normal, although segmental wall motion abnormalities may be seen immediately after VT termination. However, LV dysfunction can occur as a consequence of idiopathic VT, due to a tachycardia-induced cardiomyopathy. Such a myopathy can develop without persistent tachycardia if there are very frequent PVCs (i.e., >20,000 per day). This is a very important condition to recognize, as the LV dysfunction is reversible with treatment of the arrhythmia [11].
- The exercise stress test should be normal. Coronary angiography should also be normal.
- Cardiovascular magnetic resonance imaging (CMR) may reveal mild structural abnormalities of the RV in patients with RMVT, primarily involving the free wall (focal thinning, fatty infiltration, and wall motion abnormalities). The significance of these changes is unclear, since there is a poor correlation between the origin of the RMVT and the site of the CMR abnormalities unless they are also present in the RVOT.
- RV biopsy, which is rarely performed, is usually normal, although a number of studies have reported abnormalities that are nonspecific and of no significant value [12].

Repetitive Monomorphic VT

Repetitive monomorphic VT (RMVT) is characterized by frequent short "salvos" of monomorphic nonsustained VT [13]. Although RMVT is considered to occur in "normal" hearts, magnetic resonance imaging often reveal mild structural abnormalities of the RV, primarily involving the free wall (focal thinning, fatty infiltration, and wall motion abnormalities) [14]. The functional significance of these changes is uncertain. In the few cases studied, DNA from myocardial biopsies of ventricular muscle has been normal [15].

Epidemiology and Clinical Features

RMVT occurs almost exclusively in young to middle-aged patients without structural heart disease [1–8]. A surprising number of competitive athletes (particularly cyclists) are identified in many series of RMVT.

The most common associated symptoms are palpitations and lightheadedness during episodes. Most arrhythmias are nonsustained, but up to one-half of patients have some sustained episodes, and some patients have only sustained VT. Bursts of nonsustained VT are typically provoked by emotional stress or exercise, often occurring during the "warm-down" period after exercise, a time when circulating catecholamines are at peak levels [4–7]. There may also be a circadian pattern, with prominent peaks between 7 and 11 AM and 4 and 8 PM, correlating with periods of increased sympathetic activity [16]. In some patients, a critical "window" of heart rates (upper and lower thresholds) that result in occurrence of the arrhythmia can be defined.

The inducibility of RMVT by stress or catecholamine infusion is suggestive of an abnormality in cardiac sympathetic function. Consistent with this hypothesis is evidence of regional cardiac sympathetic denervation in some patients with RMVT and structurally normal hearts.

Site of Origin

The ouflow tract (OT) regions have complex three-dimensional anatomic relationships, which make the recognition of the ventricular arrhythmia origin particularly challenging. Different electrocardiographic algorithms have been proposed to predict LVOT vs RVOT origin of OT-VAs [17–22]. However, their accuracy has been recently questioned, especially when the transition in the precordial leads occurs in V3 [23] and/or the maximum electrogram (EG) precocity is located in the septal RVOT [24].

The most frequent site of origin of idiopathic VT described in literature is the RV outflow tract. However, sites of origin have been also recognised in the RV inflow tract, the free wall of the RVOT, the root of the pulmonary artery, the left and right aortic sinus of Valsalva, the left ventricle, the mitral annulus, and the papillary muscles.

Electrocardiographic Features

(a) RVOT. The majority of RMVT episodes have a characteristic ECG appearance with left bundle branch block, inferior axis and late precordial transition (>V3) (Fig. 17.1).

(b) LV outflow tract. Two different patterns may be observed:
- A right bundle, inferior axis morphology with a monophasic R wave in V1 that arose from the left fibrous trigone.
- A pattern similar to typical RMVT from the RVOT (left bundle, inferior axis) except that the precordial transition was earlier (at V2 for the LVOT as compared to V3 or later for the RVOT).

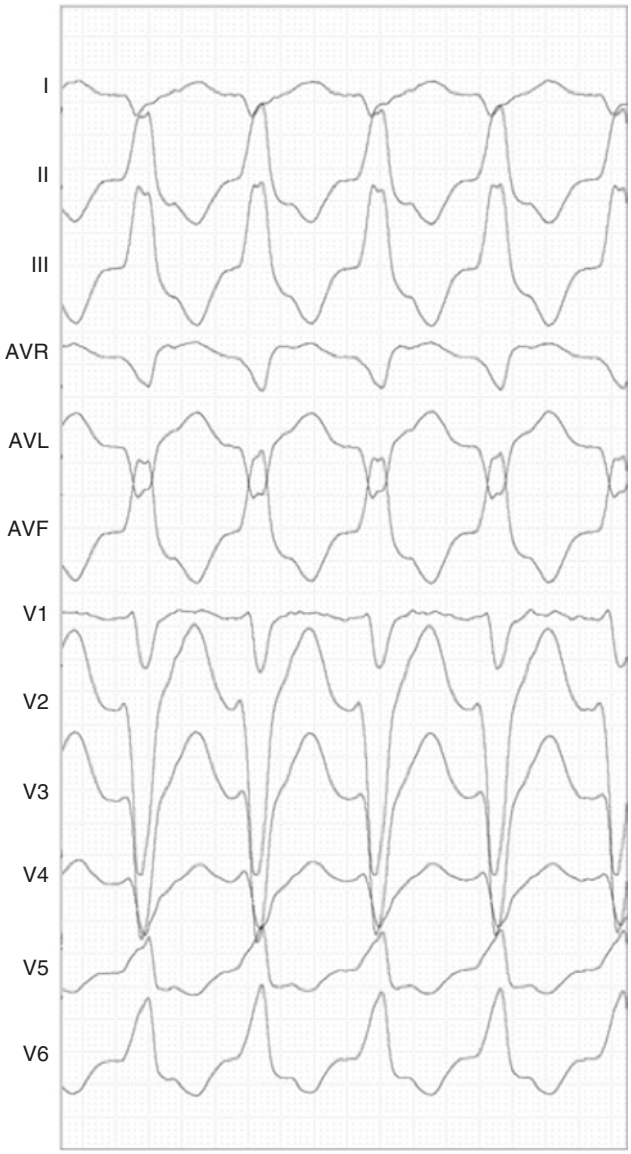


Fig. 17.1 Example of right ventricular outflow tract tachycardia

Although there is some interindividual variability, ventricular premature complexes arising from the left aortic sinus tend to be negative in lead I and have a "w" pattern in V1, while ventricular premature complexes with a broad R wave in V1 is characteristic of a right aortic cusp origin [19].

Electrophysiologic Features

RMVT can be induced in the EP laboratory, although usually not with programmed stimulation [4, 5]. In most patients, sustained or nonsustained episodes occur in response to burst atrial or ventricular pacing, and are greatly facilitated by isoproterenol or epinephrine infusion. These electrophysiologic observations suggest that triggered activity due to delayed afterpotentials, rather than reentry, is the

mechanism of RMVT. The response to "pharmacologic probes" further strengthens this hypothesis. RMVT has been terminated with adenosine, verapamil and beta blockers, all of which interfere with the cAMP-mediated slow inward calcium current. These observations are consistent with the hypothesis that RMVT results from triggered activity induced by cAMP-mediated delayed after depolarizations (DADs) [25]. However, the lack of specificity of these probes and the absence of a uniform response supports the general consensus that the mechanism of RMVT is incompletely characterized and may vary among individuals. Additional support for other mechanisms is based upon the observation that the tachycardia may, in some patients, terminate with overdrive pacing, ventricular extrastimulation, or autonomic modulation using Valsalva maneuver or carotid sinus pressure.

Prognosis

The prognosis of RMVT is almost uniformly good [26]. However, more recent studies in which these other syndromes were unlikely have identified a malignant variant of RMVT. Polymorphic VT and VF, which are malignant arrhythmias, have been demonstrated in patients with RMVT [27–29]. In these patients, VPBs are more closely coupled to prior beats than is usual for RMVT [27]. It was postulated that relatively early triggered beats occurred in a vulnerable period during repolarization, resulting in VF.

Medical Therapy

Medical therapy serves two roles in RMVT: termination of the arrhythmia; and prevention of recurrence. RMVT can be terminated with adenosine, verapamil and beta blockers, all of which interfere with the cAMP-mediated slow inward calcium current. For prevention of recurrence, verapamil and beta blockers are often used as first-line agents. In those cases refractory to verapamil and beta blockers, the combination of a beta blocker with a class I drug may be useful.

Radiofrequency Ablation

There has been increasing use of radiofrequency (RF) ablation in patients with symptomatic RMVT. Success rates for RF catheter ablation range from 80 to 100% [30–34]. The success rate depends in part upon the location of the focus; the success of catheter ablation for idiopathic VTs in atypical positions is generally not as high as for RVOT locations [31]. Radiofrequency ablation is generally associated with a low rate of procedural complications. However, recent studies have shown that a significant proportion of patients may present VT recurrence during long-term follow up, although with a lower burden [35]. The likelihood of successful ablation may be less when the site of origin is not endocardial or not definitively identified during mapping.

Idiopathic Left Ventricular Tachycardia (ILVT)

Belhassen was the first to report the characteristic termination of this VT with intravenous verapamil [36], accounting for its two descriptive eponyms: Belhassen VT; and verapamil-responsive VT.

Clinical Features

The typical patient with ILVT presents at age 20–40, but often reports symptomatic episodes dating back to adolescence. The clinical characteristics of ILVT appear to be more uniform than those of the idiopathic RV tachycardias [9, 36].

- It has a more variable association with physical activity, and is not usually provoked by exercise.
- It frequently produces symptoms such as palpitations and presyncope; syncope is uncommon.
- Cardiac arrest is rare, but isolated cases have been reported.
- Tachycardia-related cardiomyopathy has been reported, but is unusual since episodes are typically infrequent.

Site of Origin

Endocardial mapping during the VT demonstrates that the site of earliest activation is the inferoseptal region of the left ventricle in patients with a left frontal axis [9]. Mapping for catheter ablation also consistently localizes this VT to the inferior aspect of the midseptal region. In comparison, the anterosuperior left ventricle is the initial site in those patients with VT that has a right frontal axis.

Electrocardiographic Features

Corresponding to its left ventricular origin, ILVT has a right bundle branch block morphology with a left superior frontal plane axis and a relatively narrow QRS duration (typically 0.12–0.14 s). A small subset of patients with ILVT has a right frontal plane. ILVT is often confused with supraventricular tachycardia because of its characteristic ECG morphology, and the response to verapamil (Fig. 17.2).

Electrophysiologic Features

ILVT is typically reproduced in the electrophysiology laboratory using programmed stimulation employing extrastimuli and, on occasion, with rapid atrial or ventricular pacing. In contrast to RMVT, ILVT is not usually provoked by isoproterenol infusion.

The His bundle is commonly activated early in a retrograde fashion during ILVT, and a distinct Purkinje spike typically precedes the onset of the QRS. However, the retrograde His bundle deflection can be dissociated from the QRS complex by premature stimulation in the ventricle, atrium, or His region, implying that the reentrant circuit does not require the His bundle. These findings also suggest that the

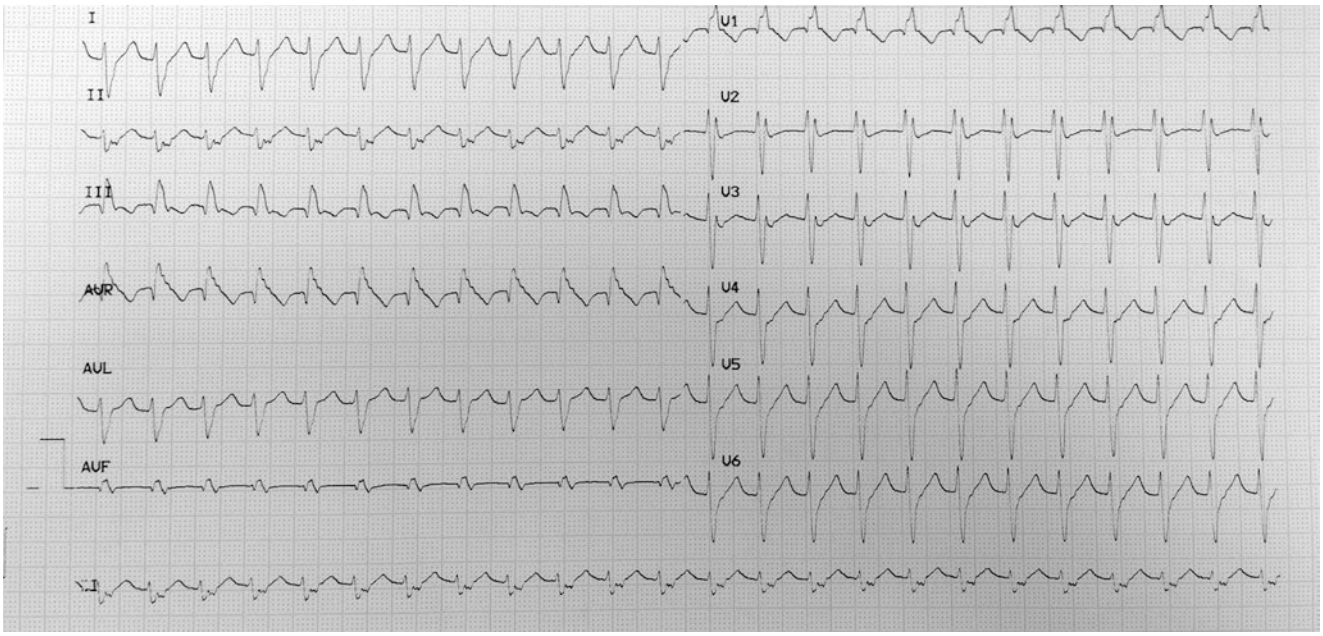


Fig. 17.2 Electrocardiographic pattern of fascicular tachycardia

posterior fascicle of the left bundle branch may be a part of, or at least in close proximity to the VT circuit. The terms fascicular ventricular tachycardia and fascicular tachycardia have been used to describe this arrhythmia.

Treatment of ILVT

Verapamil is usually effective in the treatment of ILVT, both for the termination of acute episodes and the prevention of recurrence. Catheter ablation has been performed with efficacy rates of 85–100% in patients with resistant or incessant ILVT or those intolerant of medications. Selection of ablation target sites focuses on pace mapping techniques and/or activation mapping, with particular attention to the mid-diastolic potential and/or presystolic Purkinje activation [37, 38].

Polimorphic VT and VF in the Absence of Apparent SHD

In addition to monomorphic VT, both polymorphic VT and VF can occur in the absence of structural heart disease. In contrast to the generally good prognosis associated with idiopathic monomorphic VT, these syndromes are associated with an increased risk of SCD.

Congenital Long QT Syndrome (LQTS)

The long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG) and an increased risk of sudden cardiac death [39]. This syndrome is associated with an increased risk of a characteristic life-threatening polymorphic ventricular tachycardia known as torsades de pointes [40].

While mutations in numerous genes have been identified in patients with congenital LQTS, two clinical phenotypes have been described that differ in the type of inheritance and the presence or absence of sensorineural hearing loss: the more common autosomal dominant form, the Romano-Ward syndrome, has a purely cardiac phenotype. On the other hand, the autosomal recessive form, the Jervell and Lange-Nielsen syndrome, is associated with LQTS and sensorineural deafness, and a more malignant clinical course.

Epidemiology

Although it is difficult to determine accurately, the incidence of congenital LQTS has been estimated between 1 in 2500 and 1 in 7000 in the general population [41].

Clinical Manifestations

The clinical manifestations of congenital LQTS are highly variable. Many patients have no symptoms, while symptoms (generally resulting from an arrhythmia) can range from palpitations to sudden cardiac death. Patients without symptoms typically come to medical attention because they have an affected family member or a prolonged QTc is identified on an electrocardiogram obtained for some other reason. Patients with arrhythmias may present with palpitations, presyncope, syncope, or sudden cardiac arrest. Many times the arrhythmias are transient or self-terminating, resulting in palpitations or presyncope. Patients may present with

syncope or sudden cardiac arrest if the arrhythmia is sustained or results in hemodynamic collapse.

Patients with LQTS frequently present with syncope and/or an apparent seizure due to an arrhythmia, typically polymorphic VT. Syncopal episodes associated with ventricular arrhythmias due to LQTS may have tonic-clonic movements and may be misdiagnosed as a primary seizure disorder. Distinguishing between a primary seizure disorder and seizures secondary to LQTS may be challenging, and the entities may overlap. In addition, patients with epilepsy and a recent seizure (within the preceding 2 years) as well as patients who are taking anti-epileptic medications with sodium channel blocker properties (e.g., phenytoin, carbamazepine, gabapentine, etc) appear to have an increased risk of sudden cardiac death. A screening ECG should be performed in all patients following a first afebrile seizure or unexplained syncope, including episodes consistent with neurocardiogenic (vasovagal) syncope. Those with borderline or prolonged QT intervals should be referred to a cardiologist for further evaluation. Emotional stress or physical exertion preceding syncope or seizure may suggest the possibility of LQTS-associated arrhythmia.

The majority of arrhythmias in patients with congenital LQTS are ventricular tachyarrhythmias, although bradycardia, atrioventricular block, and atrial arrhythmias are present in a minority of patients.

The classic arrhythmia associated with LQTS is a form of polymorphic VT called torsades de pointes. Polymorphic VT is defined as a ventricular rhythm faster than 100 beats per minute with frequent variations of the QRS axis, morphology, or both [42]. In the specific case of torsades de pointes, these variations take the form of a progressive, sinusoidal, cyclic alteration of the QRS axis. The peaks of the QRS complexes appear to "twist" around the isoelectric line of the recording, hence the name torsades de pointes.

Arrhythmias in patients with LQTS are frequently triggered by external events (e.g., noise, exercise, stress, etc.) and are often pause dependent (the beat triggering the arrhythmia is preceded by an ectopic beat and a subsequent pause). In addition, factors that contribute to the development of acquired LQTS, such as medications known to prolong the QT interval and electrolyte disturbances, can provoke arrhythmias in patients with congenital LQTS which is "mild" or previously unknown to the patient.

While over one dozen genotypes have been described, the great majority of cases of LQTS are accounted for by three genotypes: LQT1 (40–55%), LQT2 (35–45%), and LQT3 (8–10%). There is an association between the triggers that initiate arrhythmic events and the specific genotype of LQTS [43]. Arrhythmic events in patients with LQT1 are most often related to exercise. Acute arousal events (such as exercise, emotion, or noise) are much more likely triggers in LQT1 and LQT2 than LQT3 [35]. Events triggered by auditory stimuli, such as an alarm clock or telephone ringing, are most typically seen in LQT2 [44]. Pause-dependent torsades de pointes is common among patients with LQT2, but rare in patients with LQT1. Patients with LQT2 and LQT3 are at highest risk of events when at rest or asleep (68% of events), compared with LQT1 in which only 3% of events occurred at rest or when asleep.

Diagnosis

The diagnostic approach to LQTS includes evaluation of the specific clinical setting (cardiac event, asymptomatic family member, or incidentally discovered QT prolongation) and assessment of the ECG features described above.

LQTS score: A weighted scoring system for the diagnosis of congenital LQTS, also called the Schwartz score, incorporates the measured QTc interval and other clinical and historical factors [43]. An algorithm was developed in which diagnostic criteria were assigned points (Table 17.1).

The points are added to calculate the LQTS score. The probability of having LQTS is rated as low, intermediate, or high for scores of ≤1, 1.5 to 3, and ≥3.5, respectively.

Exercise testing. In most children and young adults, the QT interval shortens with exercise and increased heart rate. In contrast, in individuals with LQT1 or LQT2, the QT interval may fail to shorten or may lengthen with exertion and higher heart rates and may be prolonged during the recovery phase after exercise.

In some patients, the diagnosis of LQTS may be uncertain after application of the diagnostic criteria outlined above.

Table 17.1 Schwartz score for LQTS diagnosis

Diagnostic criteria	Points
ECG findings	
Corrected QT intervalo (ms)	
≥480	3
460–470	2
450–460	1
Corrected QT at 4th minute after stress test ≥480 ms	1
Torsade de pointes (in the absence of drugs that prolong QT)	2
T-wave alternans	1
Notched T wave in three leads	1
Resting heart rate below second percentile for age (restricted to children)	0.5
Clinical findings	
Syncope	
With stress	2
Without stress	1
Family history	
Family members with LQTS	1
Unexplained SCD in immediate family members <30 years of age	0.5

Additional testing, including ambulatory monitoring or drug testing, may be helpful in such patients.

Drug testing. Evaluation of the QT interval after provocative testing with drugs may help differentiate patients with suspected LQTS from normal patients, and among those with LQTS may distinguish one genetic defect from another. The most commonly used drugs are beta-adrenergic agonists, such as isoproterenol and epinephrine.

Treatment

Cuurent guidelines recommend [45]:

- Lifestyle modification is recommended for all patients with either a clinical or genetic diagnosis of LQTS: avoidance of drugs that prolong the QT interval or reduce the serum concentrations of potassium or magnesium; avoidance of competitive sports or strenuous activity.
- Beta blocker therapy is recommended for patients with QT prolongation and suggested for patients with a molecular diagnosis of congenital LQTS but a normal QT interval.
- ICD implantation is recommended for survivors of a cardiac arrest who have a reasonable expectation of survival with a good functional status for at least 1 year.
- ICD implantation is suggested for patients who experience sustained VT and/or a syncopal event consistent with a tachyarrhythmia while on beta blocker therapy.
- Beta blocker therapy should be initiated or continued in all patients who receive an ICD.

Brugada Syndrome

The Brugada syndrome is an autosomal dominant genetic disorder with variable expression characterized by abnormal findings on the surface electrocardiogram in conjunction with an increased risk of ventricular tachyarrhythmias and sudden cardiac death. Typically, the ECG findings consist of a pseudo-right bundle branch block and persistent ST segment elevation in leads V1–V3 [46].

Two terms, distinguished by the presence or absence of symptoms, have been used. Patients with typical ECG features who are asymptomatic and have no other clinical criteria are said to have the **Brugada pattern**. Patients with typical ECG features who have experienced sudden cardiac death or a sustained ventricular tachyarrhythmia, or who have one or more of the other associated clinical criteria, are said to have the **Brugada syndrome**.

Pathogenesis

Genetics. Genetic analysis has led to the identification of causative mutations in the SCN genes SCN5A and SCN10A, encoding subunits of a cardiac sodium channel.

Sodium channel genes. The defective myocardial sodium channels reduce sodium inflow currents, thereby reducing the duration of normal action potentials. In the right ventricular outflow tract epicardium, there is a prominent transient outward current, called I(to), which causes marked shortening of the action potential in the setting of reduced sodium inflow [47].

The relationship between sodium channel abnormalities and ST segment elevation is not fully understood. The ventricular myocardium is composed of at least three electrophysiologically distinct cell types: epicardial, endocardial, and M cells. The ST segment elevation and T wave inversions seen in the right precordial leads in Brugada syndrome are thought to be due to an alteration in the action potential in the epicardial and possibly the M cells, but not the endocardial cells [47]. The resulting dispersion of repolarization across the ventricular wall, which on noninvasive electrocardiogram mapping is isolated in the RV outflow tract, results in a transmural voltage gradient that is manifested in the electrocardiogram as ST segment elevation [48]. In addition, noninvasive ECG mapping has also shown evidence of an arrhythmogenic substrate in the RV outflow tract with delayed activation, slow conduction, and steep repolarization gradients between the RV outflow tract and the rest of the right ventricle [48]. This substrate may predispose to local reentry and ventricular arrhythmias.

SCN5A. Mutations in SCN5A, have been found in 18–30% of families with Brugada syndrome [49, 50]. The SCN5A mutations seen in Brugada syndrome are "loss of function" mutations and result in a variety of abnormalities in sodium channel activity including failure of expression, alterations in the voltage and time dependence of activation, and accelerated or prolonged recovery from inactivation. In addition, mutations may explain the ability of sodium channel blockers to expose the ECG changes in some patients with this disorder [49].

SCN10A. Mutations in SCN10A have been reported in 17% of Brugada syndrome probands, which is comparable to the 20 percent of probands found to have SCN5A mutations [51]. Coexpression of the mutant SCN10A gene with wild-type SCN5A causes a major loss of function of the sodium channel, with reduced current and slower recovery from inactivation. A longer PR interval, longer QS duration, and higher incidence of ventricular tachyarrhythmias and sudden death were noted in patients carrying mutations of SCN10A compared with gene-negative patients with Brugada syndrome.

Ventricular arrhythmias and phase two reentry. Ventricular arrhythmias may result from the heterogeneity of myocardial refractory periods in the RV. This heterogeneity arises from the presence of both normal and abnormal sodium channels in the same tissue, and from the

differential impact of the sodium current in the three layers of the myocardium. Within the epicardium, the juxtaposition of myocytes with different refractory periods can produce the triggers that initiate sustained arrhythmias via a unique type of reentry called phase two reentry. In cardiac myocytes with defective sodium channels, initial depolarization is blunted (phase zero), and the counterbalancing effect of I(to) (phase 1) may be more significant. This phenomenon is more dramatic in the RV outflow tract epicardium where I(to) currents are greater. In combination, this results in less initial depolarization and reduced activation of the calcium channels that maintain the depolarized state during phase two. Thus, phase two of the cardiac action potential can be dramatically shortened. The cells with impaired sodium channel function may fail to propagate the action potential, resulting in localized conduction block. However, due to the abbreviation of phase two, these same cells have a much shorter refractory period and recover excitability before the surrounding cells. The combination of localized conduction block and a shortened refractory period provides the substrate for localized reentry, which, in this case, is referred to as phase two reentry. The closely-coupled ventricular premature beats that result from phase two reentry may precipitate sustained ventricular arrhythmias [52].

Autonomic tone. An imbalance between sympathetic and parasympathetic tone may be important in the pathogenesis of Brugada syndrome, as suggested by the nocturnal occurrence of the associated tachyarrhythmias and the alteration of typical ECG changes by pharmacologic modulation of autonomic tone [53–55].

Fever. Data from a retrospective review of 111 patients with Brugada syndrome suggest that fever is a trigger for ECG changes and cardiac arrest [56]. In patients with possible Brugada syndrome, obtaining an ECG during a febrile illness can be useful.

Clinical Features

Most clinical manifestations of the Brugada syndrome are related to life-threatening ventricular arrhythmias. Sudden cardiac arrest may be the initial presentation of Brugada syndrome in as many as one-third of patients. Patients may also present with an episode of syncope with features suggestive of a tachyarrhythmic cause of the syncope. Palpitations related to ventricular tachyarrhythmia are not common in the Brugada syndrome, but patients may present with palpitations related to atrial fibrillation, which is associated with Brugada syndrome and may be the first presentation of the disease. Nocturnal agonal respiration is also described and is part of the diagnostic criteria.

ECG Patterns

There are two distinct patterns of ST elevation [57]:

- Type 1 ECG (coved type): the elevated ST segment (≥2 mm) descends with an upward convexity to an inverted T wave (Fig. 17.3).
- Type 2 pattern: the ST segment has a "saddle back" ST-T wave configuration, in which the elevated ST segment descends toward the baseline, then rises again to an upright or biphasic T wave.

Moving the right precordial chest leads superiorly to the second or third intercostal space may increase the sensitivity of detecting these abnormalities and should be performed when there is a doubt about the diagnosis.

Diagnosis

*Diagnostic criteria. D*iagnostic criteria have been proposed by professional societies from both Europe and North America [58]. In practice, most patients are diagnosed using the following diagnostic criteria:

- Appearance of type 1 ST segment elevation (coved type) in more than one right precordial lead (V1–V3) in the presence or absence of a sodium channel blocker, plus at least one of the following:
- Documented ventricular fibrillation
- Polymorphic ventricular tachycardia (VT)
- Family history of sudden cardiac death at less than 45 years of age
- Family history of type 1 Brugada pattern ECG changes
- Inducible VT during electrophysiology study
- Unexplained syncope suggestive of a tachyarrhythmia
- Nocturnal agonal respiration

Diagnostic Testing and Risk Stratification

Once the diagnosis of Brugada syndrome is suspected based on the clinical presentation and electrocardiogram findings, additional testing may be considered to further confirm the diagnosis of Brugada syndrome and to provide an estimate of risk of ventricular arrhythmias and sudden cardiac death in the individual patient.

Drug challenge. Among patients with the type 2 Brugada ECG pattern, the type 1 Brugada ECG pattern can occasionally be unmasked by sodium channel blockers (flecainide, ajmaline or procainamide). The importance of unmasking the type 1 Brugada ECG pattern relates to its relevance in confirming the diagnosis of Brugada syndrome, particularly in patients without symptoms.

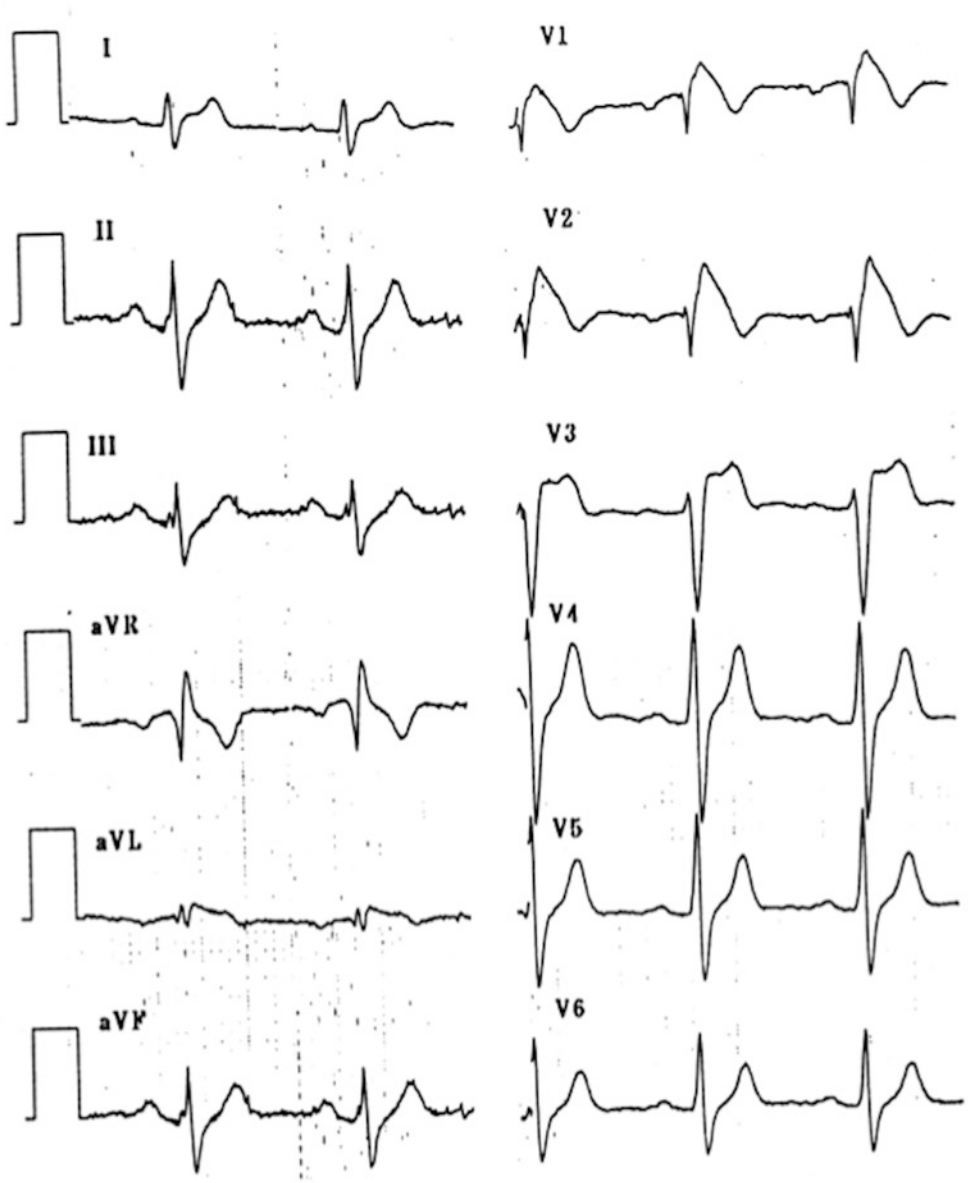


Fig. 17.3 Type 1 Brugada ECG pattern

Electrophysiology testing. The value of the inducibility of VA by programmed electric stimulation (PES) remains controversial. Several consensus documents have addressed this issue and the recommendation of PES for risk stratification has dropped from a IIa indication in the Second Brugada Syndrome Consensus Conference [49] to a IIb in the 2013 Expert Consensus Statement [58]. In a recent study with 403 patients presenting with spontaneous or drug-induced Brugada type I ECG, programmed ventricular stimulation was a good predictor of outcome in individuals with Brugada syndrome. This data suggests that electrophysiology testing might be of special value to guide further management when performed in asymptomatic individuals [59].

Genetic testing. Genetic testing for Brugada syndrome, which typically involves sequencing SCN5A, can be useful in confirming the presence of a mutation in a patient with the suspected diagnosis of Brugada syndrome. In patients with a clinical diagnosis of Brugada syndrome, genetic testing may also allow family screening and risk stratification. However, the genetic and clinical heterogeneity of Brugada syndrome limit the utility of genetic testing, as the absence of a mutation in SCN5A does not exclude Brugada syndrome, and the presence of a mutation in SCN5A does not confirm the diagnosis of Brugada syndrome.

Treatment

Treatment for patients diagnosed with the Brugada syndrome is primarily focused around termination of any ventricular arrhythmias with an implantable cardioverter-defibrillator (ICD). Current guidelines [58] recommend ICD implantation for: patients with Brugada syndrome who have survived SCA or who have documented spontaneous sustained ventricular tachycardia (class I); patients with spontaneous type I Brugada pattern ECG with a history of syncope likely caused by ventricular arrhythmias (class IIa); patients with Brugada syndrome who develop ventricular fibrillation during programmed stimulation during electrophysiology testing (class IIb).

Initial pharmacologic therapy for arrhythmia prevention has been tried in the Brugada syndrome with relatively little success, so ICD implantation should be the first line therapy for nearly all patients. However, patients with the Brugada syndrome who experience recurrent ventricular arrhythmias resulting in ICD shocks may require therapy with an antiarrhythmic drug in an effort to reduce the frequency of ICD shocks.

Isoproterenol has proved to be useful for treating electrical storm in BS. Quinidine has also proved to be useful for treating electrical storm in BS patients [60]. It prevents induction of VF and suppresses spontaneous ventricular arrhythmias, being used in patients with BS and multiple ICD discharges. It has been suggested that it also could be useful as a bridge to ICD, and as an alternative to it in children; however, it has a high rate of secondary effects. Finally, patients with only the Brugada ECG pattern do not require any specific therapy.

The use of RF ablation of the right ventricular epicardium has been initially advocated by Nademannee et al. [61] in patients with electrical storms and has now been extended to patients with a type I ECG and inducible arrhythmias in a very recent series published by Brugada, Pappone et al. [62]. Modifying the right ventricular epicardial layer by using RF ablation universally normalizes the ECG and prevents unmasking it by flecainide and inducibility of arrhythmias in patients with clear abnormal ECG's and inducible arrhythmias before the procedure. Follow-up at 6 months confirms persistence of normal ECG and negative drug challenging with flecainide. How this technique is going to influence the therapy in asymptomatic patients will require larger studies.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic VT (CPVT) is a genetic disorder that generally presents as familial although some sporadic cases have been reported. Basal ECG is normal but adrenergic stimulus like exercise or mental stress can trigger ventricular arrhythmias, ventricular extrasystoles, bidirectional tachycardia (Fig. 17.4) or polymorphic VT and

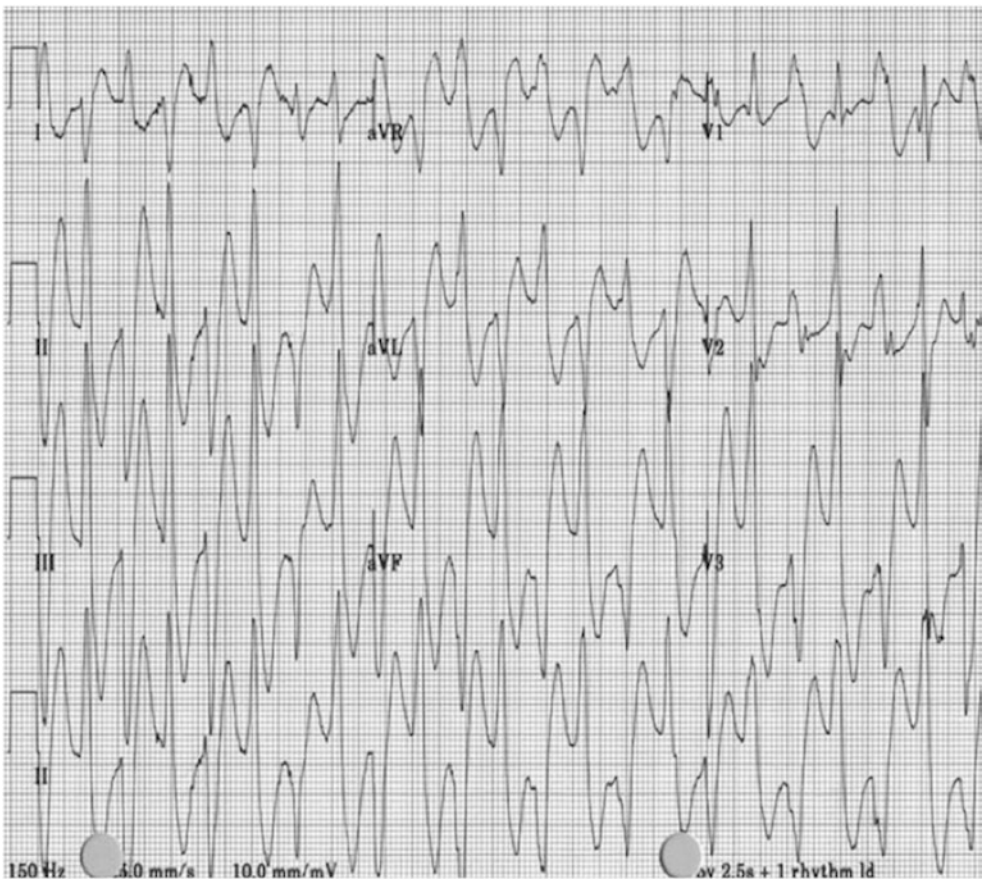


Fig. 17.4 Bidirectional ventricular tachycardia in a patient with diagnosis of CPVT

VF. Risk factors for sudden death include documented VF, a family history of sudden death, and onset of symptoms in childhood. More than 200 genetic abnormalities in different genes have been linked to the disease. The Ryanodine RYR2 gene is the most often altered protein. The mutation produces an excess in the intracellular calcium resulting in late after depolarizations and finally ventricular malignant arrhythmias. Other genes like CASQ2, KCNJ2, CALM1 and TRDN have been also linked to the same phenotypic behaviour. Beta blockers are often given for primary prevention and should be used for secondary prevention, although the response is not uniform. Flecainide has been added in cases with poor response [63]. The role of left cardiac sympathetic denervation in patients refractory to beta blocker therapy has not been clearly defined yet. Patients with risk factors for sudden death and no response to pharmacological therapy often receive an ICD.

Early Repolarization

Early repolarization (ER) is defined as either a sharp well-defined positive deflection or notch immediately following a positive QRS complex at the onset of the ST segment, or the presence of slurring at the terminal part of the QRS complex. Most literature defines ER as being present on the electrocardiogram when there is J-point elevation of ≥0.1 mV in two adjacent leads with either a slurred or notched morphology.

The ER pattern describes the patient with appropriate ECG findings in the absence of symptomatic arrhythmias. The ER syndrome applies to the patient with both appropriate ECG findings and symptomatic arrhythmias.

Persons with either the ER pattern or ER syndrome can have identical findings on surface ECG. However, the mere presence of ER pattern on ECG should not lead to a classification of ER syndrome in the absence of symptoms or documented VF.

The prevalence of ER ranges from 5 to 13%. The perception that ER was a benign finding devoid of clinical significance has changed, with numerous studies suggesting a two- to threefold increased risk of death in those with ER versus those without ER. While ER appears to increase one's risk of sudden cardiac death (SCD), the absolute risk of SCD remains exceedingly low in otherwise healthy people. Therefore the incidental identification of ER should not be interpreted as a high-risk marker for arrhythmic death due to the relatively low odds of SCD based on ER alone.

The purported mechanisms of ER and idiopathic VF all reflect an imbalance in the ion channel currents responsible for the terminal portion of depolarization and the early portion of repolarization.

Given its relatively high prevalence in the general population in comparison to the incidence of idiopathic VF, the ER pattern is almost always an incidental ECG finding. For patients with the incidental finding of the ER pattern on their ECG, observation without therapy is recommended. For patients with ER and ongoing acute VF (VF storm) requiring frequent defibrillation, intravenous isoproterenol is recommended.

For patients with ER syndrome with prior resuscitated SCD due to VF, an ICD should be implanted. In order to prevent recurrent ICD therapies due to VF, quinidine may be useful.

References

1. Brooks R, Burgess J. Idiopathic ventricular tachycardia. A review. Medicine (Baltimore). 1988;67:271.
2. Belhassen B, Viskin S. Idiopathic ventricular tachycardia and fibrillation. J Cardiovasc Electrophysiol. 1993;4(3):356–68. PubMed PMID: 8269305. Epub 1993/06/01.eng.
3. Froment R, Gallavardin L, Cahen P. Paroxysmal ventricular tachycardia; a clinical classification. Br Heart J. 1953;15(2):172–8. PubMed PMID: 13041996. Pubmed Central PMCID: PMC479483. Epub 1953/04/01.eng.
4. Rahilly GT, Prystowsky EN, Zipes DP, Naccarelli GV, Jackman WM, Heger JJ. Clinical and electrophysiologic findings in patients with repetitive monomorphic ventricular tachycardia and otherwise normal electrocardiogram. Am J Cardiol. 1982;50(3):459–68. PubMed PMID: 6810685. Epub 1982/09/01.eng.
5. Buxton AE, Waxman HL, Marchlinski FE, Simson MB, Cassidy D, Josephson ME. Right ventricular tachycardia: clinical and electrophysiologic characteristics. Circulation. 1983;68(5):917–27. PubMed PMID: 6137291. Epub 1983/11/01.eng.
6. Deal BJ, Miller SM, Scagliotti D, Prechel D, Gallastegui JL, Hariman RJ. Ventricular tachycardia in a young population without overt heart disease. Circulation. 1986;73(6):1111–8. PubMed PMID: 3698245. Epub 1986/06/01.eng.
7. Lemery R, Brugada P, Bella PD, Dugernier T, van den Dool A, Wellens HJ. Nonischemic ventricular tachycardia. Clinical course and long-term follow-up in patients without clinically overt heart disease. Circulation. 1989;79(5):990–9. PubMed PMID: 2713978. Epub 1989/05/01.eng.
8. Mont L, Seixas T, Brugada P, Brugada J, Simonis F, Kriek E, et al. The electrocardiographic, clinical, and electrophysiologic spectrum of idiopathic monomorphic ventricular tachycardia. Am Heart J. 1992;124(3):746–53. PubMed PMID: 1514503. Epub 1992/09/01.eng.
9. Ohe T, Shimomura K, Aihara N, Kamakura S, Matsuhisa M, Sato I, et al. Idiopathic sustained left ventricular tachycardia: clinical and electrophysiologic characteristics. Circulation. 1988;77(3):560–8. PubMed PMID: 3342487. Epub 1988/03/01.eng.
10. Kinoshita O, Kamakura S, Ohe T, Aihara N, Takaki H, Kurita T, et al. Frequency analysis of signal-averaged electrocardiogram in patients with right ventricular tachycardia. J Am Coll Cardiol. 1992;20(5):1230–7. PubMed PMID: 1401626. Epub 1992/11/01.eng.
11. Penela D, Van Huls Vans Taxis C, Aquinaga L, Fernández-Armenta J, Mont L, Castel MA, et al. Neurohormonal, structural, and functional recovery pattern after premature ventricular complex ablation is independent of structural heart disease status in patients with depressed left ventricular ejection fraction. J Am Coll Cardiol. 2013;62(13):1195–202.
12. Oakes DF, Manolis AS, Estes NA III. Limited clinical utility of endomyocardial biopsy in patients presenting with ventricular tachycardia without apparent structural heart disease. Clin Cardiol. 1992;15(1):24–8. PubMed PMID: 1541071. Epub 1992/01/01.eng.

13. Callans DJ, Menz V, Schwartzman D, Gottlieb CD, Marchlinski FE. Repetitive monomorphic tachycardia from the left ventricular outflow tract: electrocardiographic patterns consistent with a left ventricular site of origin. J Am Coll Cardiol. 1997;29(5):1023–7. PubMed PMID: 9120154. Epub 1997/04/01.eng.
14. Carlson MD, White RD, Trohman RG, Adler LP, Biblo LA, Merkatz KA, et al. Right ventricular outflow tract ventricular tachycardia: detection of previously unrecognized anatomic abnormalities using cine magnetic resonance imaging. J Am Coll Cardiol. 1994;24(3):720–7. PubMed PMID: 8077544. Epub 1994/09/01.eng.
15. Lerman BB, Stein K, Engelstein ED, Battleman DS, Lippman N, Bei D, et al. Mechanism of repetitive monomorphic ventricular tachycardia. Circulation. 1995;92(3):421–9. PubMed PMID: 7634458. Epub 1995/08/01.eng.
16. Hayashi H, Fujiki A, Tani M, Usui M, Mizumaki K, Shimono M, et al. Circadian variation of idiopathic ventricular tachycardia originating from right ventricular outflow tract. Am J Cardiol. 1999;84(1):99–101. A8. PubMed PMID: 10404862. Epub 1999/07/15.eng.
17. Hutchinson MD, Garcia FC. An organized approach to the localization, mapping, and ablation of outflow tract ventricular arrhythmias. J Cardiovasc Electrophysiol. 2013;24(10):1189–97.
18. Betensky BP, Park RE, Marchlinski FE, Hutchinson MD, Garcia FC, Dixit S, et al. The V(2) transition ratio: a new electrocardiographic criterion for distinguishing left from right ventricular outflow tract tachycardia origin. J Am Coll Cardiol. 2011;57(22):2255–62. PubMed PMID: 21616286. Epub 2011/05/28.eng.
19. Ouyang F, Fotuhi P, Ho SY, Hebe J, Volkmer M, Goya M, et al. Repetitive monomorphic ventricular tachycardia originating from the aortic sinus cusp: electrocardiographic characterization for guiding catheter ablation. J Am Coll Cardiol. 2002;39(3):500–8. PubMed PMID: 11823089. Epub 2002/02/02.eng.
20. Yang Y, Saenz LC, Varosy PD, Badhwar N, Tan JH, Kilicaslan F, et al. Using the initial vector from surface electrocardiogram to distinguish the site of outflow tract tachycardia. Pacing Clin Electrophysiol. 2007;30(7):891–8. PubMed PMID: 17584271.
21. Bala R, Garcia FC, Hutchinson MD, Gerstenfeld EP, Dhruvakumar S, Dixit S, et al. Electrocardiographic and electrophysiologic features of ventricular arrhythmias originating from the right/left coronary cusp commissure. Heart Rhythm. 2010;7(3):312–22. PubMed PMID: 20097621. Epub 2010/01/26.eng.
22. Yamada T, Yoshida N, Murakami Y, Okada T, Muto M, Murohara T, et al. Electrocardiographic characteristics of ventricular arrhythmias originating from the junction of the left and right coronary sinuses of Valsalva in the aorta: the activation pattern as a rationale for the electrocardiographic characteristics. Heart Rhythm. 2008;5(2):184–92. PubMed PMID: 18242537. Epub 2008/02/05.eng.
23. Yoshida N, Yamada T, McElderry HT, Inden Y, Shimano M, Murohara T, et al. A novel electrocardiographic criterion for differentiating a left from right ventricular outflow tract tachycardia origin: the V2S/V3R index. J Cardiovasc Electrophysiol. 2014;25(7):747–53.
24. Herczku C, Berruezo A, Andreu D, Fernandez-Armenta J, Mont L, Borras R, et al. Mapping data predictors of a left ventricular outflow tract origin of idiopathic ventricular tachycardia with V3 transition and septal earliest activation. Circulation. 2012;5(3):484–91.
25. Farzaneh-Far A, Lerman BB. Idiopathic ventricular outflow tract tachycardia. Heart. 2005;91(2):136–8. PubMed PMID: 15657214. Pubmed Central PMCID: PMC1768719. Epub 2005/01/20.eng.
26. Ritchie AH, Kerr CR, Qi A, Yeung-Lai-Wah JA. Nonsustained ventricular tachycardia arising from the right ventricular outflow tract. Am J Cardiol. 1989;64(10):594–8. PubMed PMID: 2571287. Epub 1989/09/15.eng.
27. Viskin S, Rosso R, Rogowski O, Belhassen B. The "short-coupled" variant of right ventricular outflow ventricular tachycardia: a not-so-benign form of benign ventricular tachycardia? J Cardiovasc Electrophysiol. 2005;16(8):912–6. PubMed PMID: 16101636. Epub 2005/08/17.eng.
28. Noda T, Shimizu W, Taguchi A, Aiba T, Satomi K, Suyama K, et al. Malignant entity of idiopathic ventricular fibrillation and polymorphic ventricular tachycardia initiated by premature extrasystoles originating from the right ventricular outflow tract. J Am Coll Cardiol. 2005;46(7):1288–94. PubMed PMID: 16198845. Epub 2005/10/04.eng.
29. Sadek MM, Benhayon D, Sureddi R, Chik W, Santangeli P, Supple GE, et al. Idiopathic ventricular arrhythmias originating from the moderator band: electrocardiographic characteristics and treatment by catheter ablation. Heart Rhythm. 2015;12(1):67–75. PubMed PMID: 25240695. Epub 2014/09/23.eng.
30. Klein LS, Shih HT, Hackett FK, Zipes DP, Miles WM. Radiofrequency catheter ablation of ventricular tachycardia in patients without structural heart disease. Circulation. 1992;85(5):1666–74. PubMed PMID: 1572025. Epub 1992/05/01.eng.
31. Calkins H, Kalbfleisch SJ, el-Atassi R, Langberg JJ, Morady F. Relation between efficacy of radiofrequency catheter ablation and site of origin of idiopathic ventricular tachycardia. Am J Cardiol. 1993;71(10):827–33. PubMed PMID: 8456762. Epub 1993/04/01.eng.
32. Wilber DJ, Baerman J, Olshansky B, Kall J, Kopp D. Adenosine-sensitive ventricular tachycardia. Clinical characteristics and response to catheter ablation. Circulation. 1993;87(1):126–34. PubMed PMID: 8418999. Epub 1993/01/01.eng.
33. Timmermans C, Rodriguez LM, Crijns HJ, Moorman AF, Wellens HJ. Idiopathic left bundle-branch block-shaped ventricular tachycardia may originate above the pulmonary valve. Circulation. 2003;108(16):1960–7. PubMed PMID: 14530199. Epub 2003/10/08.eng.
34. Rodriguez LM, Smeets JL, Timmermans C, Wellens HJ. Predictors for successful ablation of right- and left-sided idiopathic ventricular tachycardia. Am J Cardiol. 1997;79(3):309–14. PubMed PMID: 9036750. Epub 1997/02/01.eng.
35. Baser K, Bas HD, LaBounty T, Yokokawa M, Good E, Latchamsetty R, et al. Recurrence of PVCs in patients with PVC-induced cardiomyopathy. Heart Rhythm. 2015;12(7):1519–23.
36. Belhassen B, Rotmensch HH, Laniado S. Response of recurrent sustained ventricular tachycardia to verapamil. Br Heart J. 1981;46(6):679–82. PubMed PMID: 7317238. Pubmed Central PMCID: PMC482717. Epub 1981/12/01.eng.
37. Nogami A, Naito S, Tada H, Taniguchi K, Okamoto Y, Nishimura S, et al. Demonstration of diastolic and presystolic Purkinje potentials as critical potentials in a macroreentry circuit of verapamil-sensitive idiopathic left ventricular tachycardia. J Am Coll Cardiol. 2000;36(3):811–23. PubMed PMID: 10987604. Epub 2000/09/15.eng.
38. Nakagawa H, Beckman KJ, McClelland JH, Wang X, Arruda M, Santoro I, et al. Radiofrequency catheter ablation of idiopathic left ventricular tachycardia guided by a Purkinje potential. Circulation. 1993;88(6):2607–17. PubMed PMID: 8252671. Epub 1993/12/01.eng.
39. Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazzara R. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. Prog Cardiovasc Dis. 1988;31(2):115–72. PubMed PMID: 3047813. Epub 1988/09/01.eng.
40. El-Sherif N, Turitto G. Torsade de pointes. Curr Opin Cardiol. 2003;18(1):6–13. PubMed PMID: 12496496. Epub 2002/12/24.eng.
41. Earle N, Crawford J, Smith W, Hayes I, Shelling A, Hood M, et al. Community detection of long QT syndrome with a clinical registry: an alternative to ECG screening programs? Heart Rhythm. 2013;10(2):233–8. PubMed Epub 2012/11/06.eng.

42. Khan IA. Clinical and therapeutic aspects of congenital and acquired long QT syndrome. Am J Med. 2002;112(1):58–66. PubMed PMID: 11812408. Epub 2002/01/29.eng.
43. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103(1):89–95. PubMed PMID: 11136691. Epub 2001/01/04.eng.
44. Moss AJ, Robinson JL, Gessman L, Gillespie R, Zareba W, Schwartz PJ, et al. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. Am J Cardiol. 1999;84(8):876–9. PubMed PMID: 10532503. Epub 1999/10/26.eng.
45. Epstein AE, JP DM, Ellenbogen KA, NAM E III, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;51(21):e1–62.
46. Brugada R, Brugada P, Brugada J. Electrocardiogram interpretation and class I blocker challenge in Brugada syndrome. J Electrocardiol. 2006;39(4 Suppl):S115–8. PubMed PMID: 16934827. Epub 2006/08/29.eng.
47. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation. 1999;100(15):1660–6. PubMed PMID: 10517739. Epub 1999/10/12.eng.
48. Zhang J, Sacher F, Hoffmayer K, O'Hara T, Strom M, Cuculich P, et al. Cardiac electrophysiological substrate underlying the ECG phenotype and electrogram abnormalities in Brugada syndrome patients. Circulation. 2015;131(22):1950–9. PubMed PMID: 25810336. Pubmed Central PMCID: PMC4452400. Epub 2015/03/27.eng.
49. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. 2005;111(5):659–70. PubMed PMID: 15655131. Epub 2005/01/19.eng.
50. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Brignole M, et al. Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: a prospective evaluation of 52 families. Circulation. 2000;102(20):2509–15. PubMed PMID: 11076825. Epub 2000/11/15.eng.
51. Hu D, Barajas-Martinez H, Pfeiffer R, Dezi F, Pfeiffer J, Buch T, et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. J Am Coll Cardiol. 2014;64(1):66–79. PubMed PMID: 24998131. Pubmed Central PMCID: PMC4116276. Epub 2014/07/07.eng.
52. Aiba T, Shimizu W, Hidaka I, Uemura K, Noda T, Zheng C, et al. Cellular basis for trigger and maintenance of ventricular fibrillation in the Brugada syndrome model: high-resolution optical mapping study. J Am Coll Cardiol. 2006;47(10):2074–85. PubMed PMID: 16697328. Epub 2006/05/16.eng.
53. Mizumaki K, Fujiki A, Tsuneda T, Sakabe M, Nishida K, Sugao M, et al. Vagal activity modulates spontaneous augmentation of ST elevation in the daily life of patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2004;15(6):667–73. PubMed PMID: 15175062. Epub 2004/06/04.eng.
54. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol. 1996;27(5):1061–70. PubMed PMID: 8609322. Epub 1996/04/01.eng.
55. Matsuo K, Kurita T, Inagaki M, Kakishita M, Aihara N, Shimizu W, et al. The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. Eur Heart J. 1999;20(6):465–70. PubMed PMID: 10213350. Epub 1999/04/23.eng.
56. Amin AS, Meregalli PG, Bardai A, Wilde AA, Tan HL. Fever increases the risk for cardiac arrest in the Brugada syndrome. Ann Intern Med. 2008;149(3):216–8. PubMed PMID: 18678856. Epub 2008/08/06.eng.
57. Bayes de Luna A, Brugada J, Baranchuk A, Borggrefe M, Breithardt G, Goldwasser D, et al. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J Electrocardiol. 2012;45(5):433–42. PubMed PMID: 22920782. Epub 2012/08/28.eng.
58. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10(12):1932–63. PubMed PMID: 24011539. Epub 2013/09/10.eng.
59. Sieira J, Conte G, Ciconte G, de Asmundis C, Chierchia G-B, Baltogiannis G, et al. Prognostic value of programmed electrical stimulation in Brugada syndrome: 20 years experience. Circulation. 2015;8(4):777–84. PubMed PMID: 25904495.
60. Maury P, Hocini M, Haissaguerre M. Electrical storms in Brugada syndrome: review of pharmacologic and ablative therapeutic options. Indian Pacing Electrophysiol J. 2005;5(1):25–34. PubMed PMID: 16943940. Pubmed Central PMCID: PMC1502067. Epub 2006/09/01.eng.
61. Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation. 2011;123(12):1270–9. PubMed PMID: 21403098. Epub 2011/03/16.eng.
62. Brugada J, Pappone C, Berruezo A, Vicedomini G, Manguso F, Ciconte G, et al. Brugada syndrome phenotype elimination by epicardial substrate ablation. Circ Arrhythm Electrophysiol. 2015;8(6):1373–81. PubMed PMID: 26291334. Epub 2015/08/21.eng.
63. van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol. 2011;57(22):2244–54. PubMed PMID: 21616285. Pubmed Central PMCID: PMC3495585. Epub 2011/05/28.eng.

Bradyarrhythmias/Heart Blocks

18

L. Brent Mitchell

Abstract

A cardiac bradyarrhythmia may be the result of disordered impulse formation, disordered impulse conduction, or both. Human anatomy and physiology of the cardiac electrophysiological system are reviewed to provide a framework for an understanding of the patterns of sinus node, AV node, and His-Purkinje system dysfunction that result in clinical bradyarrhythmias. The important pathologic processes leading to these clinical bradyarrhythmias are discussed. The symptoms of the bradyarrhythmias are considered along with the details of treatment approaches with an emphasis on the indications for and appropriate selection of the platforms of implanted permanent cardiac pacemakers.

Keywords

AV node block • Bradyarrhythmia • Bradycardia • First degree AV block • His-Purkinje system block • Pacemaker • Second degree AV block • Sinus node arrest • Sinus node exit block • Third degree AV block

Introduction

Like other cardiac arrhythmias, bradyarrhythmias can be due to disorders of impulse formation, disorders of impulse conduction, or both. Many cell types in the heart are capable of generating electrical impulses by virtue of spontaneous phase 4 depolarization that reaches the threshold potential for creating an action potential (normal automaticity) [1]. Normal automaticity is most commonly expressed by the sinus node, by the AV node and surrounding regions (the junction), by AV ring atrial tissue, and by His-Purkinje cells with a hierarchy of rates in that order. Because the rate of normal automaticity in cells in the sinus node is the fastest, the sinus node is generally the heart's dominant pacemaker. Nevertheless, under influences that slow the rate of normal automaticity in the sinus node, another region, that normally has a slower rate of normal automaticity, becomes the dominant pacemaker—usually first the junction region (junctional rhythm), then the low atrial region (nonsinus atrial rhythm), and then the His-Purkinje system (idioventricular rhythm).

The sinus node is located on the anterolateral aspect of the junction of the right atrium and the superior vena cava (Fig. 18.1). It is a larger structure than is usually envisioned and may extend more than halfway down the crista terminalis on the lateral aspect of the right atrium [1]. The sinus node receives its blood supply from the sinus node artery, which it surrounds. The sinus node artery originates from the right coronary artery in 65% of individuals, from the circumflex coronary artery in 25% of individuals, and from both in 10% of individuals. During sinus rhythm, the site of the nodal cell with the fastest rate of normal automaticity may change from one moment to the next generating depolarizing wavefronts that may activate the right atrium from slight different directions manifest as sinus rhythms with slightly different P-wave morphologies (more so in the inferosuperior domain than in the anteroposterior or left-right domains).

L. Brent Mitchell, M.D., F.R.C.P.C.
Department of Cardiac Sciences, Calgary Zone, Alberta Health Services and Libin Cardiovascular Institute of Alberta, Calgary, AB, Canada
e-mail: Brent.Mitchell@albertahealthservices.ca

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_18

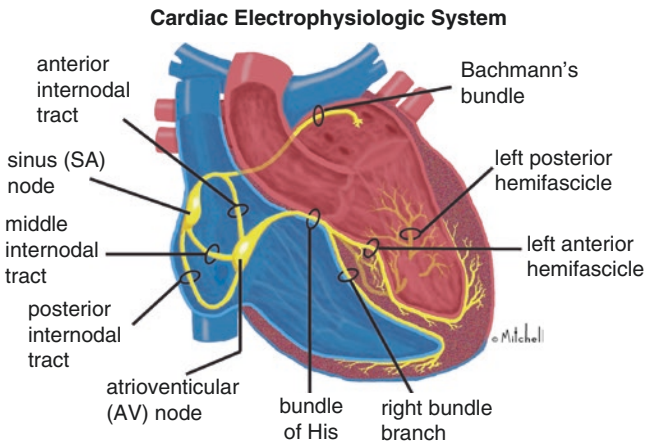


Fig. 18.1 Anatomic representation of the electrical system of the heart

The depolarizing wave front exits the sinus node through tissue whose electrophysiological function, like that of the AV node, is dominated by calcium channel activation rather than by sodium channel activation [1]. Accordingly, the sinus nodal exit zones share characteristics with the AV node that include slow and decremental conduction and a propensity to repeating cycles of gradually slowing conduction followed by conduction block (Wenckebach block).

There are preferential conduction pathways in the atria – the anterior, middle, and posterior internodal tracts that conduct the depolarizing wavefront from the sinus node to the AV node and Bachmann's bundle that conducts the depolarizing wavefront over the roof of the right and left atria thereby enhancing interatrial synchrony [2]. Whether these tracts are structural or functional is still debated [1, 2]. Nevertheless, in almost all clinical circumstances atrial depolarization is more conveniently considered to result from radial spread of the depolarization wavefront from the upper lateral right atrium down and to the left until all atrial tissue has been activated. The one circumstance when consideration of the existence of the atrial preferential conduction pathways is important is the special case of sinoventricular rhythm [3]. The cells of atrial preferential conduction pathways are more resistant to the conduction blocking effects of hyperkalemia than are working atrial myocytes. Thus, in a narrow range of potassium concentrations during hyperkalemia, it is possible that the atrial preferential conduction pathways will be functional when the working atrial myocytes are no longer able to conduct electrical impulses. The result is sinus rhythm directing the AV node and subsequent structures through the atrial preferential conduction pathways without atrial activation and without P-waves on the surface ECG. This rhythm is characterized by a supraventricular rhythm without identifiable P-waves in the rate range of normal sinus rhythm (faster than junctional rhythm) that demonstrates the large rate variations in response to autonomic influences that are characteristic of sinus rhythm (but not of junctional rhythm) [3].

The atrial depolarizing wavefront is then presented to the AV node, a low septal right atrial structure that is posterior to and below the bundle of His at the apex of the triangle of Koch (Fig. 18.1). The conduction properties of the AV node described above make this portion of the AV conduction system the dominant site of the physiologic atrioventricular delay [1]. The depolarizing wavefront then traverses the His bundle to reach the right and left bundle branches on the summit of the muscular interventricular septum. The subsequent near simultaneous delivery of the depolarizing wavefront to both ventricles via this His-Purkinje system results in a narrow QRS complex (<120 ms) that is possible only with a rhythm that originates above the bifurcation of the His bundle and uses the rapidly conducting His-Purkinje system to activate both ventricles simultaneously. The left bundle functions as a broad "waterfall" of conduction fibers leaving the septal summit over its left side that provides the first evidence of ventricular myocyte activation in the mid left portion of the interventricular septum as a depolarizing wavefront travelling toward the right side of the septum. Because it is broad, the function of the left bundle may be compromised in either of its anterior portion (left anterior fascicular block) or it posterior portion (left posterior fascicular block) or both (left bundle branch block). The right bundle functions more like a small insulated cable and does not provide evidence of ventricular myocyte activation until further down its length at the anteroapical portion of the right ventricle near the base of the anterior papillary muscle approximately 5–10 ms after activation of the left side of the interventricular septum [4]. Because of its small initial diameter, the function of right bundle, when compromised, is usually altered as a unit (right bundle branch block), in contrast to the left bundle where isolated block of the left anterior fascicle or of the left posterior fascicle can be observed.

The Sinus Node-Related Bradycardias

Patterns of Sinus Node Dysfunction

The normal sinus rhythm rate is 60 to 100 beats per minute in an awake and resting adult (the usual circumstances of a clinical examination or electrocardiogram). Of course, higher rates are expected under conditions of augmentation of sympathetic autonomic tone /withdrawal of vagal autonomic tone associated with exercise or emotional stress. Similarly, lower rates are expected under conditions of withdrawal of sympathetic tone/augmentation of vagal tone associated with sleep or in conditioned athletes.

Accordingly, simple sinus bradycardia is defined as a sinus rhythm with a rate less than 60 beats per minute in a resting, awake, non-athletic, adult individual (Fig. 18.2). Other patterns of sinus node dysfunction include chronotropic incompetence, sinus arrest, and sinus node exit block.

Chronotropic Incompetence

With respect to sinus node function, chronotropic incompetence refers to exercise intolerance secondary to the inability of the sinus heart rate to increase adequately with activity. Chronotropic incompetence has no widely accepted definition. Some commonly used definitions include a maximum heart rate less than 75, 85, or 95% of the predicted maximum heart rate using the formula for predicted maximal heart rate of 220 minus age, an absolute maximum heart rate of less than 100 or 120 beats per minute, or a subnormal heart rate response to submaximal exercise normalized to metabolic equivalents (METS) workload [5, 6].

Sinus Arrest

Sinus arrest is the consequence of failure of sinus node automaticity such that an expected sinus nodal depolarizing wavefront does not occur. The subsequent pause in depolarization may be terminated by resumption of sinus nodal automaticity (after a pause that is statistically unlikely to be a multiple of the underlying sinus nodal rate) (Fig. 18.3) or an expression of normal automaticity from a subsidiary pacemaker (often junctional).

Sinus Node Exit Block

Sinoatrial (SA) exit block describes normal automaticity of the sinus node but failure of some or all of the resultant sinus

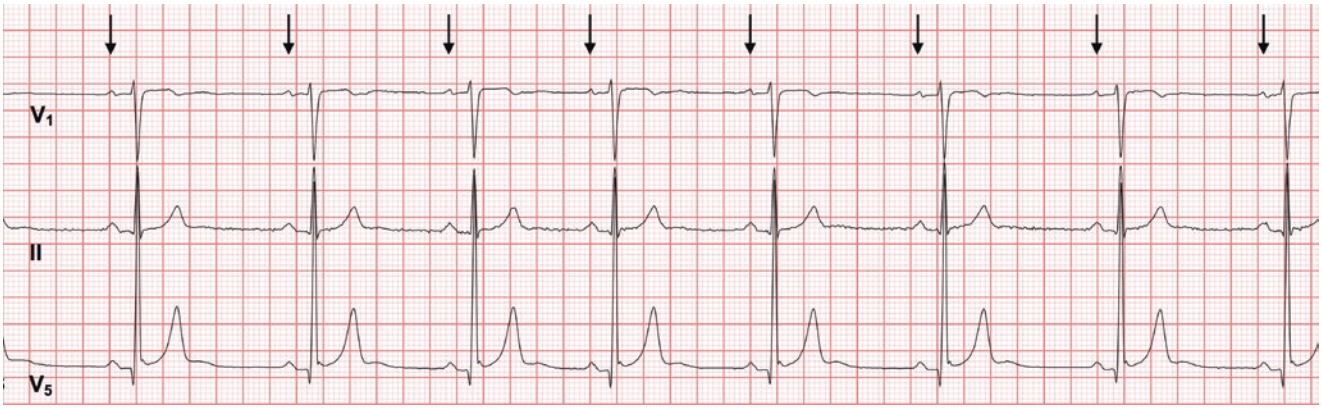


Fig. 18.2 Marked sinus bradycardia. Simultaneously recorded leads V_1, II, and V_5. The vertical arrows denote sinus P-waves. When due to augmentation of vagal tone/withdrawal of sympathetic tone, the sinus bradycardia is often associated, as it is here, with sinus arrhythmia (gradual acceleration of heart rate with inspiration and corresponding gradual deceleration of heart rate with expiration) and with first-degree AV block

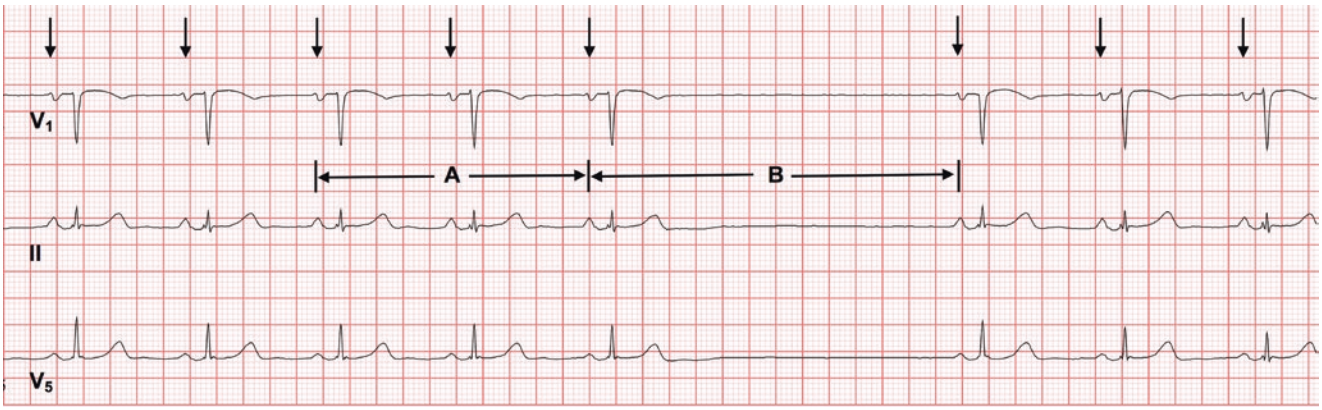


Fig. 18.3 Sinus arrest. Simultaneously recorded leads V_1, II, and V_5. The vertical arrows denote sinus P-waves. The PP interval spanning the pause (B) is not a multiple of the sum of the two previous PP intervals (A)

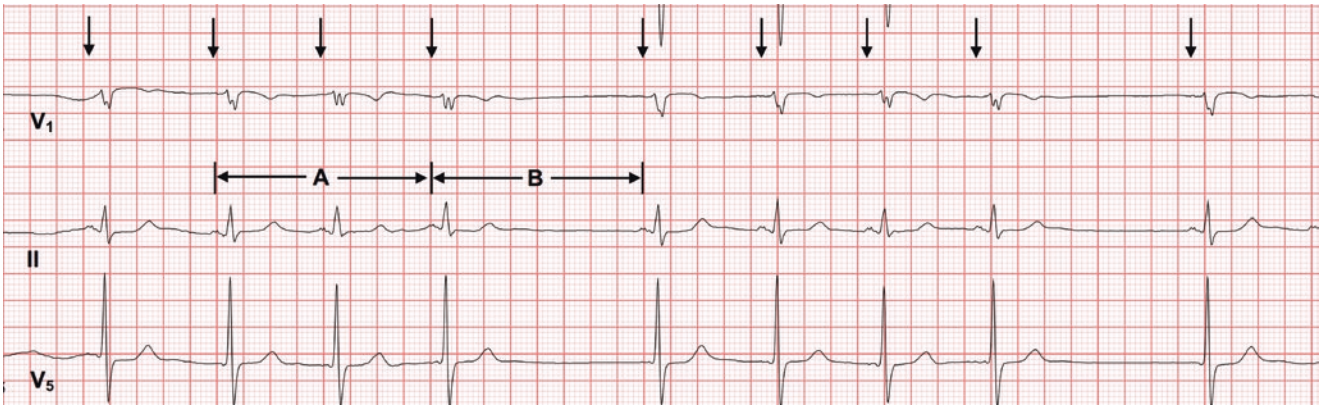


Fig. 18.4 Sinus exit block. Simultaneously recorded leads V_1, II, and V_5. The vertical arrows denote sinus P-waves. The PP interval spanning the pause (B) is a multiple of the sum of the two previous PP intervals (A), in this case the same interval

nodal depolarizations to exit the sinus node. SA exit block may be first-degree SA block (expressed as a prolonged sinoatrial conduction time which has no ECG marker and is of no clinical consequence), Mobitz type I second-degree SA block (expressed as gradual shortening of PP intervals during groups of PP cycles followed by a pause that is less than twice any PP interval immediately preceding block), Mobitz type II second-degree SA block (expressed as stable PP intervals during groups of PP cycles followed by a pause that is twice the PP intervals preceding block) (Fig. 18.4), high-grade second-degree SA block (in the case of 2:1 high-grade SA block expressed as a persistent halving of the PP intervals preceding block), or third-degree SA block (expressed as the absence of evident sinus nodal activity).

Causes of Sinus Node Dysfunction

Sinus bradycardia is not synonymous with sinus node disease in that many influences extrinsic to the sinus node may produce sinus bradycardia. The most common of these influences are augmentation of vagal tone, withdrawal of sympathetic tone, hypothyroidism, and pharmaceutical agents that decrease the rate of normal automaticity of the sinus node including Vaughan William's Class Ia antiarrhythmic drugs (disopyramide, procainamide, quinidine, tricyclic antidepressants), Class Ic antiarrhythmic drugs (flecainide, propafenone), Class II antiarrhythmic drugs (beta-andrenergic blockers), Class III antiarrhythmic drugs (amiodarone, dofetilide, dronedarone, sotalol), Class IV antiarrhythmic drugs (non-dihydropyridine calcium antagonists such as diltiazem and verapamil), and funny current blockers (ivabradine). Other such external influences are listed in Table 18.1.

In the absence of the external influences described above, sinus bradycardia, particularly when symptomatic, is ascribed to sinus node dysfunction. Essentially any structural heart disease may produce sinus node dysfunction. Nevertheless, the

Table 18.1 Causes of sinus bradycardia

Extrinsic
Normal augmentation of vagal tone/withdrawal of sympathetic tone
1. Sleep
2. Conditioned athletes
3. Situational (coughing, defecation, micturition, vomiting)
Abnormal augmentation of vagal tone / withdrawal of sympathetic tone
1. Neurocardiogenic (vasovagal) reflex activation
2. Carotid sinus hypersensitivity
3. Raised intracranial pressure
4. Obstructive sleep apnea
Metabolic abnormalities
1. Hypothyroidism
2. Hypothermia
3. Hypokalemia/hyperkalemia
4. Hypoxia
Drugs/toxins
1. Class I and Class III antiarrhythmic drugs
2. Beta-adrenoreceptor blockers
3. Non-dihydropyridine calcium antagonists
4. Digoxin
5. Lithium
Intrinsic
1. Idiopathic sick sinus syndrome (usually with advancing age with or without a familial pattern)
2. Brady-tachy variant of the sick sinus syndrome
3. Sinus node ischemia
4. Myocarditis
5. Infiltrative disorders (amyloid, hemochromatosis, sarcoidosis)
6. Collagen-vascular diseases (RA, scleroderma, SLE)
7. Surgical trauma
8. Sinus node remodeling in association with other structural heart diseases
9. Myotonic dystrophy

Abbreviations: *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosis

most common cause is age-related degenerative disease that likely results from either or both of fibrosis or ion channel dysregulation. When sinus node dysfunction is accompanied by symptoms, a diagnosis of sick sinus syndrome is made.

Sinus Node Disease (Sick Sinus Syndrome)

Symptomatic sinus node disease (sick sinus syndrome) occurs with an annual incidence of approximately 1:1000 persons [7]. Risk factors for its development include older age, obesity, congestive heart failure, renal disease, and hypertension [7]. Sinus node dysfunction is usually asymptomatic in its early phases but can lead to pronounced bradycardia in response to other external factors (Table 18.1). Subsequently, symptomatic sinus bradycardia and/or symptomatic sinus nodal chronotropic incompetence ensues. More advanced forms of sinus nodal dysfunction are typically symptomatic.

Many patients with sinus nodal disease also have evidence of other conduction system disease (either AV nodal dysfunction or His-Purkinje system dysfunction) suggesting that their sinus node disease has an etiology that may also affect other portions of the conduction system (e.g. calcific degenerative disease). Finally, some patients with sinus node disease also have atrial tachyarrhythmias such as atrial fibrillation, atrial flutter, or atrial tachycardia. The co-existence of sinus node disease and atrial tachyarrhythmias is termed the brady-tachy variant of the sick sinus syndrome or, simply, the brady-tachy syndrome [8].

The AV Conduction System-Related Bradycardias

Patterns of AV Block

In first-degree AV block all atrial depolarizing events (P-waves) create ventricular depolarizing events (QRS complexes) but the time required to traverse the AV conduction system (estimated by the PR interval) is longer than normal. In third-degree AV block no atrial depolarizing events (P-waves) create ventricular depolarizing events (QRS complexes). In second-degree AV block some atrial depolarizing events (P-waves) create ventricular depolarizing events (QRS complexes) but some do not.

First-Degree AV Block

First-degree AV "block" (better termed delay) is defined by a PR interval greater than 0.2 s (Fig. 18.5). Although the PR interval measures the time for conduction from the initial depolarization of atrial tissue to the initial depolarization of ventricular tissue, first-degree AV block is nearly always the result of delay in conduction though the AV node even when it occurs in association with other evidence of atrial or His-Purkinje system disease. Of course, delayed AV conduction does not slow the heart rate; nevertheless, first-degree AV block often co-exists with sinus bradycardia and with other AV conduction system dysfunction because of the substantial overlap in the causes of these phenomena.

Second-Degree AV Block

In second-degree AV block not all of the P-waves are conducted to the ventricles. Second-degree AV block can result from either AV nodal dysfunction or from His-Purkinje system dysfunction. When due to AV nodal dysfunction, the AV block usually follows the pattern of Mobitz type I second-degree AV block that is also known as Wenckebach AV block (Fig. 18.6). Mobitz type I second-degree AV block is characterized by groups of QRS complexes separated by pauses. Within each group, the first PR interval is the shortest and each subsequent PR interval gets longer until there is AV nodal block (an infinite PR interval) and a QRS complex is dropped. The sequence may then repeat. Because the RR interval across the pause includes the shortest PR interval, the RR interval across the pause is less than twice any other RR interval. During each cycle, the PR interval progressively prolongs but

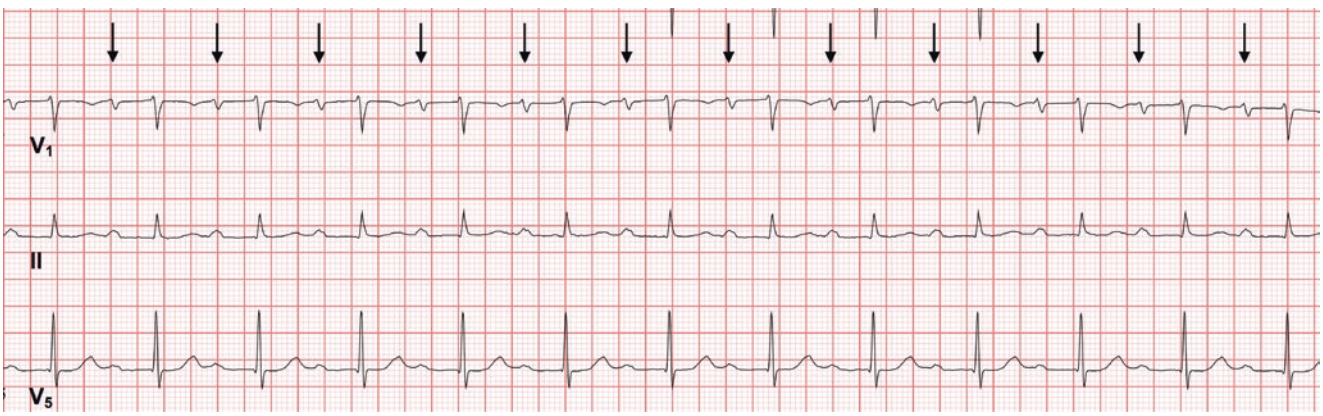


Fig. 18.5 First-degree AV block. Simultaneously recorded leads V_1, II, and V_5. The vertical arrows denote sinus P-waves. The PR interval is 340 ms

each increment in PR interval is less than the previous increment in PR interval. Accordingly, during each cycle, the RR intervals that are not spanning a pause are actually getting progressively shorter. The rules of Wenckebach related to the PR intervals are termed the input rules as the PR interval represents the input to the tissue exhibiting Wenckebach conduction (in this case, the AV node). The rules of Wenckebach related to the RR intervals are termed the output rules as the RR interval represents the output of the tissue exhibiting Wenckebach conduction (in this case, the AV node). When other cardiac tissues exhibit Wenckebach block, there will be parallel input and output rules. Sinoatrial (SA) Wenckebach block, where only the output rules can be appreciated on the surface ECG, is described above under patterns of sinus node dysfunction. Wenckebach block is a characteristic of decrementally-conducting tissues (the AV node and the sinus node). Nevertheless, other cardiac tissues, if partially depolarized by disease, may become decremental and exhibit Wenckebach block. Accordingly, although Mobitz type I second-degree AV block implies AV nodal block it is not pathognomonic of AV nodal disease.

When due to His-Purkinje system dysfunction, the AV block usually follows the pattern of Mobitz type II second-degree AV block (Fig. 18.7). Simplistically, type II block is an "all or none" block. Accordingly, Mobitz type II second-degree AV block is characterized by groups of QRS complexes separated by pauses. Within each group, the PR interval is stable and, therefore, so is the RR interval until there is AV nodal block (an infinite PR interval) and a QRS complex is dropped. The sequence may then repeat. The absence of decremental conduction and the consequent absence of gradual prolongation of the PR interval in Mobitz type II second-degree AV block results in the RR interval spanning the pause being twice the other (stable) RR intervals.

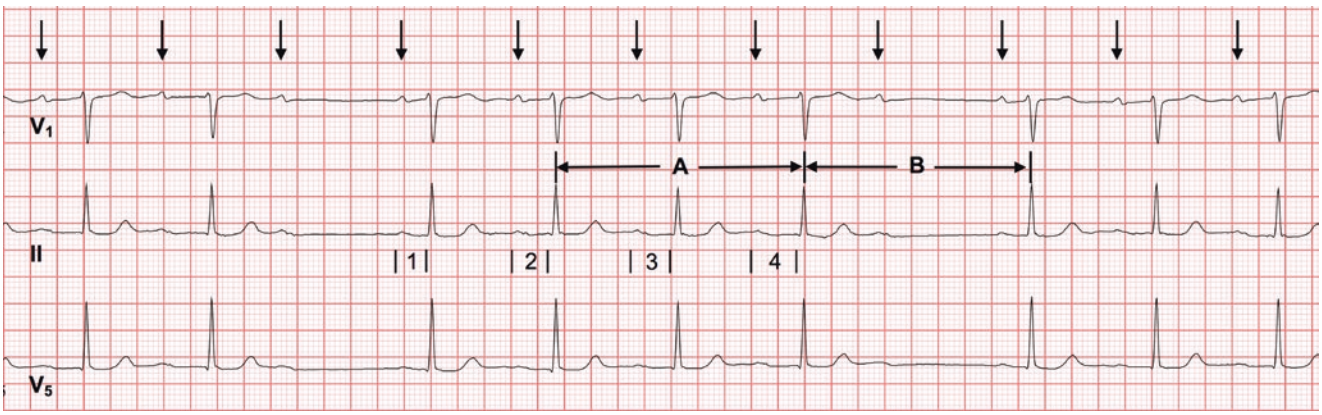


Fig. 18.6 Mobitz type I second-degree AV block. Simultaneously recorded leads V_1, II, and V_5. The vertical arrows denote sinus P-waves. There is group beating with pauses between groups. The PR interval gradually increases through the group (PR interval 1 is 230 ms, PR interval 2 is 270 ms, PR interval 3 is 300 ms, PR interval 4 is 340 ms). The duration of the pause (B) is less than twice the sum of the preceding two RR intervals (A)

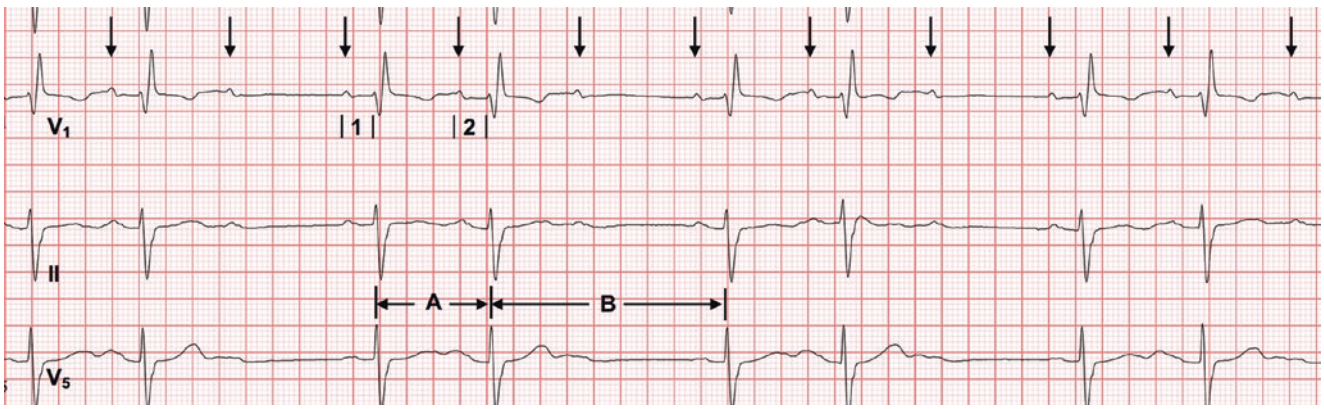


Fig. 18.7 Mobitz type II second-degree AV block. Simultaneously recorded leads V_1, II, and V_5. The vertical arrows denote sinus P-waves. There is group beating with pauses between groups. The PR interval is stable through the group (PR interval 1 and 2 are both 240 ms). The duration of the pause (B) is precisely twice the previous RR interval (A). As is often the case, there is underlying evidence of His-Purkinje system disease (in this case, bifascicular block in the form of RBBB and left anterior fascicular block)

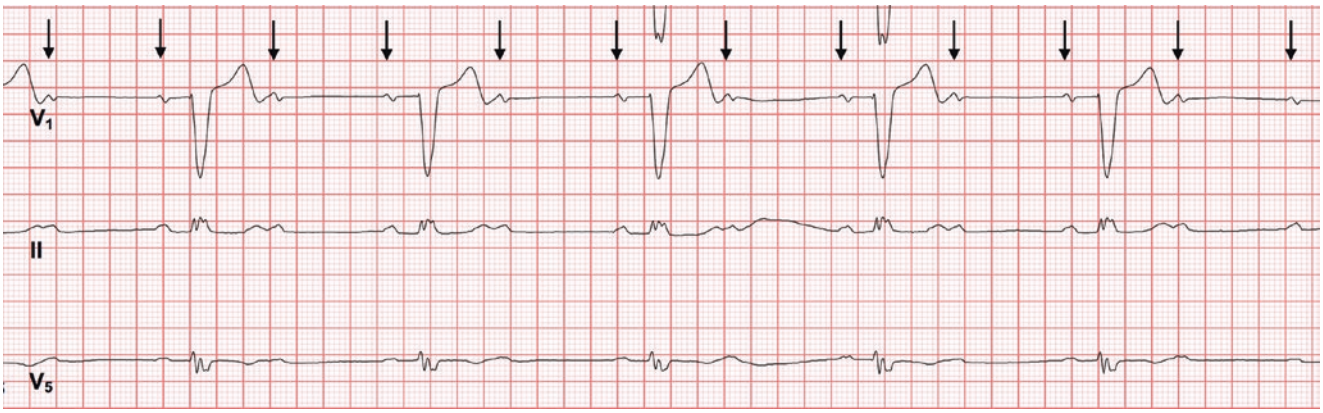


Fig. 18.8 High-grade second-degree AV block. Simultaneously recorded leads V_1, II, and V_5. The vertical arrows denote sinus P-waves. There are never two conducted P-waves in a row precluding determination of whether the second-degree AV block is Mobitz type I or Mobitz type II. In this case, there is also bifascicular block in the form of LBBB suggesting, but not proving, that the block is in the His-Purkinje system

High-grade AV block is a special form of second-degree AV block in which the block ratio is every second beat or higher (Fig. 18.8). In such cases, there are never two or more conducted P-waves in a row. Accordingly, the distinguishing features of Mobitz type I and of Mobitz type II AV block cannot be identified. Furthermore, if the block ratio is stable during high-grade AV block there are not groups of QRS complexes separated by pauses but rather there is a marked ventricular bradycardia that may not be interpreted as being secondary to AV block if the blocked P-waves are not identified.

It is important to determine whether second-degree AV block is of the Mobitz type I or Mobitz type II variety in that the former is characteristic of AV nodal block while the latter is characteristic of His-Purkinje system block. Mobitz II second-degree AV block is a higher–risk condition and is generally treated with pacemaker implantation. When Mobitz type I second-degree AV nodal block progresses to third-degree AV block there will typically be a junctional escape rhythm in the rate range of 30 to 45 beats per minute that is reliable. When Mobitz type II second-degree His-Purkinje system block progresses to third-degree AV block there will typically be an idioventricular escape rhythm in the rate range of 20 to 40 beats per minute that is not reliable and may give way to ventricular asystole. Ancillary clues suggesting that high-grade second degree AV block is the result of Mobitz type I second degree AV block include prior evidence of AV nodal dysfunction, a narrow QRS complex associated with conducted beats, and improvement in the degree of AV block with sympathetic stimulation such as exercise. Ancillary clues suggesting that high-grade second degree AV block is the result of Mobitz type II second degree AV block include prior evidence of His-Purkinje system dysfunction, a wide QRS complex associated with conducted beats, and worsening in the degree of AV block with sympathetic stimulation such as exercise.

The second-degree AV blocks are causes of pauses in an otherwise regular supraventricular rhythm that must be differentiated from the most common cause of such pauses, a premature atrial depolarization that is not conducted by the normal AV conduction system because its depolarizing wavefront has impinged upon the refractory period of the AV node. Such premature atrial depolarizations are identified by searching for the premature P-wave in or near the T-wave of the preceding conducted event (Fig. 18.9).

Third-Degree AV Block

In third-degree AV block no atrial depolarizations can reach the ventricles and ventricular depolarization is accomplished by a slower escape junctional or idioventricular rhythm (Fig. 18.10). Third-degree AV block is one form of AV dissociation. The other form of AV dissociation is third-degree VA block wherein ventricular depolarizations are faster than atrial depolarizations and the ventricular rhythm should, therefore, be driving the atrial rhythm but, because of VA block, is not. Third-degree VA block is not necessarily abnormal as it is present in nearly one-half of normal patients during an electrophysiologic study.

During third-degree AV block the ventricular rate is usually quite slow. Since the QT interval is determined, in part, by heart rate, very slow ventricular rates may produce very long QT intervals and may, in susceptible individuals, produce torsade de pointes ventricular tachycardia, which may, in turn, degenerate into ventricular fibrillation.

A peculiar form of third-degree AV block, termed paroxysmal AV block has been described. In paroxysmal AV block, the patient's normal sinus rhythm is suddenly interrupted by the abrupt onset of third-degree AV block that then persists for several seconds before reverting to normal sinus rhythm just as abruptly. There appear to be at least two vari-

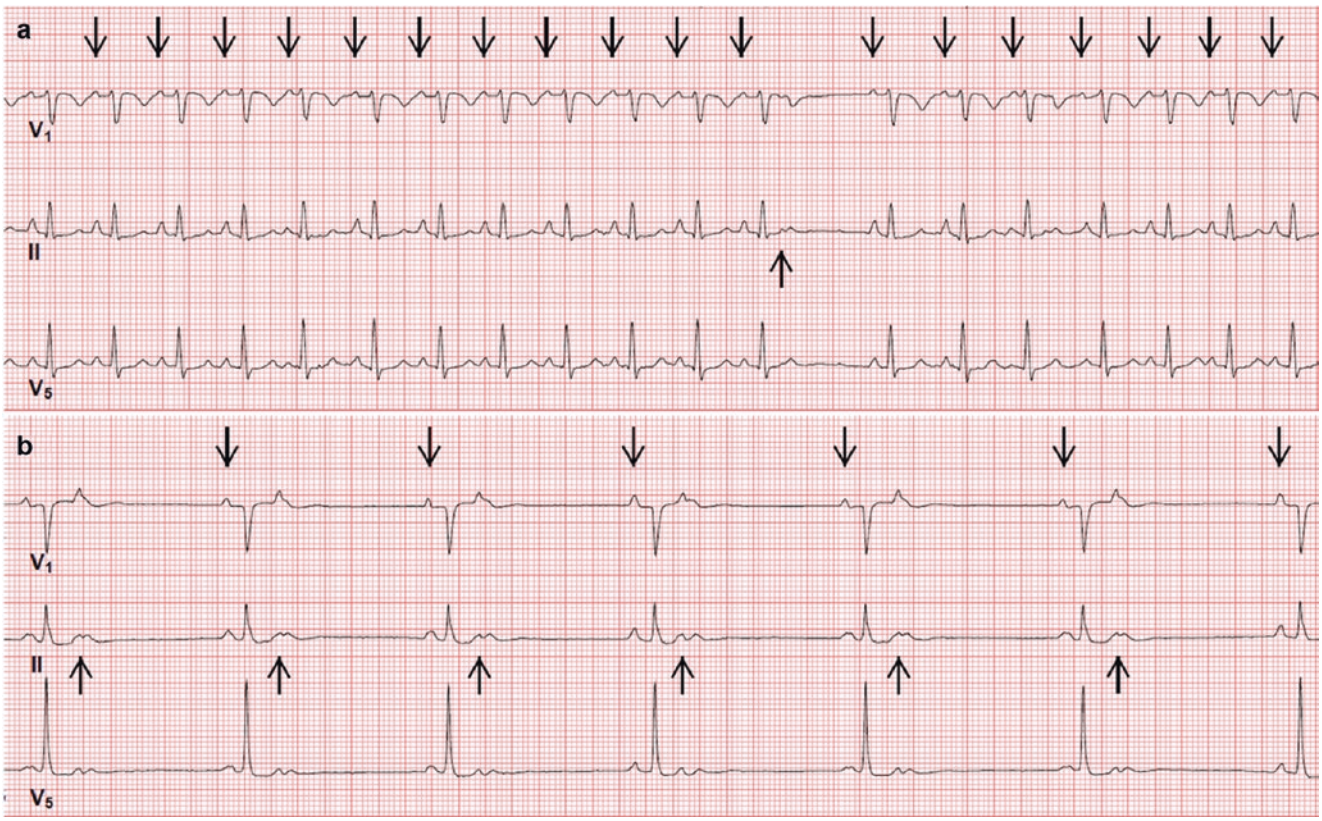


Fig. 18.9 Pauses secondary to blocked premature atrial contractions. Panel (**a**). Simultaneously recorded leads V_1, II, and V_5. The vertical arrows denote sinus P-waves. The upward-facing arrow shows a change in the ST segment and T-wave that is the premature, abnormal P-wave. Provided the AV node refractory period exceeds the coupling interval of the premature P-wave to the previous P-wave, the premature P-wave is not conducted leading to a pause in the rhythm the cause of which can only be determined by careful inspection of the ST segment and T-wave preceding the pause. Panel (**b**). Simultaneously recorded leads V_1, II, and V_5. The vertical arrows denote sinus P-waves. The *upward-facing arrows* show changes in the ST segment and T-wave that are blocked premature abnormal P-waves occurring in a pattern of bigeminy. The resultant ventricular bradycardia could be mistaken for a sinus bradycardia if the blocked premature atrial contractions are not recognized

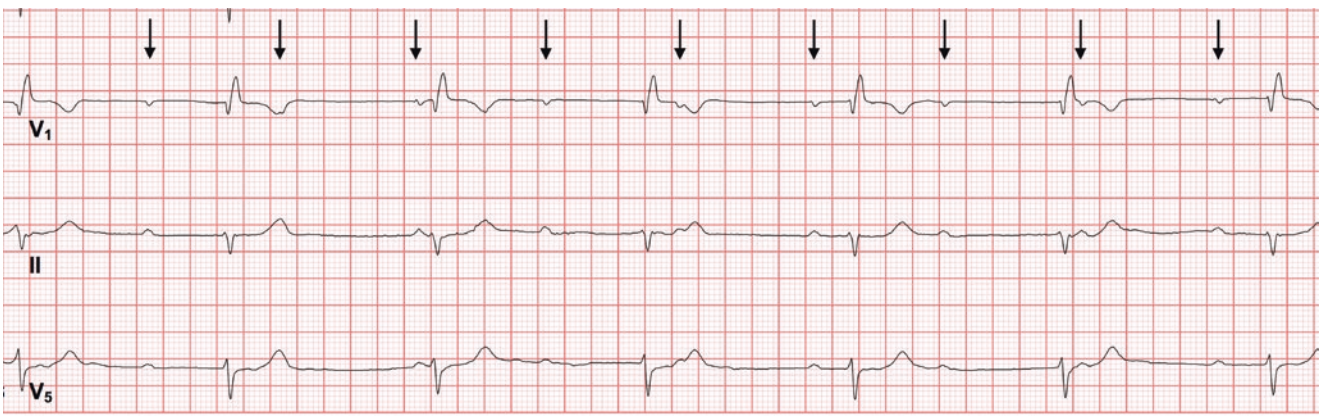


Fig. 18.10 Third-degree AV block. Simultaneously recorded leads V_1, II, and V_5. The *vertical arrows* denote sinus P-waves. There are more P-waves that QRS complexes and there is no relationship between the P-waves and the QRS complexes. The escape rhythm is either a junctional rhythm with aberrant conduction (RBBB and left anterior fascicular block) or a ventricular escape rhythm originating in or near the left posterior fascicle at a rate of 38 beats per minute

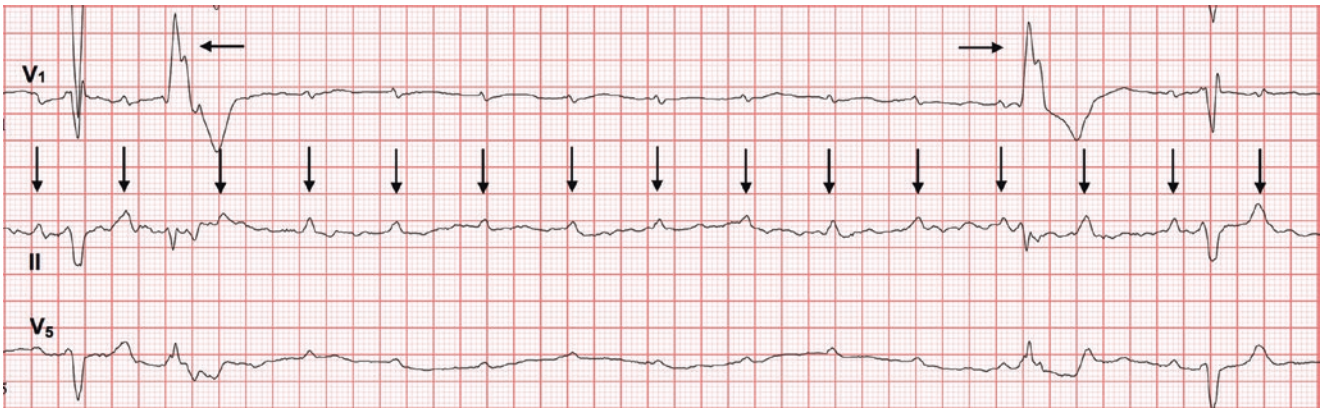


Fig. 18.11 Paroxysmal AV block. Simultaneously recorded leads V_1, II, and V_5. The *vertical arrows* denote sinus P-waves. The first and last QRS complexes on this strip are conducted from their respective preceding P-waves. In each instance, that QRS complex is followed by a nonconducted P-wave indicating underlying high-grade (2:1) AV block. A premature ventricular beat (denoted by the *left facing horizontal arrow*) initiates paroxysmal complete AV block. An escape ventricular beat (denoted by the right facing horizontal arrow) re-establishes the underlying high-grade (2:1) AV block. Even on the conducted beats there is bifascicular block in the form of RBBB and left anterior fascicular block

ants of the phenomenon. In some, otherwise normal individuals, paroxysmal AV block appears to be an unusual expression of the neuromediated (vasovagal) reflex wherein AV node dysfunction is sudden and complete in the absence of concomitant evidence of sinus node dysfunction [9]. In other individuals, most often in association with other evidence of AV conduction system disease, paroxysmal AV block follows a premature supraventricular or premature ventricular beat and is terminated by an escape supraventricular or ventricular beat (Fig. 18.11). This form of paroxysmal AV block has been ascribed to phase 4 conduction block and seems to be a harbinger of future more serious AV conduction disturbances [10].

Incomplete His-Purkinje System Blocks

Although the incomplete forms of His-Purkinje system block do not lead to manifest bradycardia, they may be warning signs that herald the future development of complete block and severe bradycardia or asystole. Furthermore, the presence of an incomplete form of His-Purkinje system block is strongly associated with the presence of structural heart disease and, even in those patients with a structurally normal heart, the onset of His-Purkinje conduction defects is associated with an increased risk of developing structural heart disease in the future [11]. Although clearly an oversimplification, the incomplete forms of His-Purkinje system disease are grouped as unifascicular blocks, bifascicular blocks, and trifascicular blocks (Table 18.2) [12].

The unifascicular blocks are isolated right bundle branch block, isolated left anterior fascicular block, and isolated left posterior fascicular block. In the absence of structural heart disease, the rates of progression of each of these unifascicular blocks to complete AV block are very low at less than 1% per year [11].

The bifascicular blocks are left anterior fascicular block with left posterior fascicular block manifest as left bundle branch block, right bundle branch block with left anterior fascicular block, and right bundle branch block with left posterior fascicular block. In the absence of evident structural heart disease, the rates of progression of the bifascicular blocks to complete AV block are 1–2% per year [11]. Of course, the probabilities of progression to complete heart block for each of the unifascicular and bifascicular blocks are increased in patients with underlying structural heart disease and in patients who present with symptoms that may represent prior experience with transient complete heart block (e.g. syncope or near syncope).

The term trifascicular block is best avoided. When used correctly, the term refers to incomplete His-Purkinje system blocks that occur in combinations that indicate dysfunction of all of the His-Purkinje system—alternating periods of right bundle branch block and left bundle branch block or alternating periods of right bundle branch block with left anterior fascicular block and right bundle branch block with left posterior fascicular block. Patients with trifascicular block have a high probability of experiencing early progression to complete AV block such that urgent permanent pacemaker placement is recommended. Unfortunately, the term trifascicular block is also erroneously applied to one of the patterns of bifascicular block in association with a

Table 18.2 ECG diagnosis of uncomplicated incomplete His-Purkinje system blocks in adults

Complete RBBB
1. QRS duration ≥120 ms
2. rsr′, rsR′, or rSR′ (less commonly broad, usually notched R) in leads V_1 or V_2.
3. S duration greater than R duration in leads I and V_6
4. Normal R peak time in V_5 and V_6 but >50 ms in lead V_1
Incomplete RBBB
1. QRS duration between 110 ms and 119 ms
2. Other criteria as for complete RBBB
Complete LBBB
1. QRS duration ≥120 ms
2. Broad notched or slurred R in leads I, aVL, V_5, and V_6
3. Absent q in leads I, V_5, and V_6 but narrow q may persist in aVL
4. R peak time > 60 ms in leads V_5 and V_6 but normal in leads V_1–V_3
Incomplete LBBB
1. QRS duration between 110 and 119 ms
2. Other criteria as for complete LBBB
Left anterior fascicular block
1. QRS duration <120 ms
2. Mean frontal plane QRS axis between −45° and −90°
3. qR pattern in lead aVL
4. R peak time in lead aVL of ≥45 ms
Left posterior fascicular block
5. QRS duration <120 ms
6. Mean frontal plane QRS axis between 90° and 180°
7. rS pattern in lead aVL
8. qR pattern in leads III and aVF

Where q(Q) indicates an initial negative defection in the QRS complex, r(R) indicates a positive deflection in the QRS complex, s(S) indicates a negative deflection following a positive deflection in the QRS complex, and r′(R′) indicates a positive deflection following an s(S) deflection in the QRS complex. In each instance, a lower case letter indicates a small deflection and an upper case letter indicates a large deflection. R peak time indicates the interval between the beginning of the QRS complex and the peak of the last r(R) deflection (normally <40 ms in leads V_1 and V_2 and <50 ms in leads V_5 and V_6. Adapted from Surawicz B et al. [12]

prolonged PR interval (first-degree AV block). In these circumstances, the first-degree AV block is almost always the result of AV nodal conduction delay rather than conduction delay in the His-Purkinje system fascicle that is still functioning and such individuals have a lower probability of experiencing progression to complete AV block than do patients with true trifascicular block. Determination of the site of AV conduction delay is possible with measurement of AV nodal conduction time (the atrium to His bundle, or AH, interval) and His-Purkinje system conduction time (the His bundle to ventricle, or HV, interval) at the time of a transvenous catheter electrophysiologic study. Measurement of an HV interval greater than 100 ms (normal 35 to 55 ms) has been proposed as an indicator of a permanent pacemaker requirement particularly in patients who have symptoms that may be compatible with covert transient complete AV block. Conduction delay in the His bundle itself is usually not expressed on the ECG or clinically. Nevertheless, in rare instances, very prolonged His bundle conduction delay may produce first-degree AV block.

Causes of AV Node Dysfunction

The atrioventricular (AV) node is, in the absence of a ventricular pre-excitation syndrome, the only pathway for an atrial depolarizing wavefront to reach the ventricles. The normal AV node transit time is 60 to 140 ms at rest [13] and the AV node will conduct atrial depolarizing wavefronts 1:1 at atrial rates at least 130 beats per minute at rest [14]. Like the sinus node, the AV node is very sensitive to autonomic tone with its conduction velocity and 1:1 following frequency increasing with augmentation of sympathetic tone / withdrawal of vagal tone and its conduction velocity and 1:1 following frequency decreasing with withdrawal of sympathetic tone/augmentation of vagal tone.

Accordingly, AV nodal dysfunction is not synonymous with AV nodal disease in that many influences external to the AV node may alter its function. These extrinsic influences are essentially the same as those extrinsic influences that affect sinus nodal function (Table 18.1). One very common clinical scenario involves the simultaneous onset of sinus nodal dysfunction, AV nodal dysfunction, and suppression of other subsidiary pacemakers. The co-incident onset of sinus nodal and AV nodal dysfunction strongly suggests that the mechanism of the nodal dysfunction is extrinsic, most commonly a sudden vagal surge secondary to the Bezold-Jarisch reflex or secondary to neuromediated (vasovagal) presyncope or syncope (Fig. 18.12).

Many, if not all, structural heart diseases can lead to AV node dysfunction, although there are several circumstances that merit further discussion.

Congenital Heart Block

Congenital heart block has an incidence of approximately 1 in 20,000 births [15]. It is thought to result from a fetal inflammatory disorder of the cardiac conduction system as a consequence of the transplacental transmission of SSA/Ro or SSB/La antibodies from mothers with an autoimmune disorder. The majority of these mothers are asymptomatic. Because mothers with anti-Ro antibodies are uncommon and because only a small minority of such mothers will bear a child with heart block, maternal screening is not performed

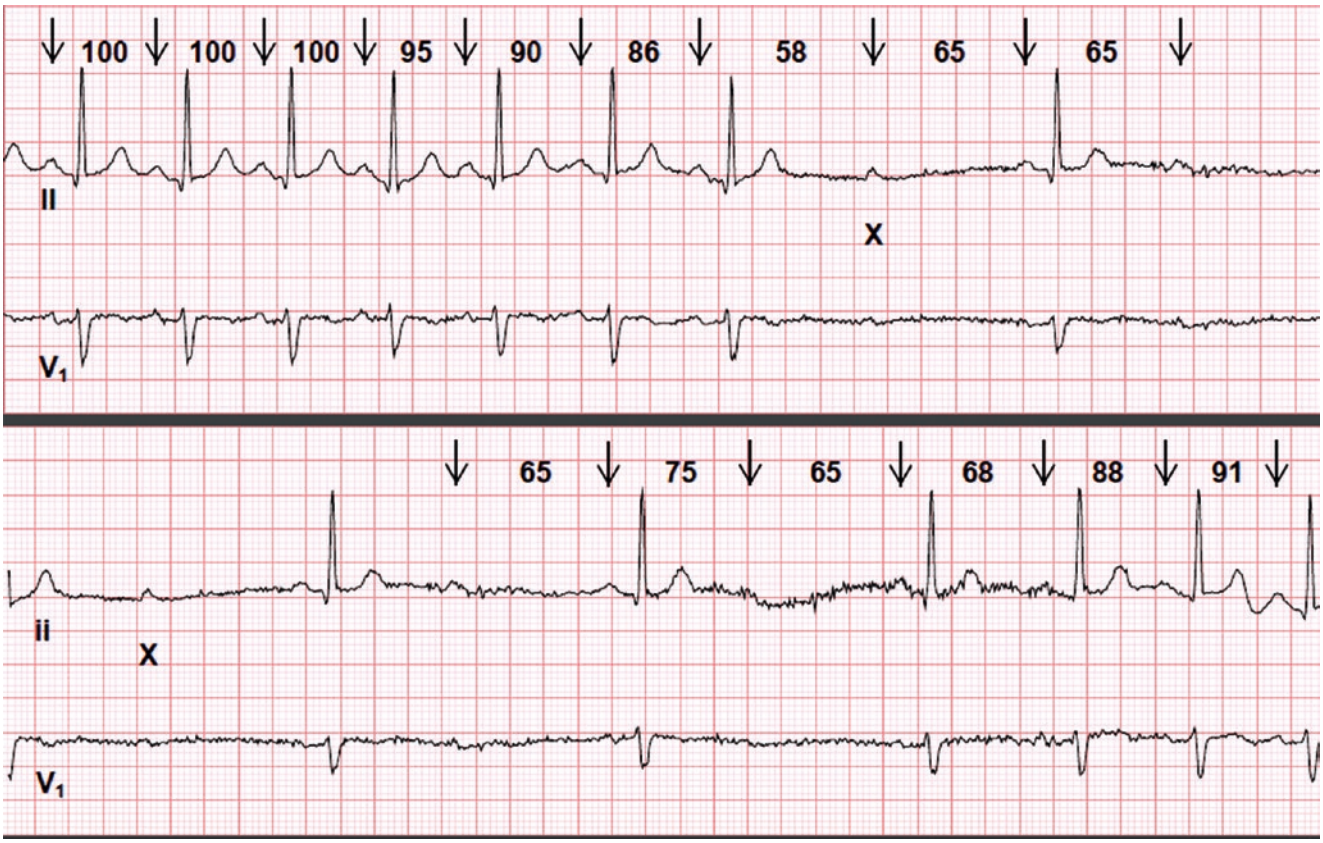


Fig. 18.12 Simultaneous onset of sinus node and AV node dysfunction characteristic of a neuromediated (vasovagal) extrinsic cause of nodal dysfunction. Simultaneously recorded leads II and V_1. The two rhythm strips overlap at the point indicated on each with an X. The vertical arrows denote sinus P-waves. The numbers between the vertical arrows represent the instantaneous heart rate at that moment. The heart rate is initially 100 beats per minute. After the first three beats the heart rate begins to slow and, near simultaneously, high-grade (2:1) block develops at the X. Shortly thereafter, both sinus node and AV node function return to normal

for this purpose. Nevertheless, once a mother has had a child with congenital heart block, the risk in subsequent pregnancies may be as high as 25% [15]. In contemporary practice, the diagnosis of congenital heart block is usually made in utero during fetal ultrasound or in childhood by routine surveillance or testing of symptomatic patients. Although congenital heart block may affect any portion of the AV conduction system, most such patients have block in the AV node with a reliable, narrow QRS complex, junctional escape rhythm in the 40 to 50 beat per minute range. When present, the symptoms of congenital heart block include any of the symptoms of bradycardia discussed below in children who can report such symptoms or pre-or post-natal growth retardation, failure to thrive, and abnormal tiredness in those who cannot report symptoms. Unfortunately, the symptom range also includes congestive heart failure and nocturnal sudden death. Finally, a few such patients are first identified as adults. In the patient population with congenital heart block, unique treatment considerations include the technical difficulties of chronic pacing in small and growing children and surveillance for timing of a pacing intervention in patients who are asymptomatic for, ultimately, essentially all patients with congenital AV block will require a permanent pacemaker.

Lyme Disease

Lyme disease is an inflammatory carditis with a predilection for the cardiac conduction system that is caused by *Borrelia burgdorferi* spirochete infection transmitted by an Ixodes tick in an endemic area [16]. After infection, the disease is usually first manifest after 1 to 4 weeks with a influenza-like illness and a characteristic erythema migrans rash. These symptoms pass over a similar period of time. Thereafter, evidence of organ system involvement emerges at any time up to 7 months later (usually 2 to 5 weeks). Cardiac involvement may include myopericarditis, acute heart failure, and supraventricular and ventricular tachyarrhythmias. However, the most common presentation is with AV block. The AV

block may originate at any level of the AV conduction system but is usually the result of AV nodal disease. The AV block is initially progressive but almost always resolves within six weeks of presentation. The diagnosis is made by suspicion in an individual who lives in or has visited an endemic area in the previous six months that is further assessed by a specific ELISA test that, if positive, is confirmed by B burgdorferi-specific IgM and IgG testing. Treatment is with antibiotics (typically IV ceftriaxone during a period of in-hospital monitoring). Temporary pacing is occasionally required [16] and may be needed for several weeks in which case temporary placement of a permanent pacemaker may be considered.

Cardiac Sarcoidosis

Sarcoidosis has an incidence of approximately 1 in 40,000 individuals per year. Cardiac involvement in systemic sarcoidosis is relatively common (up to 25% in autopsy studies) but is not commonly symptomatic (estimated 2–5% incidence) [17]. Nevertheless, isolated, advanced, otherwise unexplained, AV conduction system disease in a young individual is the result of a sarcoid granuloma in up to 35% of cases [18]. Any portion of the conduction system may be involved and the apparent severity of the conduction system block may wax and wane without apparent reason from one encounter to the next. In addition to conduction disturbances, cardiac involvement in sarcoidosis may result in congestive heart failure, atrial arrhythmias, ventricular arrhythmias, and sudden cardiac death. The diagnosis of sarcoidosis is established by histology showing non-caseating granuloma with no alternative cause. Because myocardial involvement in cardiac sarcoidosis is patchy, endomyocardial biopsy may be negative. Accordingly, diagnostic criteria for cardiac sarcoidosis in the absence of a positive endomyocardial biopsy have been proposed [17]. The indications for pacemaker therapy in patients with cardiac sarcoidosis parallel those in other settings but the choice of pacing platform is complicated by the possibility of life-threatening ventricular rhythms in some patients with cardiac sarcoidosis for whom an implantable cardioverter defibrillator may be the most appropriate pacemaker platform. Patients with unexplained syncope, ventricular systolic dysfunction, biventricular involvement, inducible sustained ventricular tachycardia at a catheter electrophysiologic study, or evidence of scar on cardiac magnetic resonance imaging may benefit from ICD implantation [19]. Steroid and other immunosuppressant therapy has not been demonstrated to prevent or to reverse conduction system disease to an extent that permanent pacemaker therapy can be avoided when otherwise indicated.

AV Block Associated with Ischemic Heart Disease

The AV node artery provides the blood supply to the AV node and arises from the dominant coronary artery (the right coronary artery in 80%, the circumflex coronary artery in 10%, and both of these arteries in 10%) at the posterior crux of the heart. Acute inferior myocardial infarction may result in AV nodal dysfunction. Nevertheless, it is likely that this AV nodal dysfunction is the result of suppression of AV nodal function by posterior vagal plexus dysfunction as suggested by the observation that post-mortem studies of such patients do not usually show structural abnormalities of the AV node and by the observation that essentially all patients whose acute inferior infarction is complicated by AV nodal dysfunction will recover AV nodal function within two weeks of the initial insult [20].

Causes of His-Purkinje System Dysfunction

His-Purkinje system dysfunction can also be due to extrinsic or intrinsic causes. Extrinsic causes of His-Purkinje system dysfunction are much less common than extrinsic causes of sinus nodal or AV nodal system dysfunction and include Vaughan William's Class Ia antiarrhythmic drugs (disopyramide, procainamide, quinidine, tricyclic antidepressants), Class Ib antiarrhythmic agents (lidocaine, mexiletine), Class Ic antiarrhythmic drugs (flecainide, propafenone), and Class III antiarrhythmic drugs (amiodarone, dofetilide, dronedarone, sotalol).

The shortest interval between two successive depolarizing wavefronts that can be conducted normally by a particular tissue is termed its relative refractory period if conduction still occurs but with a slowed conduction velocity or its absolute refractory period if conduction does not occur at all. Different tissues in the AV conduction system His-Purkinje system have different refractory periods and these refractory periods have different responses to changes in rate and autonomic tone. Under specific conditions in normal individuals both the AV node and His bundle may have refractory periods shorter than that of the right bundle branch, the left anterior fascicle, the left posterior fascicle, or the left bundle branch leading to functional fascicular blocks or bundle branch blocks, alone or in combinations, that are not indicative of His-Purkinje system dysfunction [21]. With sudden shortening of the coupling interval between two successive depolarizing wavefronts the second wavefront may impinge on the refractory period of one of the bundle branches (usually that of the right bundle) producing aberrant AV conduction and a wide QRS complex termed Ashman's phenomenon [22]. Such rate changes are most common with premature atrial beats or during atrial

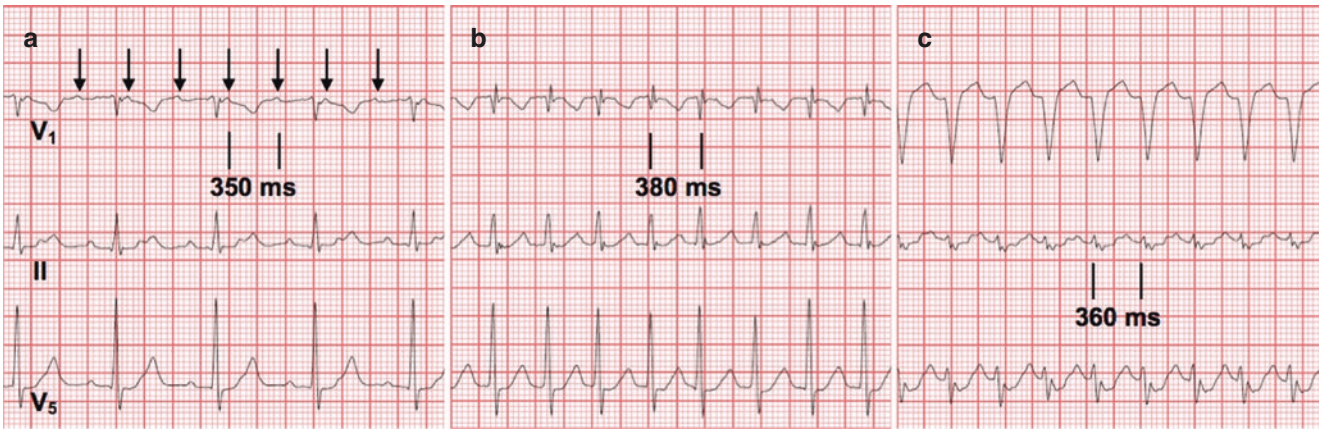


Fig. 18.13 Functional AV block and functional left bundle branch block. Simultaneously recorded leads V_1, II, and V_5 from a patient with an atrial tachycardia. Panels (**a**), (**b**), and (**c**) were recorded hours apart. Panel (**a**): Atrial tachycardia with functional 2:1 AV block. The vertical arrows denote P-waves. At this time the atrial cycle length was 350 ms and was conducted 2:1. The site of functional AV block was the AV node. Panel (**b**): The atrial cycle length slows to 380 ms and 1:1 AV conduction can then occur (indicating that the AV node refractory period was >350 ms and <380 ms). Panel (**c**): The atrial cycle length accelerates slightly to 360 ms and, although 1:1 AV conduction can still occur (indicating that the AV node refractory period was >350 ms and <360 ms), functional left bundle branch block is now present (indicating that the left bundle branch refractory period was >360 ms and <380 ms)

fibrillation. Sustained functional bundle branch block may occur at heart rates over 135 beats per minute (particularly when the heart rate is inappropriate for the current level of autonomic tone as in a supraventricular tachycardia) and tends to manifest right bundle branch block at lower fast heart rates and left bundle branch block at higher fast heart rates [21], conditions referred to as rate-dependent functional bundle branch block (Fig. 18.13).

Other forms of His-Purkinje system dysfunction are ascribed to His-Purkinje system disease. Essentially any structural heart disease that affects the ventricles may produce intrinsic His-Purkinje system disease. Although idiopathic and congenital forms of His-Purkinje system disease do occur (often referred to as Lev's [23] or Lenègre's disease [24]), new-onset His-Purkinje system disease should alert the clinician to the possibility of occult underlying structural heart disease, usually ischemic heart disease or nonischemic cardiomyopathy. In the former instance, it is noteworthy that the blood supply to the AV node arises from the dominant coronary artery that also serves the inferior left ventricle. The blood supply to the His bundle, the anterior portion of the left bundle branch, and the right bundle branch arises from the left anterior descending coronary artery that also serves the anterior left ventricle. The posterior portion of the left bundle branch receives a dual blood supply from both the dominant coronary artery and the left anterior descending coronary artery. As a consequence of these blood supplies, AV nodal dysfunction is associated with inferior myocardial infarction, His-Purkinje system dysfunction is associated with anterior infarction, and left posterior fascicular block is the least common form of His-Purkinje system dysfunction in patients with ischemic heart disease.

Symptoms of the Bradycardias

Symptoms of bradycardia may include any symptom of cardiac insufficiency (weakness, pre-syncope, syncope, dyspnea, or, rarely, chest discomfort) particularly when expressed as effort intolerance. Indeed, on occasion, the only objective evidence of sinus node disease is effort intolerance secondary to inability to mount an exercise-related sinus tachycardia (chronotropic incompetence). Of course, the more severe the bradycardia the more severe the symptoms might be expected to be, culminating, in the case of ventricular asystole, with sudden cardiac death. Sometimes symptoms of bradycardia can be more subtle including such cognitive difficulties as inability to concentrate.

Sudden cardiac death is the most worrisome consequence of the bradycardias. Nevertheless, it should be noted that sudden death as a consequence of asystole is very rare in individuals who do not have severe underlying structural heart disease manifest with severe congestive cardiomyopathy. In other individuals, sudden death related to a bradycardia is more likely to be the consequence of the bradycardia permitting the emergence of torsade de pointes ventricular tachycardia and ventricular fibrillation (Fig. 18.14).

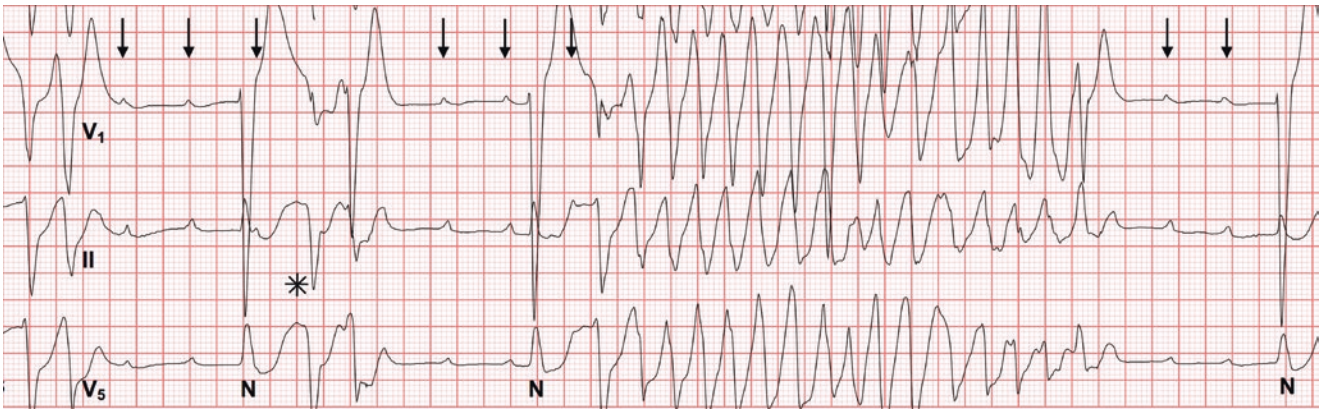


Fig. 18.14 Third-degree AV block leading to QT interval prolongation and torsade de pointes ventricular tachycardia. Vertical arrows denote visible sinus P-waves representing an underlying sinus rhythm at 120 beats/min. The first two QRS complexes on this strip are of ventricular origin. They are followed by two nonconducted P-waves, which, in turn, are followed by a narrow QRS complex escape beat (N). Note the very prolonged QT interval of this beat, best seen as the subsequent positive undulation in leads II and V_5 peaking at the asterix. Just after the peak of this T-wave there are a pair of polymorphic ventricular beats followed by another series of non-conducted P-waves and then another narrow QRS complex escape beat with marked QT interval prolongation. This beat is followed by a run of torsade de pointes ventricular tachycardia

Treatment of the Bradycardias

The goals of treatment of the bradycardias include acute therapy for stabilization, correction of reversible causes, reversal of symptoms, and prevention of serious subsequent events including syncope and sudden cardiac death.

Acute therapy for stabilization is required for severely symptomatic patients, for patients with unstable hemodynamics, and for patients with evidence of impending torsade de pointes ventricular tachycardia (ventricular premature beats near the peak of the T-wave in the setting of a long QT interval, particularly when the ventricular premature beats are bigeminal, polymorphic, or display repetitive forms). On balance, the best of the acute therapies for stabilization in this setting is placement of a temporary transvenous pacemaker. Nevertheless, in many instances, this therapy cannot be provided immediately. Alternative therapies that may be used until a temporary transvenous pacemaker can be placed include transcutaneous pacing and pharmaceutical agents that enhance normal automaticity and/or shorten the refractory periods of the tissues responsible for the bradycardia. With respect to the pharmaceutical approach, atropine is frequently used. Nevertheless, in that this therapy only interferes with vagal traffic, it will likely be ineffective in situations other that of a vagal surge. The most effective agents are beta-1 sympathomimetic agents such as isoproterenol, dobutamine, dopamine, or epinephrine and adenosine antagonists such as aminophylline or theophylline (the American Heart Association Advanced Cardiac Life Support guidelines specifically recommend IV epinephrine 2–10 μg/min or IV dopamine 2–10 μg/kg/min [25]). Although theophylline may be used orally for longer periods of time [26], pharmaceutical approaches to treatment of patients with bradycardias are generally only temporary measures.

As soon as a patient presents with a bradycardia, efforts are made to identify any reversible or transient causes that may be reversed or outwaited. In the former category, it is important to modify extrinsic influences that slow normal automaticity or prolong the refractory periods of components of the AV conduction system (most often correction of electrolyte, acid-base, and/or oxygenation abnormalities, the withdrawal of drugs with negative chronotropic or negative dromotropic effects, or the treatment of hypothyroidism). When AV nodal dysfunction is the result of acute insults such as an inferior myocardial infarction or immediately after cardiac surgery, recovery of AV nodal function is usual with in the subsequent 2 weeks.

Asymptomatic patients are followed for one of three outcomes that recommend intervention—serial clinical assessments for the development of symptoms, serial ambulatory electrocardiographic monitoring for severe and prolonged bradycardia (usually defined as daytime heart rates below 40 beat per minute) or prolonged (usually nocturnal) pauses generally defined as greater than 3 s in the absence of atrial fibrillation and five seconds in the presence of atrial fibrillation, and serial echocardiographic examinations for adverse remodeling of the left ventricle generally defined as enlargement to abnormal left ventricular diameters or volume.

Patients who are symptomatic with a bradycardia that cannot be reversed or with bradycardia in a setting that requires drugs with negative chronotropic or negative dromotropic effects are treated with a permanent implanted pacemaker. Asymptomatic patients who display warning signs of serious subsequent events such as worrisome

bradycardia-dependent QT interval prolongation, prolonged pauses, or adverse left ventricular remodeling are also treated with a permanent implantable pacemaker. Selected guidelines for pacing are summarized in Tables 18.3, 18.4, and 18.5 and are detailed in multiple guideline documents [27, 28].

The most commonly used pacemaker systems are AAI (a single chamber atrial demand pacemaker that requires one lead), VVI (a single chamber right ventricular demand pacemaker that requires one lead), VDD (a dual chamber pacemaker with electrodes in the body of a single lead that can sense right atrial activity and other electrodes at the tip of that lead that can sense and pace the right ventricle), DDD (a dual chamber pacing system that requires two leads), and CRT (a cardiac resynchronization pacemaker that paces both of ventricles and, often, also the right atrium and requires at least two leads; three leads if the right atrium is also paced and/or sensed). When an implantable cardioverter defibrillator (ICD) is indicated, ICD systems also come in VVI, DDD, and CRT pacing platforms.

Table 18.3 Selected indications for permanent pacing in sinus node disease

Class I recommendations
1. Permanent pacemaker implantation is indicated for SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. (Level of Evidence: C)
2. Permanent pacemaker implantation is indicated for symptomatic chronotropic incompetence. (Level of Evidence: C)
3. Permanent pacemaker implantation is indicated for symptomatic sinus bradycardia that results from required drug therapy for medical conditions. (Level of Evidence: C)
Class IIa recommendations
1. Permanent pacemaker implantation is reasonable for SND with heart rate less than 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented (Level of Evidence: C)
2. Permanent pacemaker implantation is reasonable for syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiological studies. (Level of Evidence: C)
Class IIb recommendation
1. Permanent pacemaker implantation may be considered in minimally symptomatic patients with chronic heart rate less than 40 bpm while awake. (Level of Evidence: C)
Class III recommendations
1. Permanent pacemaker implantation is not indicated for SND in asymptomatic patients. (Level of Evidence: C)
2. Permanent pacemaker implantation is not indicated for SND in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia. (Level of Evidence: C)
3. Permanent pacemaker implantation is not indicated for SND with symptomatic bradycardia due to nonessential drug therapy.(Level of Evidence: C)

Adapted from Epstein et al. [27]

Table 18.4 Selected indications for permanent pacing in AV conduction system disease

Class I recommendations
1. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be due to AV block. (Level of Evidence: C)
2. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia. (Level of Evidence: C)
3. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level in awake, symptom-free patients in sinus rhythm, with documented periods of asystole greater than or equal to 3.0 s or any escape rate less than 40 bpm, or with an escape rhythm that is below the AV node. (Level of Evidence: C)
4. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level in awake, symptom-free patients with AF and bradycardia with one or more pauses of at least 5.0 s or longer. (Level of Evidence: C)
5. Permanent pacemaker implantation is indicated for second-degree AV block with associated symptomatic bradycardia regardless of type or site of block. (Level of Evidence: B)
6. Permanent pacemaker implantation is indicated for asymptomatic persistent third-degree AV block at any site with average awake ventricular rates of ≥40 bpm if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node. (Level of Evidence: B)
Class IIa recommendations
1. Permanent pacemaker implantation is reasonable for persistent third-degree AV block with an escape rate greater than 40 bpm in asymptomatic adult patients without cardiomegaly (Level of Evidence: C)
2. Permanent pacemaker implantation is reasonable for asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiological study. (Level of Evidence: B)
3. Permanent pacemaker implantation is reasonable for first- or second-degree AV block with symptoms of pacemaker syndrome or hemodynamic compromise. (Level of Evidence: B)
Class IIb recommendations
1. Permanent pacemaker implantation may be considered for AV block in the setting of drug use and/or drug toxicity when the block is expected to recur even after the drug is withdrawn. (Level of Evidence: B)
2. Permanent pacemaker implantation may be considered in minimally symptomatic patients with chronic heart rate less than 40 bpm while awake. (Level of Evidence: C)
Class III recommendations
1. Permanent pacemaker implantation is not indicated for asymptomatic first-degree AV block. (Level of Evidence: B)
2. Permanent pacemaker implantation is not indicated for asymptomatic type I second-degree AV block at the supra-His (AV node) level or that which is not known to be intra- or infra-Hisian. (Level of Evidence: C)
3. Permanent pacemaker implantation is not indicated for AV block that is expected to resolve and is unlikely to recur (e.g., drug toxicity, Lyme disease, or transient increases in vagal tone or during hypoxia in sleep apnea syndrome in the absence of symptoms). (Level of Evidence: B)

Adapted from Epstein et al. [27]

Table 18.5 Selected indications for permanent pacing in chronic bifascicular block

Class I recommendations
1. Permanent pacemaker implantation is indicated for advanced second-degree AV block or intermittent third-degree AV block. (Level of Evidence: B)
2. Permanent pacemaker implantation is indicated for type II second-degree AV block. (Level of Evidence: B)
3. Permanent pacemaker implantation is indicated for alternating bundle-branch block. (Level of Evidence: C)
Class IIa recommendations
1. Permanent pacemaker implantation is reasonable for syncope not demonstrated to be due to AV block when other likely causes have been excluded, specifically ventricular tachycardia. (Level of Evidence: B)
2. Permanent pacemaker implantation is reasonable for an incidental finding at electrophysiological study of a markedly prolonged HV interval (greater than or equal to 100 ms) in asymptomatic patients. (Level of Evidence: B)
3. Permanent pacemaker implantation is reasonable for an incidental finding at electrophysiological study of pacing induced infra-His block that is not physiological. (Level of Evidence: B)
Class III recommendations
1. Permanent pacemaker implantation is not indicated for fascicular block without AV block or symptoms. (Level of Evidence: B)
2. Permanent pacemaker implantation is not indicated for fascicular block with first-degree AV block without symptoms. (Level of Evidence: B)

Adapted from Epstein et al. [27]

The traditional choice of mode of permanent pacing has been between use of a VVI pacing system versus use of potentially more physiologic pacing systems such as a DDD pacing system (or an AAI pacing system if AV conduction is intact) that are also capable of pacing the atrium and providing AV synchrony. The major presumed advantage of VVI pacing is that the system is simple and should be associated with the lowest probability of a system-related complication. Such systems may be used for either patients with sinus node disease or for patients with AV conduction system disease. The major presumed disadvantage of VVI pacing is that atrioventricular synchrony cannot be achieved during pacing as the atria cannot be either sensed or paced. This may result in symptoms of cardiac dysfunction during pacing collectively referred to as the pacemaker syndrome. The reported incidence of pacemaker syndrome with VVI pacing when rigorously defined using objective criteria is approximately 7% [29] while the reported incidence of the ability to discern any symptomatic benefit of DDD pacing over VVI pacing is approximately 84% [30]. The major presumed advantage of DDD pacing is that physiologic AV synchrony is preserved in all patients. The major presumed disadvantage of DDD pacing is the increased probability of complications that will be associated with more complex pacing systems. The major presumed advantage of AAI pacing is that physiologic AV synchrony can be achieved with a single lead system. The major disadvantage of AAI pacing is that it will not meet the goals of pacing for patients with AV block or for those patients with sinus node disease who develop AV block after pacemaker placement (a risk estimated at 2% per year [31]). Each of the pacing systems that include right ventricular pacing have the potential disadvantage of inducing interventricular dyssynchrony wherein sequential right then left ventricular contraction during pacing diminishes ventricular systolic efficiency thereby worsening systolic left ventricular function and, perhaps, even causing left ventricular systolic dysfunction. Cardiac resynchronization therapy (CRT) pacing re-establishes interventricular synchrony and is used to treat congestive heart failure in patients with electrical evidence of interventricular dyssynchrony (typically patients with LBBB) and to prevent worsening interventricular dyssynchrony in patients who are expected to be continually paced from the right ventricular and who are thought to be at risk of developing left ventricular systolic dysfunction. These presumed advantages and disadvantages of various pacing systems have been investigated in a number of large randomized clinical trials.

Five studies of ventricular based pacing (VVI) versus atrial based pacing (AAI or DDD), involving nearly 35,000 patient years of follow-up, were summarized in an individual patient data meta-analysis published by Healey et al. [32]. This meta-analysis found that nearly all of the pre-specified outcome measures evaluated had a hazard ratio point estimate that favored atrial based pacing (AAI or DDD) over ventricular based pacing (VVI). Some of these beneficial outcomes were statistically-significant (follow-up outcome, HR, 95% CI, p-value: atrial fibrillation, 0.80, 0.72 to 0.89, $p = 0.00003$ and stroke, 0.81, 0.67 to 0.99, $p = 0.035$) but others were not (follow-up outcome, HR, 95% CI, p-value: all-cause mortality, 0.95, 0.87 to 1.03, $p = 0.19$; stroke or cardiovascular death, 0.94, 0.85 to 1.04, $p = 0.18$; and, heart failure hospitalization, HR, 0.89, 0.77 to 1.03, $p = 0.12$). A pre-specified subgroup analyses suggested greater benefit for atrial based pacing (AAI or DDD) over ventricular based

pacing (VVI) for the outcome of the composite of stroke or cardiovascular death in patients with sinus node disease (HR, 95% CI, p-value: 0.83, 95%, 0.72 to 0.97, p = 0.04). However, subgroup analyses of patient characteristics often considered to favor atrial based pacing (AAI or DDD) over ventricular based pacing (VVI), including left ventricular systolic dysfunction, hypertension, heart failure, and a low unpaced heart rate, did not show differences based on pacing mode [32].

Although there are data suggesting that atrial based pacing (AAI or DDD) is associated with a better quality of life than that associated with ventricular based pacing (VVI) [30, 33], especially in patients with sinus node disease [34, 35], the randomized clinical trial data summarized by Healey et al. [32] suggests that the outcome advantages of atrial based pacing (AAI or DDD) over ventricular based pacing (VVI) are small. Furthermore, this advantage comes with a cost. The meta-analysis of Healey et al. also found, as expected, that the complication rate of atrial based pacing (AAI or DDD) at 6.2% was nearly twice that of ventricular based pacing (VVI) at 3.2%. Of course, this difference will depend on the relative proportions of AAI versus DDD platforms in the atrial based pacing group. In the Danish trial included in this meta-analysis, 225 patients with sinus node disease were randomly assigned to receive AAI versus VVI pacing platforms [36]. The follow-up device complication rates requiring re-operation were 3.7% in the AAI patient group annualized over a mean follow-up of 5.7 years and 2.6% in the VVI patient group annualized over a mean follow-up of 5.5 years. This difference was accounted for by the higher dislodgement rate of atrial leads (annualized 1.6%) compared to ventricular leads (annualized 0.4%).

A meta-analysis of eight randomized clinical trials of cardiac resynchronization therapy (CRT) in 3380 patients with symptomatic congestive heart failure secondary to systolic left ventricular systolic dysfunction with left ventricular ejection fractions ≤0.35 and QRS durations >120 ms reported that CRT pacing reduced all-cause mortality (odds ratio 0.72, 95% CI 0.59 to 0.88), reduced heart failure related hospitalization (odds ratio 0.55, 95% CI 0.44 to 0.68), and improved quality of life [37]. These benefits were experienced predominantly in patients in sinus rhythm, with a QRS duration ≥150 ms, and with typical left bundle branch block. The importance of these observations to patients with bradyarrhythmias relates to the concept that right ventricular pacing may be equivalent to left bundle branch block with respect to the creation of interventricular dyssynchrony. The BLOCK-HF trial [38] studied 918 patients with NYHA Class I to Class III congestive heart failure, with a left ventricular ejection fraction ≤0.50, and with a standard indication for a pacemaker because of high-grade AV block who received a CRT pacemaker or, if indicated, a CRT defibrillator (the platform also included atrial pacing in patients without persistent atrial tachyarrhythmias). The patients were then randomized to have the CRT component of the pacing system activated or not. The primary outcome was time to first event of the composite of all-cause mortality, urgent care visit for worsening heart failure that included IV therapy, or an increase in left ventricular end diastolic volume of ≥15%. Patients randomized to receive CRT pacing had fewer of these adverse outcomes (hazard ratio 0.74; 95% CI 0.60 to 0.90). Each of the individual components of the composite outcome also occurred statistically-significantly less often in patients randomized to receive CRT pacing except for all-cause death (hazard ratio 0.83; 95% CI 0.61 to 1.14), an singular event that the study was not powered to detect. Whether or not CRT pacing is superior to other pacing modes in patients AV block was also evaluated by a meta-analysis of five randomized clinical trials comparing CRT pacing to RV pacing in either parallel-group or crossover trial designs involving 686 patients (most of whom had left ventricular systolic dysfunction) who had AV block secondary to purposeful AV junction ablation in the setting of atrial fibrillation [39]. This analysis suggested that patients randomized to receive CRT pacing had a lower probability of admission to hospital for treatment of heart failure, an improvement in left ventricular ejection fraction, and a reduction in left ventricular end diastolic volume compared to patients randomized to standard RV pacing. The analysis showed no statistically-significant difference between these two patient groups with respect to all-cause mortality, 6-minute wall test distance, or quality of life as measured by the Minnesota Living with Heart Failure Questionnaire. Whether or not CRT pacing is superior to other pacing modes in patients without symptomatic left ventricular dysfunction has not been adequately studied.

Flow diagrams to assist in the selection of the most appropriate pacing mode for patients with isolated sinus nodal dysfunction (Fig. 18.15) and for patients with isolated AV conduction system dysfunction (Fig. 18.16) were suggested by the 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities [27].

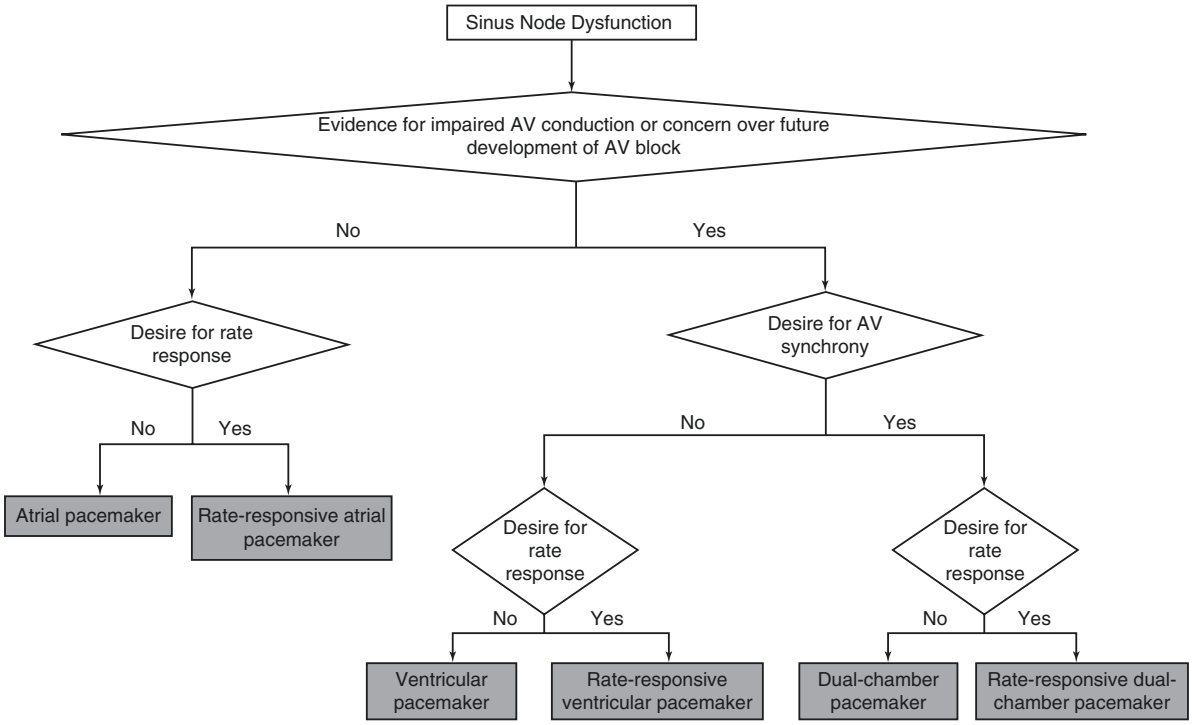


Fig. 18.15 Selection of pacemaker mode for patients with sinus node dysfunction. Decisions are illustrated by diamonds. Shaded boxes indicate type of pacemaker. AV indicates atrioventricular. From Epstein et al. [27] with permission

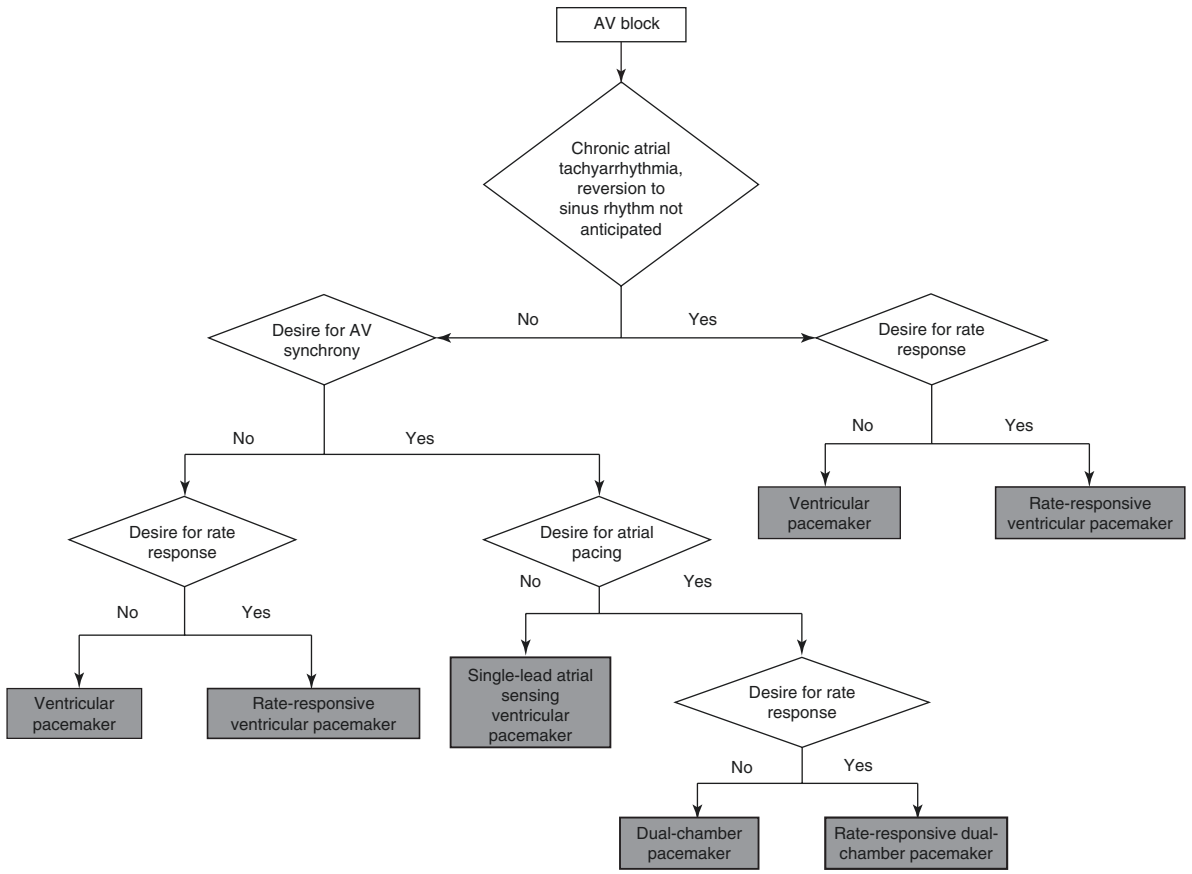


Fig. 18.16 Selection of pacemaker mode for patients with AV block. Decisions are illustrated by diamonds. Shaded boxes indicate type of pacemaker. AV indicates atrioventicular. From Epstein et al. [27] with permission

References

1. Dobrzynski H, Anderson RH, Atkinson A, Borbas Z, D'Souza A, Fraser JF, Inada S, Logantha SJRJ, Monfredi O, Morris GM, Moorman AFM, Nikolaidou T, Schneider H, Szuts V, Temple IP, Yanni J, Boyett MR. Structure, function and clinical relevance of the cardiac conduction system, including the atrioventricular ring and outflow tract tissues. Pharmacol Ther. 2013;139:260–88.
2. Anderson RH, Ho SY. The architecture of the sinus node, the atrioventricular conduction axis, and the internodal atrial myocardium. J Cardiovasc Electrophysiol. 1998;9:1233–48.
3. Liu R, Chen J. Sinoventricular conduction with Wenckebach block: danger signs of hyperkalemia. Herz. 2015;40:82–4.
4. Durrer D, van Dam RT, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. Circulation. 1970;41:899–912.
5. Katritsis D, Camm AJ. Chronotropic incompetence: a proposal for definition and diagnosis. Br Heart J. 1993;70:400–2.
6. Wilkoff BL, Corey J, Blackburn G. A mathematical model of exercise cardiac chronotropic response to exercise. J Electrophysiol. 1989;3:176–80.
7. Jensen PN, Gronroos NN, Chen LY, Folsom AR, de Filippi C, Heckbert SR, Alonso A. Incidence of and risk factors for sick sinus syndrome in the general population. J Am Coll Cardiol. 2014;64:531–8.
8. Moss AJ, Davis RJ. Brady-tachy syndrome. Prog Cardiovasc Dis. 1974;16:439–54.
9. Brignole M, Deharo J-C, De Roy L, Menozzi C, Blommaert D, Dabiri L, Ruf J, Guieu R. Syncope due to idiopathic paroxysmal atrioventricular block: long-term follow-up of a distinct form of atrioventricular block. J Am Coll Cardiol. 2011;58:167–73.
10. Lee S, Wellens HJJ, Josephson ME. Paroxysmal atrioventricular block. Heart Rhythm. 2009;6:1229–34.
11. McAnulty JH, Rahimtoola SH. Bundle branch block. Prog Cardiovasc Dis. 1983;26:333–54.
12. Surawicz B, Childers R, Deal BJ, Gettes LS. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances. J Am Coll Cardiol. 2009;53:976–81.
13. Akhtar M, Damata AN. Clinical uses of His bundle electrocardiography. Am Heart J. 1976;91:520–6.
14. Kerr CR, Tyers FO, Vorderbrugge S. Atrial pacing: efficacy and safety. PACE. 1989;12:1049–53.
15. Bordachar P, Whinnett Z, Ploux S, Labrousse L, Haissaguerre M, Thambo J-B. Pathophysiology, clinical course, and management of congenital complete heart block. Heart Rhythm. 2013;10:760–6.
16. Robinson ML, Kobayashi T, Higgins Y, Calkins H, Melia MT. Lyme carditis. Infect Dis Clin N Am. 2015;29:255–68.
17. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, Judson MA, Kron J, Mehta D, Nielsen JC, Patel AR, Ohe T, Raatikainen P, Soejima K. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014;11:1304–23.
18. Nery P, Beanlands RS, Nair GM, Green M, Yang J, McArdle BA, Davis D, Ohira H, Gollob MH, Leung E, Healey JS, Birnie DH. Atrioventricular block as the initial manifestation of cardiac sarcoidosis in middle-age adults. J Cardiovasc Electrophysiol. 2014;25:875–81.
19. Kron J, Ellenbogen KA. Cardiac sarcoidosis: contemporary review. J Cardiovasc Electrophysiol. 2015;26:104–9.
20. Clemmensen P, Bates ER, Califf RM, Hlatky MA, Aronson L, George BS, Lee KL, Kereiakes DJ, Gacioch G, Berrios E, Topol EJ, TAMI Study Group. Complete atrioventricular block complicating inferior wall acute myocardial infarction treated with reperfusion therapy. Am J Cardiol. 1991;67:225–30.
21. Chilson DA, Zipes DP, Heger JJ, Browne KF, Prystowski EN. Functional bundle branch block: discordant response of right and left bundle branches to changes in heart rate. Am J Cardiol. 1984;54:313–6.
22. Alraies MC, Eisa NE, Alraies AH, Shaheen K. The long and short of it: Ashman's phenomenon. Am J Med. 2013;126:962–3.
23. Lev M. The pathology of complete atrioventricular block. Prog Cardiovasc Dis. 1964;6:317–26.
24. Lenègre J. Eliology and pathology of bilateral bundle branch block in relation to complete heart block. Prog Cardiovasc Dis. 1964;6:409–44.
25. Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, Kudenchuk PJ, Ornato JP, McNally B, Silvers SM, Passman RS, White RD, Hess EP, Tang W, Davis D, Sinz E, Morrison LJ. Part 8:adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(suppl 3):S729–67.
26. Dixon WC, Bauch TD. Effects of theophylline on exercise indices in a patient with chronotropic incompetence. Clin Cardiol. 2000;23:787–9.
27. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA III, Ferguson TB Jr, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD. American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. J Am Coll Cardiol. 2013;61:e6–75.
28. European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliot PM, Gorenek B, Isreal CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013;15:1070–118.
29. Ausubel K, Furman S. The pacemaker syndrome. Ann Intern Med. 1985;103:420–9.
30. Heldman D, Mulvihill D, Nguyen H, Messenger JC, Rylaarsdam A, Evans K, Castellanet MJ. True incidence of pacemaker syndrome. PACE. 1990;13:1742–50.
31. Kristensen L, Nielsen JC, Pedersen AK, Mortensen PT, Andersen HR. AV block and changes in pacing mode during long-term follow-up of 399 consecutive patients with sick sinus syndrome treated with an AAI/AAIR pacemaker. PACE. 2001;24:358–65.
32. Healey JS, Toff WD, Lamas GA, Andersen HR, Thorpe KE, Ellenbogen KA, Lee KL, Skene AM, Schron EB, Skehan JD, Goldman L, Roberts RS, Camm AJ, Yusuf S, Connolly SJ. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. Circulation. 2006;114:11–7.
33. Link MS, Hellkamp AS, Estes NA 3rd, Orav EJ, Ellenbogen KA, Ibrahim B, Greenspoon A, Rizo-Patro C, Goldman L, Lee KL, Lamas GA. High incidence of pacemaker syndrome in patients with sinus node dysfunction treated with ventricular-based pacing in the Mode Selection Trial (MOST). J Am Coll Cardiol. 2004;43:2066–71.
34. Lamas GA, Orav EJ, Stambler BS, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. Pacemaker Selection in the Elderly Investigators. N Engl J Med. 1998;338:1097–104.

35. Fleischmann KE, Orav EJ, Lamas GA, et al. Pacemaker implantation and quality of life in the Mode Selection Trial (MOST). Heart Rhythm. 2006;3:653–9.
36. Andersen HR, Nielsen JC, Thomsen PEB, Thuesen L, Mortensen PTM, Vesterlund T, Pedersen AK. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet. 1997;350:1210–6.
37. Freemantle N, Tharmanathan P, Calvert MJ, Abraham WT, Ghosh J, Cleland JGF. Cardiac resynchronisation for patients with heart failure due to left ventricular systolic dysfunction—a systematic review and meta-analysis. Eur J Heart Fail. 2006;8:433–40.
38. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, St. John Sutton M. Biventricular versus right ventricular pacing in heart failure patients with atrioventricular block (BLOCK HF) trial investigators. N Engl J Med. 2013;368:1585–93.
39. Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: a meta-analysis. Europace. 2012;14:1490–7.

Syncope and Risk of Sudden Death

19

Wayne O. Adkisson, Balaji Krishnan, and David G. Benditt

Abstract

This chapter focuses on the potential risk of premature death, and in particular sudden cardiac death (SCD), in patients who present with collapse and are presumed to have had syncope. However, before a clinician can attempt to assess mortality risk relative to an episode of syncope, it is first essential to determine that collapse was in fact due to syncope (i.e., transient self-limited loss of consciousness due to cerebral hypoperfusion) and not of other cause (e.g., seizure, trauma, etc.). This chapter provides an approach to establishing the accurate diagnosis of syncope. While this step may seem to be self-evident, the hectic pace of modern medicine can result in the diagnosis not being considered with sufficient care. Finally, we discuss the assessment of the risks of recurrence, mortality and sudden cardiac arrest associated with syncope of various etiologies.

Keywords

Syncope • Sudden cardiac death

Introduction

> "You've got to be very careful if you don't know where you are going, because you might not get there." Lawrence "Yogi" Berra, 1925–2015

Recently, the Heart Rhythm Society (HRS), following previous efforts of the European Society of Cardiology's (ESC) Syncope Task Force (2009), offered practitioners a consensus statement which provides a definition of syncope which may be useful in the clinic: "Syncope is defined as a transient loss of consciousness, associated with an inability to maintain postural tone, rapid and spontaneous recovery, and the absence of clinical features specific for another form of transient loss of consciousness such as an epileptic seizure" [1]. This definition, while adequate for most settings, omits the key pathophysiologic feature of syncope emphasized in the ESC work [2]; namely, that 'true syncope' is caused by transient cerebral hypoperfusion. This crucial element, while being considered by some to be only important from an epidemiologic perspective, has clinical importance in eliminating other potentially confusing clinical conditions that may be inappropriately considered to be 'syncope', such as concussion, metabolic disturbances, or intoxications (Fig. 19.1).

Given the pathophysiologic definition cited above, loss of consciousness in syncope is triggered by transient insufficiency of oxygen delivery to the brain [2–4] most often due to a self-limited period of systemic hypotension with insufficient cerebral blood flow. A wide range of conditions may be responsible; in many instances the cause is relatively benign (e.g., assumption of upright posture in patients susceptible to orthostatic faints, emotional upset, or pain causing a vasovagal faint), but in other cases the trigger for the faint may be more serious (e.g., atrioventricular block, self-terminating ventricular tachyarrhythmias or bradyarrhythmias) (Fig. 19.2).

W.O. Adkisson, M.D. (✉) • B. Krishnan, M.D. • D.G. Benditt, M.D.
Cardiovascular Division, Department of Medicine, Cardiac Arrhythmia and Syncope Center, University of Minnesota Medical School, Mail Code 508, 420 Delaware St SE, Minneapolis, MN 55455, USA
e-mail: adki0004@umn.edu; kris0145@umn.edu; bendi001@umn.edu

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_19

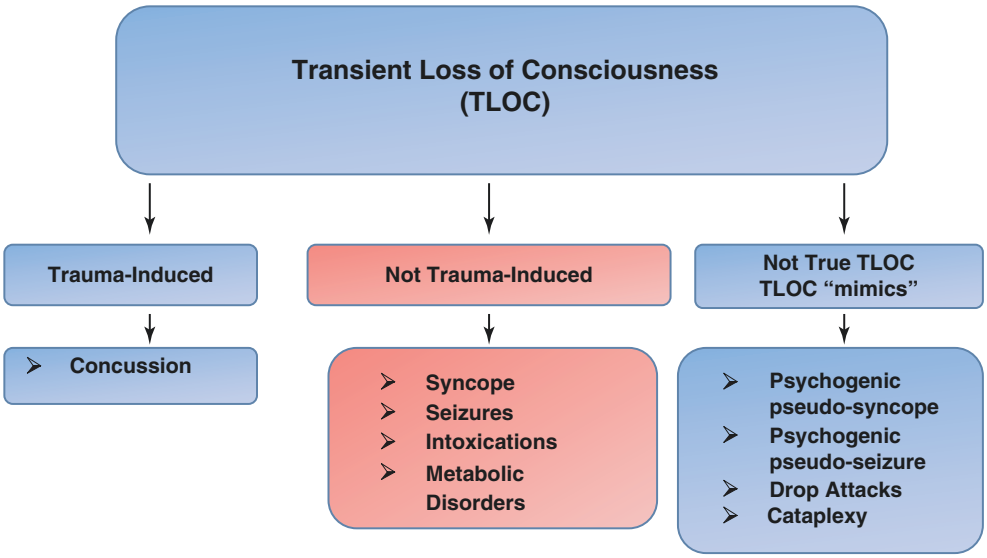


Fig. 19.1 Transient loss of consciousness (TLOC) may result from a vary of conditions. Traumatic TLOC, concussion, is rarely poses a clinical dilemma. However, the so-call "syncope mimics" can be difficult to distinguish from true syncope even with a carefully structured approach

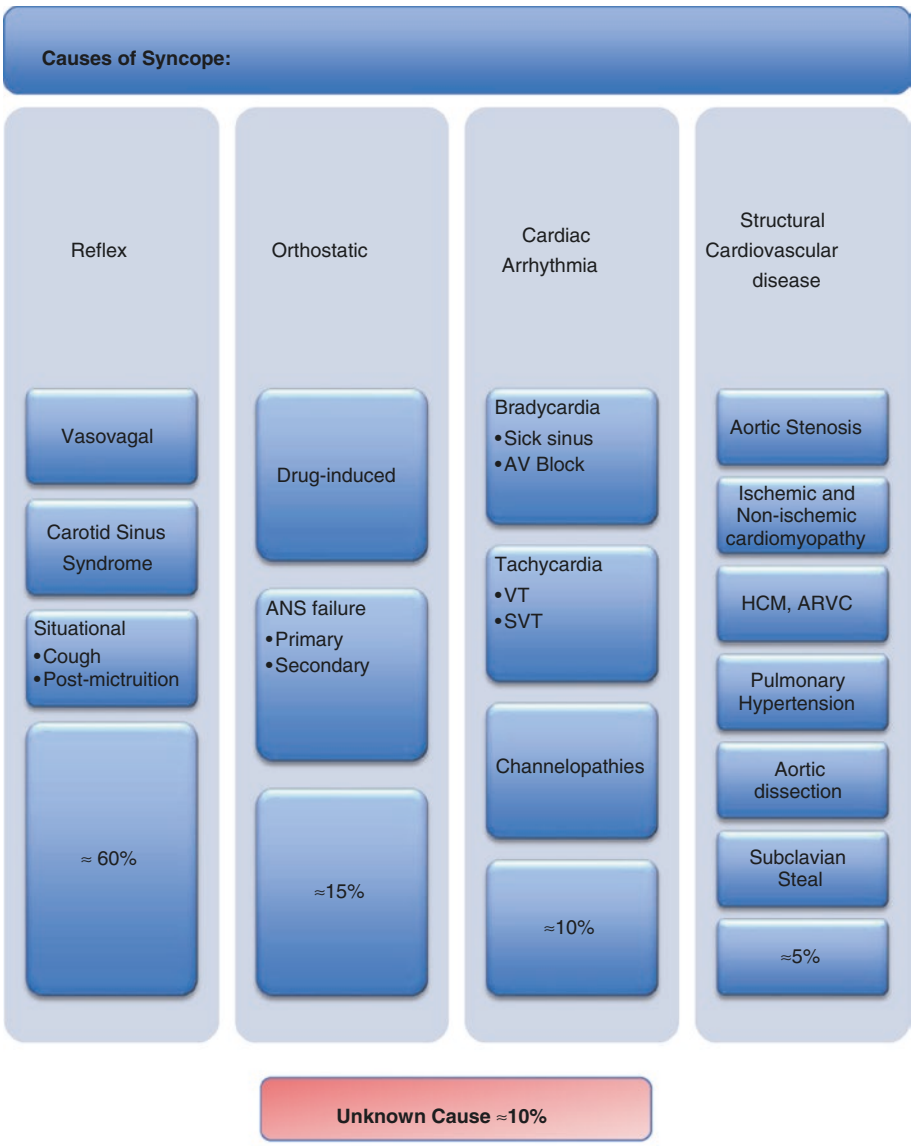


Fig. 19.2 A schematic representation of the common causes of syncope is provide. The approximate percentages included in the figure are summarized from a variety of sources. As noted in the text, these percentages may change depending on the population study. However, reflex syncope, specifically vasovagal syncope, remains the most frequent cause of syncope

Whether the etiology of the syncopal event is benign or potentially life-threatening, syncope may lead to physical injury, accidents that put the affected individual and others at risk, and substantial economic loss. Consequently, prevention is important. In this regard it is essential to identify the specific causes(s) of the faint(s), and thereafter, develop a treatment plan designed to prevent recurrences [2].

The frequency with which syncope occurs has been assessed in a variety of studies. In general, the reported prevalence of syncope, which to be more precise reflects the percentage of individuals who have experienced a faint to that point in their life, varies from 15 to 25% [2, 4, 5]. In large part differences are attributable to the nature of the population being evaluated. Nevertheless, it is clear that a substantial segment of the population may experience a syncope event.

Emergency departments (and in recent years 'Urgent Care' clinics) are often the first places that fainters present for attention. In these settings syncope and collapse is estimated to account for approximately 1% of visits in Europe, and from 1 to 6% in the United States [6–10]. In regard to the elderly, the reported frequency may well be an underestimate since many of these individuals exhibit various degrees of cognitive impairment that may affect memory of events; up to 20% of these individuals are believed to be amnestic for such episodes (i.e., retrograde amnesia) and often when queried will deny that they ever lost consciousness [11].

Assessment

Initial Assessment

For syncope to have occurred there has to have been TLOC. If TLOC has not occurred the clinician must consider other diagnoses. As always, there are caveats. Patients, especially the elderly, may not be aware of the TLOC. One must beware of a history of unexplained falls. Falling can be diagnosed if the patient has full recollection of the event (although in some cases head trauma may account for a fall with loss of memory). If the patient has no memory of the fall, or how the fall occurred, the possibility of TLOC remains. Similarly, in conditions such as cataplexy or psychogenic pseudo-syncope consciousness is not lost, thought this may be difficult for the practitioner to determine during an initial encounter.

As outlined in Fig. 19.1, TLOC is a feature of many entities other than syncope. In the case of syncope, however, unless the patient is somehow restricted from assuming a gravitationally neutral position (i.e., prevented from falling such as might occur if wearing a seatbelt or being in a very confined space, or being held upright by well-meaning but ill-informed bystanders), the episode should be transient, rarely lasting longer than 30 s. Prolonged periods (greater than 1–2 min) of loss of consciousness (LOC), or perceived LOC, should prompt consideration of other explanations for the episode. In a syncope patient, recovery should be spontaneous and complete. A patient who requires defibrillation or a bolus of intravenous glucose before regaining consciousness has not had syncope.

As already stressed, transient global cerebral hypoperfusion is the essential feature of syncope pathophysiology that distinguishes syncope from other forms of TLOC [2–4]. In the vast majority of cases, diminished cerebral perfusion is due to a transient fall in systemic blood pressure. On occasion, the victim may have jerky movements after onset of loss of consciousness; because of these muscle movements, true syncope may be mistaken for a seizure disorder or "fit" by untrained witnesses [4]. If the 'jerky' muscle movements begin prior to LOC, then the event was almost certainly an epileptic seizure and not syncope. Sometimes, non-skeletal smooth muscle function may be affected, resulting in loss of bladder (common) or bowel (rare) control and further raising concern that the patient had experienced an epileptic seizure [4].

Determining the Etiology

Establishing the cause of syncope is crucial with regard to the assessment of risk. The most common causes of syncope are the reflex syncope syndromes, and within the category of reflex syncope (i.e., vasovagal, carotid sinus syndrome and situational reflex faints), vasovagal syncope is by far the most common [2, 3, 5]. However, the prevalence of a particular cause of syncope varies depending up the population studied. Thus, vasovagal faints account for almost all forms of syncope in otherwise healthy young persons but fewer than half the causes of syncope in patients >60 years of age (Fig. 19.3) [12, 13]. For example, Ungar et al. [14] found in a study of 242 older individuals aged 65–98 years, that the combination of neural-reflex and orthostatic faints accounted for 67% of diagnoses. Vasovagal, situational and carotid sinus syndrome (CSS) (i.e., the reflex faints) made up 62% of cases in patients ≤75 years of age and 36% in patients >75 years. More recently, among 200 patients ≥65 years of age who presented to the ED due to unexplained or accidental falls, Anapalahan and Gibson found that approximately 25% of unexplained falls were due to reflex syncope [15].

Orthostatic faints and carotid sinus syndrome (CSS) tend to be more prevalent in the older (typically considered >60 years) patient [2, 9, 14]. In the case of orthostatic faints, age-related and/or disease related factors increase susceptibility; for instance, neurological causes including subtle forms of Parkinson's disease and/or autonomic failure contribute to syncope risk. Similarly, drug-induced orthostatic hypotension should not be over-looked as it is very

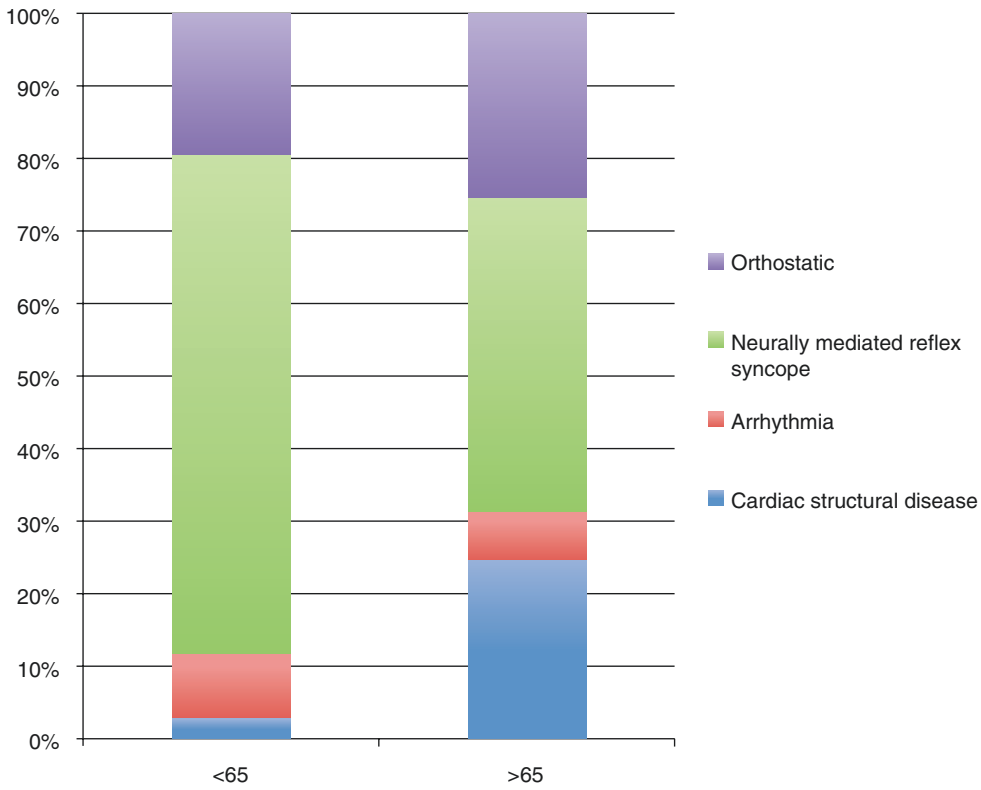


Fig. 19.3 The graph is constructed from data presented by Del Rosso [12]. In patients older than 65 years of age, cardiac causes of syncope become more common. In this age group orthostatic hypotension also becomes more common

common and often readily managed by adjustment of medications and doses. In particular diuretics and antihypertensive may substantially increase risk of orthostatic syncope in the older person.

CSS has been reported to account for ~20% of syncope in older individuals with vasovagal syncope amounting to a further 15%. Although less frequent, cardiac causes become more important with increasing age and the inevitable greater concomitant prevalence of structural heart disease [2]. It is the cardiac causes that ultimately are associated with greatest mortality and sudden death risk.

Establishing the presence or absence of structural heart disease in a patient with syncope is of critical importance both in terms of defining the risk of premature death, as well as determining the best prevention/treatment strategy. The focus of the history, the physical exam and laboratory testing, if needed, is not only to establish an etiology for the syncopal events but, of equal importance, to establish the presence or absence, and severity, of underlying cardiovascular disease.

The association of syncope with subsequent mortality has been the subject of several studies. From a broad epidemiologic perspective, Soteriades and colleagues reported observations from the Framingham database in 822 patients with syncope out of 7814 patients that had been followed for 17 years [8]. Despite the fact that the nature of the Framingham methodology inherently introduced imprecision with regard to the etiologic diagnosis, several important insights were provided. First, patients with apparent vasovagal syncope did not have an increased risk of mortality (or cardiovascular morbidity) when compared to individuals who did not have syncope. On the other hand, the hazard ratio for all-cause mortality in patients with an apparent cardiac cause of syncope was 2.01 compared to patients without syncope. The hazard ratio for myocardial infarction or death from coronary artery disease in these patients was even higher (2.66). It is important to note that while syncope may be a marker of increased concern, it is the underlying heart disease, not syncope, that is the cause of the increased risk [16].

The Framingham observation, that it is the underlying heart disease and not syncope that is the driver of increased mortality, has been demonstrated in other studies as well. This finding was illustrated in the Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) data. Olshansky and coauthors (writing for the SCD-HeFT Investigators) looked at the effect of syncope on outcomes in the SCD-HeFT patients with ischemic and non-ischemic cardiomyopathy [17]. The relative risk (RR) of mortality for patient with syncope compared with those without syncope was not significantly different across the randomization groups: amiodarone, placebo, single-chamber shock-only ICD [17]. This finding, that while syncope is often a marker of risk it is the underlying condition that results in poor outcomes, will be noted in many of the studies discussed later in this review.

Younger patients without structural heart disease tend to be primarily affected by reflex faints, especially vasovagal syncope. However, although rare, in the absence of overt structural disease, the possibility of a so-called channelopathy (e.g., long QT syndrome, Brugada syndrome, catecholaminergic paroxysmal ventricular tachycardia [VT], etc.) should not be overlooked in such patients. These possibilities are particularly important if the medical history of the patient's symptoms is not typical for reflex syncope. Channelopathies are being recognized with increasing frequency and have a worrisome prognosis; some remain as yet unidentified from a genetic perspective but nevertheless can cause life-threatening arrhythmias [2].

A 12-lead ECG should be obtained, and reviewed by an experienced ECG reader, in all patients with syncope. The ECG may suggest presence of underlying structural heart disease or provide evidence of a channelopathy. In addition, all the risk tools to be discussed below include assessment of the 12-lead ECG. Given that the ECG is a snapshot of a dynamic process, an ECG should be obtained as close in time to the event as possible. An ECG from months prior to presentation is not adequate for the evaluation of a patient being seen for new syncope.

A detailed review of the evaluation of the syncope patient is beyond the scope of this discussion. The most recent ESC report on the diagnosis and management of syncope [2] is an excellent general reference, as are several recent reviews [18, 19].

Assessment of Mortality/Life-Threatening Risk

Assessment of Long-Term Risk

The majority of patients presenting with syncope, especially young healthy patients, will have reflex syncope in which mortality risk is low, but potential for injury and adverse impact on quality-of-life are important. However, as alluded to earlier, the prognosis associated with syncope is not always benign. Those at increased injury and mortality risk typically have underlying structural heart disease or a disorder of ion channel function. In such cases, developing strategies for prevention and/or protecting the patient from potentially life-threatening consequences is a high priority.

Many studies, have attempted to address the short term (1-week to 1-month) risks associated with syncope in order to provide practitioners, particularly ED and Urgent Care physicians, guidance on which syncope patients merit immediate hospitalizations and/or urgent evaluation in a syncope clinic. However, fewer reports have focused on the 'long-term risk' of syncope, and even these studies are limited in usefulness as follow-up has generally been only one year, [8, 20, 21].

Longer-Term Risk

In terms of 'long-term' risk, the Evaluation of Syncope Guidelines (EGSYS) and EGSYS-2 [22, 23] studies highlighted the importance of identifying patients with underling cardiac disease. The EGSYS study was a prospective cohort study of emergency department (ED) patients with the intended goal of both deriving and validating a clinical score that would identify patients in whom there was a high likelihood that syncope was due to a cardiac cause. There were 260 patients in the derivation cohort and 256 in the validation cohort. Six clinical variables (out of 52 in total) were assigned a score based on the regression coefficient. The mean follow-up was 614 days.

The EGSYS score is outlined in Table 19.1. The ECG was interpreted by the ED physician and considered abnormal if it demonstrated: sinus bradycardia, AV block more severe than first-degree, bundle branch block, acute or old MI, supraventricular tachycardia, left or right ventricular hypertrophy, long QT, ventricular pre-excitation or Brugada pattern. Predisposing factors for syncope included: warm crowded place, prolonged standing, or pain/fear/emotional upset. Autonomic prodromal symptoms were limited to nausea and vomiting.

In both the derivation and validation cohort, patients with an EGSYS risk score of ≥3 had increased risk of mortality when compared to patients with a score of <3. In the derivation cohort the mortality rate during a mean follow-up 614 days in patients with a risk score ≥3 was 17% versus 3% in patients with a score <3. In the validation cohort those values were 21% versus 2% [22].

In the EGSYS-2 follow up study [23], 541 patients were evaluated for syncope in the EDs of 11 general hospitals in Italy. A total of 380 patients completed an average of 614 days follow up. Death from any cause occurred in 35 patients (9.2%). Among the deaths 82% of the patients either had an abnormal ECG and/or heart disease. Six deaths (3% of all patients, approx. 10% of all deaths) occurred in patients without heart disease and a normal ECG. Thus, the negative predictive value for mortality of the combination of absence of heart disease and a normal ECG in the overall population was 97% [23].

Table 19.1 EGSYS score

Clinical marker	Risk score
Palpitations prior to syncope	4
Heart disease or abnormal ECG or both	3
Syncope during effort	3
Syncope while supine	2
Predisposing or precipitating factors of both	−1
Autonomic prodromal symptoms	−1

See text for details, adapted from Del Rosso et al. [22] and Ungar et al. [23]

The cause of death was felt to be cardiovascular in 9 patients (20%), non-cardiovascular in 10 patients (29%) and unknown in 16 (46%) [23].

Six deaths (17%) occurred within 1 month of the index ED visit. All were related to cardiovascular causes (four to cardiac causes, two to vascular). None of the 35 deaths were considered to be sudden in nature. Treatment of the cause of syncope had no effect on mortality risk in EGSYS- 2 during the follow-up period. The cause of death was not related to the cause of syncope in this study [23].

Syncope recurred in 63 patients (16.5%) but in only a single patient during the first 30 days. The EGSYS score did not correlate with the risk of syncope recurrence. Neither was recurrence related to the cause of syncope [23].

The Osservatorio Epidemiologico sula Sincope nel Lazio (OESIL) study [24] examined the risk of total mortality at 12 months in 270 syncope patients presenting to two hospitals in Rome. The 12-lead ECGs in each patient were interpreted by the ED physician with cardiology over-reading upon request [24]. Four clinical risk factors, Table 19.2, were identified (age > 65 years, clinical history of cardiovascular disease, syncope without prodromal symptoms and abnormal ECG). Each risk factor was assigned a single 'risk' point.

An abnormal ECG was defined as: (1) abnormal rhythm (atrial fibrillation/flutter, supraventricular tachycardia, multifocal atrial tachycardia, frequent ventricular or supraventricular ectopy, ventricular tachycardia or paced rhythm), (2) AV block (including Mobitz 1 AV block), (3) ventricular hypertrophy, either right or left, (4) left axis deviation, (5) old myocardial infarction or (6) ST segment or T wave changes consistent with, or possible related to, ischemia (non-specific repolarization changes were excluded. Total mortality increased with each additional risk factor. Patients with no risk factors had no mortality at one year. Patients with a risk score of 4 had a 57.1% mortality over the subsequent 12 months [24].

Despite its title, the Short-Term Prognosis of Syncope Study (STePS) investigators examined both short-term and long-term risk in consecutive patients over the age of 18 with syncope at four hospitals in Milan, Italy [25].

This was a prospective study with pre-defined "severe outcomes" and "major therapeutic procedures". STePS assessed predictors of 'long-term' risk (11 days to one year) of severe outcomes and major therapeutic procedures.

Table 19.2 OESIL risk score

Age > 65 years
Clinical history of cardiovascular disease
Syncope without prodromal symptoms
Abnormal ECG

See text for details, adapted from Colivicchi et al. [24]

Table 19.3 Short-term prognosis of syncope (STePS) study

Clinical marker	Odds ratio	95% CI	p Value
(a) Predictors of long-term risk (11 days–1 year)			
Age > 65 years	3.4	1.6–7.4	0.001
Neoplasm	3.2	1.6–6.5	0.001
Cerebrovascular Disease	2.5	1.3–4.7	0.006
Structural heart disease	2.3	1.3–4.2	0.004
Ventricular Arrhythmia	3.9	1.0–15.3	0.049
(b) Predictors of short-term risk (0–10 days)			
Abnormal ECG	6.9	3.1–15.1	0.000
Trauma	2.9	1.4–5.9	0.004
Absence of prodrome	2.4	1.2–4.8	0.016
Male gender	2.2	1.0–4.5	0.0037

See text for details, adapted from Constantino et al. [25]

Markers of long-term risk were: (1) age> 65 years, (2) neoplasms, (3) cerebrovascular disease, (4) structural heart disease and (5) ventricular arrhythmias (Table 19.3a). There were a total of 40 deaths. Of the 40 only 11 (3 sudden, 5 cardiovascular and 3 cerebrovascular) were attributable to a cardiovascular cause. Hospitalized patients were more likely to have a major therapeutic procedure at 10 days ($p < 0.01$). The risk of death between 11 days and one year was significantly higher in patients who were hospitalized following the index event than those not hospitalized, 14.7% versus 1.8%, $p < 0.0001$ [25].

At first, the finding that hospitalized patients had worse outcomes may seem surprising. However, regardless of the presenting complaint, it is not difficult to imagine it is better to be deemed healthy enough for discharge as opposed to ill enough to require admission. Indeed, the admitted patients in the STePs trial were more likely to have hypertension, underlying cardiovascular disease and nearly half were over 65 years of age [25]. The results illustrate the larger point that it is likely the underlying disease not the syncope that confers risk. The admitted patients were more likely to undergo a major therapeutic procedure (pacemaker or ICD placement, intensive care unit admission or acute antiarrhythmic drug therapy). In other words, they were more likely to have the etiology of their syncope both identified and treated, yet this did not result in an improvement in outcomes [25]. This is similar to the findings reported by the EGSYS2 investigators [23].

Shorter-Term and Immediate Risk (7–30 days)

While potentially important, estimates of risk at one year are of limited value in the acute or sub-acute setting. As noted above, in the acute setting an estimate of short-term risk is helpful in weighing the urgency with which further evaluation should be completed.

Table 19.4 San Francisco Syncope Rule (SFSR)

Abnormal ECG (rhythm other than sinus or new ECG changes)
A complaint of shortness of breath
Hematocrit <30%
Systolic blood pressure at triage of <90 mmHg
History of congestive heart failure

See text for details, adapted from Quinn et al. [26, 27]

Quinn, et al., sought to establish a means of evaluating the short-term risk at 7 days using a population of patients seen at a large university-based teaching hospital emergency department (ED) [26]. They prospectively identified a cohort of 684 patients with syncope. The patients were assessed with a standardized tool of 50 variables felt to have possible benefit with regards to risk assessment and were followed up at seven days for the occurrence of pre-defined serious outcomes. The outcomes chosen were broad-based, ranging from death to any condition likely to result in a return visit to the ED. A total of 79 serious outcomes occurred. Multivariate analysis allowed the identification of five variables (See Table 19.4) capable of predicting seven day major outcomes with a sensitivity of 96% and a specificity of 62%. These predictors were labeled the San Francisco Syncope Rule (SFSR).

The investigators later prospectively validated the SFSR in 760 patients seen for 791 visits to the ED [27]. They found that the rule had a 98% sensitivity for predicting serious outcomes with a specificity of 56%. There were 108 serious outcomes, half identified at the time of the index ED visit. The most common serious outcome was arrhythmia with 16 bradyarrhythmia, five supraventricular tachycardia (SVT) and two ventricular dysrhythmia.

Despite the findings of Quinn et al. [27], two external validation studies found that the SFSR did not perform as well as had been previously reported. For instance, Sun et al. [28], prospectively enrolled patients presenting to a single academic emergency department (ED) in Los Angeles with syncope or near syncope. The SFSR risk factors were recorded and the patients later contacted by telephone for follow-up at 14 days. A panel of three physicians, blinded to the SFSR score, used the ED records, hospital records and telephone contact information to determine if a predetermined serious clinical event had occurred within 7 days of being evaluated in the ED. The authors reported a lower sensitivity, 89%, for identification of high risk patients using the SFSR [28].

Similarly, Birnbaum and colleagues [29] reported on a population of 713 patients presenting to a University hospital ED with syncope or near syncope. Inclusion criteria and serious clinical events were the same as those used in the SFSR trials [26, 27]. Sixty-one patients out of the 713 had a serious clinical event. Of these 61 patients, the SFSR failed to identify 16 (25%, 95% confidence interval (CI) 16–39%) as high risk [29]. In their population the ability of the SFSR to predict a serious outcome had a sensitivity of 74%, substantially less than the 98% sensitivity reported previously [26, 27].

Table 19.5 The Boston rules

I. Signs or symptoms of acute coronary syndrome
II. Worrisome cardiac history
III. Family history of sudden cardiac death
IV. Significant heart murmur
V. Signs or symptoms of conduction system disease
VI. Volume depletion
VII. Persistence of abnormal vital signs
VIII. Primary central nervous system event

See text for details, adapted from Grossman et al. [30]

Table 19.6 The Rose Rule

B	B-type natriuretic peptide ≥300 pg/mL
	Bradycardia ≤50 bpm in ED or pre-ED
R	Rectal exam showing fecal occult blood
A	Anemia, Hbg ≤ 90 g/L
C	Chest pain associated with syncope
E	ECG with Q waves (excluding lead III)
S	Saturation of oxygen ≤94% on room air

See text for details, adapted from Reed et al. [31]

Several other reports have offered insight into shorter-term risk of serious outcomes, need for intervention or all-cause mortality associated with syncope. In a collaborative study from Boston, Grossman and colleagues grouped signs and symptoms into eight different categories as found in Table 19.5. They found their rule was useful in predicting the risk of critical interventions or adverse outcomes at 30 days [30]. One could view their study as validation of the importance of obtaining a thorough history and physical examination when assessing risk related to a syncopal episode. Nonetheless, it does provide a framework for determining risk in a patient with syncope.

The ROSE (Risk Stratification of Syncope in the Emergency department) study was designed to establish a clinical decision rule to predict 1-month all-cause mortality and serious outcome risk in adult patients presenting with syncope [31]. It was a single center prospective observational study from Edinburgh, Scotland. The clinical decision rule was developed from a derivation cohort of 550 patients. It was then tested in a validation cohort of a further 550 patients [31].

From the derivation cohort the ROSE rule was developed and included seven elements (Table 19.6). The investigators suggested the pneumonic BRACES:

B BNP ≥ 300 pg/mL
Bradycardia ≤50 bpm in ED or pre-ED
R Rectal exam showing fecal occult blood
A Anemia, hemoglobin ≤90 g/L
C Chest pain associated with syncope
E ECG with Q wave (excepting lead III)
S Saturation (oxygen) ≤ 94% on room air

When applied to the validation cohort the sensitivity was 87%, and specificity was 66% for all-cause mortality and serious outcome risk. The positive predictive value was 16.5% and negative predictive value was 98.5%. The presence of any one of the seven elements noted above indicated high-risk and admission should be considered. The authors estimated that the use of the ROSE rule would result in avoiding 149 unnecessary admissions per 1000 patients presenting with syncope, at a cost of missing four high risk patients with no deaths [31].

In the STePS study [25] logistic multivariate regression revealed four key risk markers for severe outcomes in the short-term (within 10 days of index event): (1) abnormal ECG at admission, (2) trauma associated with the event, (3) absence of symptoms preceding event and (4) male gender (Table 19.3b). The risks markers for short-term risk differed from those for long-term (11 days to 1 year) risk. An abnormal ECG at presentation conferred the greatest risk. An ECG was defined as abnormal if it disclosed: (1) atrial fibrillation or tachycardia, (2) sinus pauses >2 s, (3) sinus bradycardia ranging from 35 to 45 bpm, (4) conduction disorders (including Mobitz I second-degree AV block), (5) evidence of prior myocardial infarction or ventricular hypertrophy and (6) multiple ventricular premature beats.

In the short-term (first 10 days) there were 41 (6.1%) severe outcomes, including five (0.7%) deaths. Four of the five deaths occurred within 48 h of the index ED visit, one each from: disseminated intravascular coagulation, acute pulmonary edema, aortic dissection, pulmonary embolus). One patient died of a stroke on day ten [25].

Risk of Recurrence

In our review of the above studies we have focused on assessing the risk of mortality and life-threatening complications. However, while these latter issues are undeniably important, patients are also concerned with the risk of recurrence of syncope and its potential impact on their lives. As with assessment of mortality risk it is critical to identify the cause of the syncope in order to both comment on the risk of recurrence and to discuss possible preventive measures.

In regard to the likelihood of recurrences, it is estimated that roughly one-third of patients with syncope will suffer a recurrence within three years [2, 8, 10]. Factors that predict a greater risk include: a prior history of recurrence, age less than 45 and a psychiatric diagnosis (although this last factor might include conditions that re not 'true' syncope such psychogenic pseudosyncope). Patients with a positive tilt table study and a history of more than six syncope events have a > 50% recurrence rate over two years [2, 8, 10, 32].

Specific Cardiac Conditions

Ischemic Cardiomyopathy

There is a relative paucity of studies investigating the mechanisms of syncope among heart failure patients with implantable cardioverter-defibrillators, and it is controversial whether non-arrhythmogenic syncope is associated with increased mortality. Recent review of data from the MADIT-RIT [33] data has shown that the clinical risk factors associated with syncope are related to increased cardiovascular risk profile including ischemic origin (HR 2.48, CI 1.42–4.34, P = 0.002). Both arrhythmogenic and non-arrhythmogenic syncope were significantly associated with an increased risk of mortality. While the HR for death attributable to arrhythmogenic syncope was higher than non-arrhythmogenic syncope, 4.51 versus 2.96 respectively, there was a large overlap in the 95% confidence intervals (CI). The investigators concluded that the clinical risk factors for syncope were related to markers of increased overall cardiovascular risk and that syncope was associated with increased mortality risk regardless of the etiology of syncope [33].

The AVID Registry followed patients who presented to centers participating in the AVID trial who had VT or VF regardless of the cause [34]. Patients who presented with "unexplained syncope" were also screened. A relatively high mortality rate was noted across all groups, including those with unexplained syncope. However, it needs to be emphasized that the patients with unexplained syncope, were only screened if they were found to have underlying heart disease AND had symptomatic VT induced at electrophysiology study [34]. Despite this, the patients with unexplained syncope had the highest two-year survival in patients with ejection fractions <35% at 83% [34]. Syncope in this selected group of patients was not associated with a higher risk of mortality.

Non-ischemic Cardiomyopathy

Recall that patients with syncope, compared with those without syncope, had a higher risk of all-cause mortality and of cardiovascular death but that the risk of sudden cardiac death was not significantly greater in patients with syncope compared to those without syncope. Similarly, this study did not show a difference in syncope risk between heart failure etiologies (Ischemic vs Nonischemic HR 1.05 (0.85–1.29) with p Value = 0.67 [17].

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

The role of implantable cardioverter-defibrillator (ICD) in patients with arrhythmogenic right ventricular cardiomyopathy and no prior ventricular fibrillation (VF) or sustained ventricular tachycardia is an unresolved issue. Few prospective trials address this topic. A recent report [35] studied syncope as a risk factor for arrhythmia independent of non-sustained ventricular tachycardia, familial sudden death, and inducibility of programmed ventricular stimulation. One fourth of patients with arrhythmogenic right ventricular cardiomyopathy and no prior sustained ventricular tachycardia or VF had appropriate ICD interventions. Syncope significantly predicted any appropriate ICD interventions (hazard ratio, 2.94; 95% confidence interval, 1.83 to 4.67; P = 0.013) and shocks for VF/ventricular flutter (hazard ratio, 3.16; 95% confidence interval, 1.39 to 5.63; P = 0.005) [35]. Inducibility at electrophysiology study had a poor positive predictive value, 35% for appropriate ICD intervention and 20% for ICD intervention for ventricular fibrillation (VF) or ventricular flutter (VFL). Asymptomatic patients with only family history of sudden cardiac death received no appropriate ICD interventions. In this study syncope was the strongest predictor of appropriate ICD therapy in patients without a history of cardiac arrest or sustained VT [35].

Two caveats should be kept in mind with regard to ICDs in ARVC. First, ICD placement was associated with inappropriate ICD interventions in 20 patients (19%) and 18 patients (17%) had device related complications [35]. Second, the authors postulated that ICD therapies for VF/VFL were "life-saving", a conclusion that is open to debate.

Hypertrophic Cardiomyopathy (HCM)

Syncope is a particularly worrisome clinical presentations in patients with HCM. To date one major study has assessed the prognostic significance of syncope systematically in hypertrophic cardiomyopathy, Spirito et al. assessed the relationship between syncope and sudden death in patient with HCM [36]. The results showed patients with recent unexplained syncope (within 6 months before initial evaluation) showed a 5-fold increase in risk compared with patients without syncope (adjusted hazard ratio 4.89, 95% CI 2.19 to 10.94). Patients with recent unexplained syncope also demonstrated an increased sudden death risk throughout all age groups. It is important to note that the relative risk of sudden death was 1.78 (95% confidence interval 0.88 to 3.51, P = 0.08) in patients with unexplained syncope while in those felt to have reflex syncope the relative risk of sudden death was not increased, 0.91 (95% confidence interval 0.00 to 3.83, P = 1.0). However, a recent validation trial of the 2014 European Society of Cardiology Guidelines Risk Prediction Model for the Primary Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy [37] found, in a univariate analysis, that syncope was not a predictor of SCD (HR 1.6, 95% confidence interval 0.47–5.51, p = 0.4).

Long QT Syndrome (LQTS)

Syncope is highly predictive for future fatal arrhythmias in the LQTS. Data regarding risk stratification and management strategies in the high-risk subset of LQTS patients presenting with syncope was recently summarized by Jons et al. [38]. The risk stratification was divided into 3 categories. The lowest risk was found in patients with only 1 syncopal episode occurring before the start of beta-adrenergic receptor blocker therapy. Intermediate risk was associated with patients with multiple syncopal episodes occurring before initiation of beta-adrenergic receptor blocker therapy (hazard ratio: 1.8, $p < 0.001$). The highest risk was patients experiencing syncope after starting beta-adrenergic receptor blocker therapy who had a 3.6-fold increase in the risk of severe arrhythmic events ($p < 0.001$) relative to the low-risk group. Patient who experienced syncope after starting beta-adrenergic receptor blocker had a risk of severe arrhythmic events similar to that of patients not treated with beta-blockers. The results also showed an important gender difference in the risk of experiencing syncope while being treated with beta-adrenergic receptor blockers. The risk associated with syncope is higher in women than in men (hazard ratio: 2.3, $p < 0.001$) [38].

Overall, in LQTS patients presenting with the first syncopal episode, fatal arrhythmic events are effectively prevented with beta-blocker treatment in those without recurrent syncope. However, these observations apply predominantly to LQTS Type 1 and Type 2. The impact of beta-adrenergic blockers in other LQTS types is less clear.

Brugada Syndrome

Fundamental questions remain regarding the best strategy for assessing the disease-associated arrhythmic risk in Brugada syndrome. The lack of data and recommendations regarding management the asymptomatic patient with an ECG demonstrating the Brugada pattern remains a perplexing issue for clinicians. The evidence that VT/VF inducibility is not a useful risk indicator highlights the need to establish alternative risk stratification methods.

Probst et al. [39] examined the FINGER (France, Italy, Netherlands, Germany) Brugada syndrome registry to evaluate the effect of unexplained syncope on the risk of SCD in Brugada syndrome patients. Asymptomatic patients had the

lowest cardiac event rate per year, 0.5%. Patients with prior aborted SCD had a yearly cardiac event rate of 7.7%. Patients with syncope had an intermediate risk of cardiac events at 1.9% per year. In a multivariable analysis, syncope versus asymptomatic status (HR, 3.4; CI, 1.6 to 7.4; P = 0.002) was a predictor of a shorter time to first arrhythmic event [39].

Analysis of the data from the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry showed a history of syncope and spontaneous type I ECG spontaneous HR: 4.20 (95% CI: 1.38 to 12.79, p = 0.012) were significant predictors of arrhythmia events (VF or appropriated ICD therapy) [40]. In a Kaplan-Meier analysis, patients with syncope alone were also at higher risk for arrhythmic events, log-rank P = 0.011. The authors calculated that 12.4 ICD implantations would be needed to save one life if syncope was used as a sole risk factor. The number of implants need to save one life for the spontaneous type 1 ECG pattern was 14.5. If a combination of history of syncope and spontaneous type I ECG pattern was considered, the number of ICD implants needed to save one life was 6.8 [40]. Similarly, in a large European large multicenter registry Sacher et al. [41] showed that syncope was predictive of appropriate device discharge(hazard ratio, 2.460; 95% confidence interval, 1.169–5.174).

Impact on Healthcare Costs

The soci costs of syncope are an important consideration. Many of the studies reviewed were conceived as a means of identifying which patients require urgent evaluation, including admission and which could be evaluated less urgently. In a review of syncope economics Sun et al., estimated an annual burden in the US of 740,000 ED visits and 460,000 hospital admissions at a cost of approximately $2.4 billion [42]. It is possible these costs could be reduced by more focused attention to practice guidelines. Several studies have already demonstrated the feasibility of using guide-line based evaluation strategies, such as the ones described above, to reduce hospital admissions and costs [43, 44]. The American College of Cardiology/American Heart Association/Heart Rhythm Society are expected to publish up-to-date syncope practice recommendations in 2016 which may further assist physicians to provide more cost-efficient care.

Conclusions

At this point, a fair question would be: What system do the authors use for assessing risk when evaluating mortality and SCD risk a patient with syncope?

The answer is: none of them and all of them.

When there is a multiplicity of methods, all attempting to answer the same clinical question, one is justified in concluding that there is no single best method. The studies reviewed above were well conceived and all have increased our understanding of the issues involved in risk assessment of the patient with syncope. Yet, none are sufficient to address all the questions facing the clinician and patient.

There are several recurring clinical threads that run through most of the risk assessment tools that merit consideration when attempting to define patients at higher mortality risk related to syncope:

1. Symptoms suggestive of acute coronary syndrome
2. Heart failure on presentation or history of heart failure
3. Abnormal ECG—this is often defined quite broadly
4. Older patients—in this case the age range is ill-defined but perhaps >65 years
5. Supine syncope

Red flags in younger, apparently healthy, patients include:

1. Syncope during active exertion – in this case defined as collapse in “full flight” as opposed to collapse after completion of vigorous exertion.
2. Abnormal ECG – more commonly in these patients the ECG may show ventricular pre-excitation, long or short QT, or Brugada pattern

It is commonly assumed that identification of the patient at risk implies the need for a device (pacemaker for bradyarrhythmias, implantable defibrillator for ventricular tachyarrhythmias) or a procedure, such as an ablation. It is worth noting that such interventions are only needed in a relatively few patients. More concerning, there is virtually no data indicating that such interventions impact mortality.

It is quite true that syncope in a patient with underlying heart disease is a marker of increased mortality risk but the mortality appears, with exceptions as noted above, to be primarily due to the underlying disease and not the syncope per se. In these patients, it may be more correct to view the episode of syncope as an opportunity to address and maximize therapy of the underlying cardiac condition, while also addressing evaluation and treatment of their syncope. However, in young patients with syncope and recently identified hypertrophic cardiomyopathy (HCM), the mortality risk appears to be more closely tied to the symptom of syncope and aggressive therapy, most often with an ICD, appears to be warranted [36]. Likewise, syncope in a patient with spontaneous type I Brugada ECG pattern may well warrant a more aggressive approach [40].

Other factors beyond risk alone impact the decision to admit or not admit a patient to hospital after they present

with an apparent syncope episode. Specific considerations that favor in-hospital care include:

1. Are they likely to require an intervention?
2. If there were associated injuries, do those injuries require inpatient treatment?
3. Is the patient's home environment safe?
4. Do they have adequate support systems in place for outpatient management?

All these issues must factor into the decision of where to complete the evaluation of an individual patient.

As with all clinical encounters, it is neither possible nor desirable, to reduce the evaluation of syncope to a series of check boxes and scores. Algorithms, flowsheets, care pathways, and such are invaluable tools for organizing one's approach to a patient. What they are not, is a substitute for clinical judgment.

Acknowledgments Dr. Benditt is supported in part by a grant in support of heart-brain research from the Dr. Earl E Bakken family.

References

1. Sheldon RS, et al. Heart rhythm society, expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm. 2015;12:e41–63.
2. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, Deharo JC, Gajek J, Gjesdal K, Krahn A, Massin M, Pepi M, Pezawas T, Ruiz Granell R, Sarasin F, Ungar A, van Dijk JG, Walma EP, Wieling W, Task Force for the Diagnosis and Management of Syncope, European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA), Heart Rhythm Society (HRS) Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30(21):2631–71.
3. Blanc JJ, Benditt DG. Syncope: definition, classification, and multiple potential causes. In: Benditt DG, Blanc JJ, Brignole M, Sutton RS, editors. The evaluation and treatment of syncope. A handbook for clinical practice. Elmsford: Futura Blackwell; 2003. p. 3–10.
4. Van Dijk JG, Thijs RD, Benditt DG, Wieling W. A guide to disorders causing transient loss of consciousness: focus on syncope. Nat Rev Neurol. 2009;5:438–48.
5. Lü F, Bergfeldt L. Role of electrophysiological testing in the evaluation of syncope. In: Benditt DG, Blanc JJ, Brignole M, Sutton RS, editors. The evaluation and treatment of syncope. A handbook for clinical practice. Elmsford: Futura Blackwell; 2003. p. 80–95.
6. Disertori M, Brignole M, Menozzi C, et al. Management of patients with syncope referred urgently to general hospitals. Europace. 2003;5:283–91.
7. Blanc JJ, L'Her C, Touiza A, Garo B, et al. Prospective evaluation and outcome of patients admitted for syncope over a 1 year period. Eur Heart J. 2002;23:815–20.
8. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. N Engl J Med. 2002;347:878–85.
9. Brignole M, Menozzi C, Bartoletti A, Giada F, et al. A new management of syncope: prospective guideline-based evaluation of patients referred urgently to general hospitals. Eur Heart J. 2006;27:76–82.
10. Savage DD, Corwin L, McGee DL, et al. Epidemiologic features of isolated syncope: The Framingham Study. Stroke. 1985;16:626–9.
11. McIntosh SJ, Lawson J, Kenny RA. Clinical characteristics of vasodepressor, cardioinhibitory, and mixed carotid sinus syndrome in the elderly. Am J Med. 1993;95:203–8.
12. Del Rosso A, Alboni P, Brignole M, Menozzi C, Raviele A. Relation of clinical presentation of syncope to the age of patients. Am J Cardiol. 2005;96:1431–5.
13. Parry SW, Tan MP. An approach to the evaluation and management of syncope in adults. BMJ. 2010;340:c880.
14. Ungar A, Mussi C, Del Rosso A, Noro G, Abete P, Ghirelli L, et al. Study of Syncope for the Italian Group for the Study of Syncope in the Elderly. Diagnosis and characteristics of syncope in older patients referred to geriatric departments. J Amer Geriatric Soc. 2006;54:1531–6.
15. Anpalahan M, Gibson S. Prevalence of neurally mediated syncope in older patients presenting with unexplained falls. Eur J Intern Med. 2012;23:e48–52.
16. Kapoor WN, Hanusa BH. Is syncope a risk factor for poor outcomes? Comparison of patients with and without syncope. Am J Med. 1996;100:646–55.
17. Olshansky B, Poole JE, Johnson G, Anderson J, Hellkamp AS, Packer D, Mark DB, Lee KL, Bardy GH, SCD-HeFT Investigators. Syncope predicts the outcome of cardiomyopathy patients: analysis of the SCD-HeFT stSyncope predicts the outcome of cardiomyopathy patients: analysis of the SCD-HeFT study. J Am Coll Cardiol. 2008;51:1277–82.
18. Benditt DG, Adkisson WO. Approach to the patient with syncope: venues, presentations, diagnoses. Cardiol Clin. 2013;31:9–25.
19. Adkisson WO, Benditt DG. Syncope due to autonomic dysfunction: diagnosis and management. Med Clin N Am. 2015;99:691–710.
20. Kapoor WN, Karpf M, Wieand S, Peterson JR, Levey GSA. Prospective evaluation and follow-up of patients with syncope. N Engl J Med. 1983;309:197–204.
21. Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. Ann Emerg Med. 1997;29:459–66.
22. Del Rosso A, Ungar A, Maggi R, Giada F, Petix NR, De Santo T, Menozzi C, Brignole M. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. Heart. 2008;94:1620–6.
23. Ungar A, Del Rosso A, Giada F, Bartoletti A, Furlan R, Quartieri F, Lagi A, Morrione A, Mussi C, Lunati M, De Marchi G, De Santo T, Marchionni N, Brignole M, Evaluation of Guidelines in Syncope Study 2 Group. Early and late outcome of treated patients referred for syncope to emergency department: the EGSYS 2 follow-up study. Eur Heart J. 2010;31:2021–6.
24. Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M. OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) Study Investigators. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. Eur Heart J. 2003;24:811–9.
25. Costantino G, Perego F, Dipaola F, Borella M, Galli A, Cantoni G, Dell'Orto S, Dassi S, Filardo N, Duca PG, Montano N, Furlan R, STePS Investigators. Short- and long-term prognosis of syncope, risk factors, and role of hospital admission: results from the STePS (Short-Term Prognosis of Syncope) study. J Am Coll Cardiol. 2008;51:276–83.
26. Quinn JV, Stiell IG, McDermott DA, Sellers KL, Kohn MA, Wells GA. Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. Ann Emerg Med. 2004;43:224–32.
27. Quinn J, McDermott D, Stiell I, Kohn M, Wells G. Prospective validation of the San Francisco Syncope Rule to predict patients with serious outcomes. Ann Emerg Med. 2006;47:448–54.
28. Sun BC, Mangione CM, Merchant G, Weiss T, Shlamovitz GZ, Zargaraff G, Shiraga S, Hoffman JR, Mower WR. External

validation of the San Francisco syncope rule. Ann Emerg Med. 2007;49:420–7.
29. Birnbaum A, Esses D, Bijur P, Wollowitz A, Gallagher EJ. Failure to validate the San Francisco Syncope Rule in an independent emergency department population. Ann Emerg Med. 2008;52:151–9.
30. Grossman SA, Fischer C, Lipsitz LA, Mottley L, Sands K, Thompson S, Zimetbaum P, Shapiro NI. Predicting adverse outcomes in syncope. J Emerg Med. 2007;33:233–9.
31. Reed MJ, Newby DE, Coull AJ, Prescott RJ, Jacques KG, Gray AJ. The ROSE (risk stratification of syncope in the emergency department) study. J Am Coll Cardiol. 2010;55:713–21.
32. Brignole M, Menozzi C, Bartoletti A, Giada F, Lagi A, Ungar A, Ponassi I, Mussi C, Maggi R, Re G, Furlan R, Rovelli G, Ponzi P, Scivales A. A new management of syncope: prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. Eur Heart J. 2006;27:76–82.
33. Ruwald MH, Okumura K, Kimura T, Aonuma K, Shoda M, Kutyifa V, Ruwald AC, McNitt S, Zareba W, Moss AJ. Syncope in high-risk cardiomyopathy patients with implantable defibrillators: frequency, risk factors, mechanisms, and association with mortality: results from the multicenter automatic defibrillator implantation trial-reduce inappropriate therapy (MADIT-RIT) study. Circulation. 2014;129:545–52.
34. Anderson JL, Hallstrom AP, Epstein AE, Pinski SL, Rosenberg Y, Nora MO, Chilson D, Cannom DS, Moore R. Design and results of the antiarrhythmics vs implantable defibrillators (AVID) registry. The AVID Investigators. Circulation. 1999;99:1692–9.
35. Corrado D, Calkins H, Link MS, Leoni L, Favale S, Bevilacqua M, Basso C, Ward D, Boriani G, Ricci R, Piccini JP, Dalal D, Santini M, Buja G, Iliceto S, Estes NA III, Wichter T, McKenna WJ, Thiene G, Marcus FI. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. Circulation. 2010;122:1144–52.
36. Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barilla CS, Biagini E, Quarta G, Conte MR, Bruzzi P, Maron BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119:1703–10.
37. Vriesendorp PA, Schinkel AF, Liebregts M, Theuns DA, van Cleemput J, Ten Cate FJ, Willems R, Michels M. Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Circ Arrhythm Electrophysiol. 2015;8:829–35.
38. Jons C, Moss AJ, Goldenberg I, Liu J, McNitt S, Zareba W, Qi M, Robinson JL. Risk of fatal arrhythmic events in long QT syndrome patients after syncope. J Am Coll Cardiol. 2010;55:783–8.
39. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert C, Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. Circulation. 2010;121:635–43.
40. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol. 2012;59:37–45.
41. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, Marquie C, Rosa A, Diallo A, Cassagneau R, Loizeau C, Martins R, Field ME, Derval N, Miyazaki S, Denis A, Nogami A, Ritter P, Gourraud JB, Ploux S, Rollin A, Zemmoura A, Lamaison D, Bordachar P, Pierre B, Jais P, Pasquie JL, Hocini M, Legal F, Defaye P, Boveda S, Iesaka Y, Mabo P, Haissaguerre M. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study-part 2. Circulation. 2013;128:1739–47.
42. Sun BC. Quality-of-life, health service use, and costs associated with syncope. Prog Cardiovasc Dis. 2013;55:370–5.
43. Shen WK, Decker WW, Smars PA, Goyal DG, Walker AE, Hodge DO, Trusty JM, Brekke KM, Jahangir A, Brady PA, Munger TM, Gersh BJ, Hammill SC, Frye RL. Syncope Evaluation in the Emergency Department Study (SEEDS): a multidisciplinary approach to syncope management. Circulation. 2004;110:3636–45.
44. Viqar-Syed M, Bradley DJ, Shen WK. Syncope units: impact on patient care and health-related costs. Cardiol Clin. 2013;31:39–49.

Management of Ventricular Arrhtyhmias in Nonischemic Cardiomyopathic Syndromes

20

Abhishek J. Deshmukh and Bernard J. Gersh

Abstract

The term "nonischemic cardiomyopathy" refers to a heterogeneous group of patients with nonischemic ventricular dysfunction characterized by impaired systolic function and dilatation of 1 or both ventricles. An underlying etiology e.g. infiltrations or myocarditis can be identified in approximately 50% of patients, whereas the remaining 50% are considered idiopathic. Irrespective of the etiology the principles of management remain similar. Due to multiform presentation, we highlight the key nonischemic cardiomyopathies, discuss the substrate involved and review the current management strategies.

Keywords

Ventricular arrhythmias • Substrate • Risk factors • Mapping • Ablation • Intracardiac defibrillators • Outcomes

Dilated Cardiomyopathy

Idiopathic dilated cardiomyopathy (IDCM) is an important cause of heart failure, thromboembolism, arrhythmias, and sudden cardiac death. The pathogenesis of arrhythmias stems from the structural and electrophysiological changes occurring in the myocardium secondary to the disease process. It is difficult to estimate the natural history of dilated cardiomyopathy alone, because establishing the etiology of heart failure from population-based studies is difficult and varies widely depending on diagnostic criteria, case ascertainment, and geographic location. However, IDCM accounts for a substantial proportion of the population of patients with heart failure, with only 24% of women and 32% of men having any documented coronary disease among a cohort of patients with heart failure in Olmsted County, Minnesota [1].

A.J. Deshmukh, M.D. (✉) • B.J. Gersh, M.B., Ch.B., D.Phil.
Division of Cardiovascular Medicine, Mayo Clinic,
200 First Street SW, Rochester, MN 55905, USA
e-mail: deshmukh.abhishek@mayo.edu; Gersh.bernard@mayo.edu

Reports focusing on the histologic findings in patients with dilated cardiomyopathy as well as conduction studies have demonstrated that the architecture, more than the amount of fibrosis, impacts conduction velocity [2].

Necropsy studies in IDCM patients demonstrate grossly visible scars in 14% of patients and histological examination reveals multiple patchy areas of replacement fibrosis in 35% and 57% of sections of the right and left ventricles, respectively. Mid wall fibrosis was noted in 35% of patients is also common and is an independent predictor of all-cause mortality [3]. Hypertrophied and atrophic myocytes, myofiber disarray, nuclear changes, and cytoskeletal disorganization are also observed. Human tissue experiments have shown areas of fibrosis leading to fractionated electrograms and delayed myocardial conduction due to a change in activation around these regions of conduction block [2]. Further, Anderson et al. reported that greater extent of fibrosis correlated with a higher level of conduction abnormalities [4]. Based on these initial data, it is felt that the substrate for ventricular tachycardia (VT) in patients with NICM includes fibrosis with creation of areas of conduction block, conduction slowing around these regions which leads to anisotropic conduction and creates the nidus for reentrant VT. Unlike ischemic

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_20

cardiomyopathy, where regions of scar correlate with regions of prior infarction, NICM does not follow a physiologic pattern. With the advent of electro-anatomic mapping, a relatively non-invasive method could be used to assess regions of low voltage, which correlate with myocardial scar.

In 2003, Hsia et al. [5] described the endocardial substrate in patients with NICM and monomorphic VT. All 19 patients studied had evidence of basal, perivalvular low voltage consistent with scar. More importantly, 88% of all VT induced in this cohort emanated from the basal LV, suggesting this low voltage region is the critical substrate for VT in this patient population. In 2004, Soejima et al. further described the arrhythmogenic substrate in patients with NICM undergoing VT ablation (Fig. 20.1). Twenty patients underwent endocardial mapping which revealed evidence of scar in all patients (bipolar voltage ≤1.5 mV), with the majority (63%) of patients having a basal, perivalvular extent of scar [6]. Furthermore, based on entrainment and pacemapping, 60% of patients had an identifiable endocardial isthmus which was targeted for ablation. Seven patients in this series underwent epicardial access and mapping after failed endocardial ablation with evidence of epicardial scar from the basal/lateral LV, RVOT, or basal RV. This observation confirmed the predilection of endocardial basal LV scar, but also suggested that an equally important epicardial substrate may be present and should be considered as an ablation target in patients with VT and NICM. Haqqani et al. also found that in DCM with isolated septal substrate, the morphology of VT may exhibit a precordial transition pattern break in V2 with qR/Rs morphology in V1 and V3 but reversal of this in V2, usually in the presence of an inferior-axis RBBB configuration [7].

The importance of the epicardial substrate in NICM was further elucidated by Cano. 22 patients with either EKG criteria suggesting an epicardial exit or failed prior endocardial ablation were evaluated. Based on electroanatomic mapping, 82% of patients had evidence of epicardial scar with 77% having greater epicardial scar area compared to the endocardium. Of the 18 patients with an epicardial VT identified by entrainment mapping and/or pacemapping, 14/18 patients were free from VT recurrence at followup of 18 ± 7 months [8].

The presence of epicardial scars can be inferred without accessing the epicardium from the 12-lead ECG, unipolar endocardial electrograms, and imaging studies, including intracardiac echocardiography and MRI. The presence of a Q wave in lead I during VT can predict an epicardial origin in the basal superior or lateral aspect of the LV [9, 10]. The absence of Q waves in inferior leads also suggests an epicardial VT. A 4-step algorithm combining morphology and interval criteria, which characterize delayed conduction in the initial portion of the QRS, has been proposed (Fig. 20.2). Unipolar electrograms, because of their "wider" field of view, are attenuated by the accumulation of electrically inert collagen fibers replacing excitable cardiac tissue. This is particularly useful when the scarring occurs in regions remote from the endocardium that are not detected by bipolar electrograms. Studies from U Penn demonstrate that endocardial unipolar signals of less than 8.3 mV in the LV and less than 5.5 mV in the right ventricle (RV) are predictive of epicardial and/or midmyocardial scars [11]. Intracardiac echocardiography can also identify the presence of non-endocardial substrates as increased echogenic regions (Fig. 20.3).

There are no prospective, randomized studies examining the role of catheter ablation in patients with NICM or right ventricular cardiomyopathies. Non-randomized studies have demonstrated that applying a substrate-based mapping technique combining pace-mapping and targeting late potentials for ablation appears to be less successful in patients with NICM than in patients with ischemic heart disease [12]. This is probably related to the progressive nature of the disease, remodelling of the substrate and the prevalence of epicardial and intramural reentry circuits. There are only a few single-center reports on acute outcome of VT ablation in the setting of nonischemic CMP, with short- to intermediate-term follow-up in relatively small numbers of patients. The reported variability in ablation outcomes in these studies reflects the differences in the ablation approach, the definitions of short- and long-term success, and the use of antiarrhythmic medications after ablation [6, 13–16]. Acute success in eliminating inducible VT has varied from 56 to 74% with VT recurrence of 42–75% with endocardial ablation [17]. Satisfactory control of VTs previously refractory to medical treatment can be achieved in a majority of patients (60–70%) with continuing antiarrhythmic medications, if tolerated. Outcome appears to be somewhat improved with epicardial ablation, but long-term follow-up in a large cohort of patients is lacking [18]. At present there is no consensus as to the optimal ablation strategy and lesion set for patients with NICM. There is no evidence that catheter ablation of VT reduces mortality. A future, sufficiently powered, prospective randomized study using standardized ablation and follow-up protocols will need to answer this important question.

Since the inception of ICDs, patients with IDCM have had a significant improvement in mortality [19]. The 2008 ACC/AHA/HRS guidelines offer an ICD for patients with a non-ischemic cardiomyopathy and LVEF ≤35% with NYHA class II/III as a class I indication. Yet, the same situation in a NYHA class I patient is relegated to a IIb ICD indication for no good reason except that data about this group of patients are not as extensive as in the ischemic group [20].

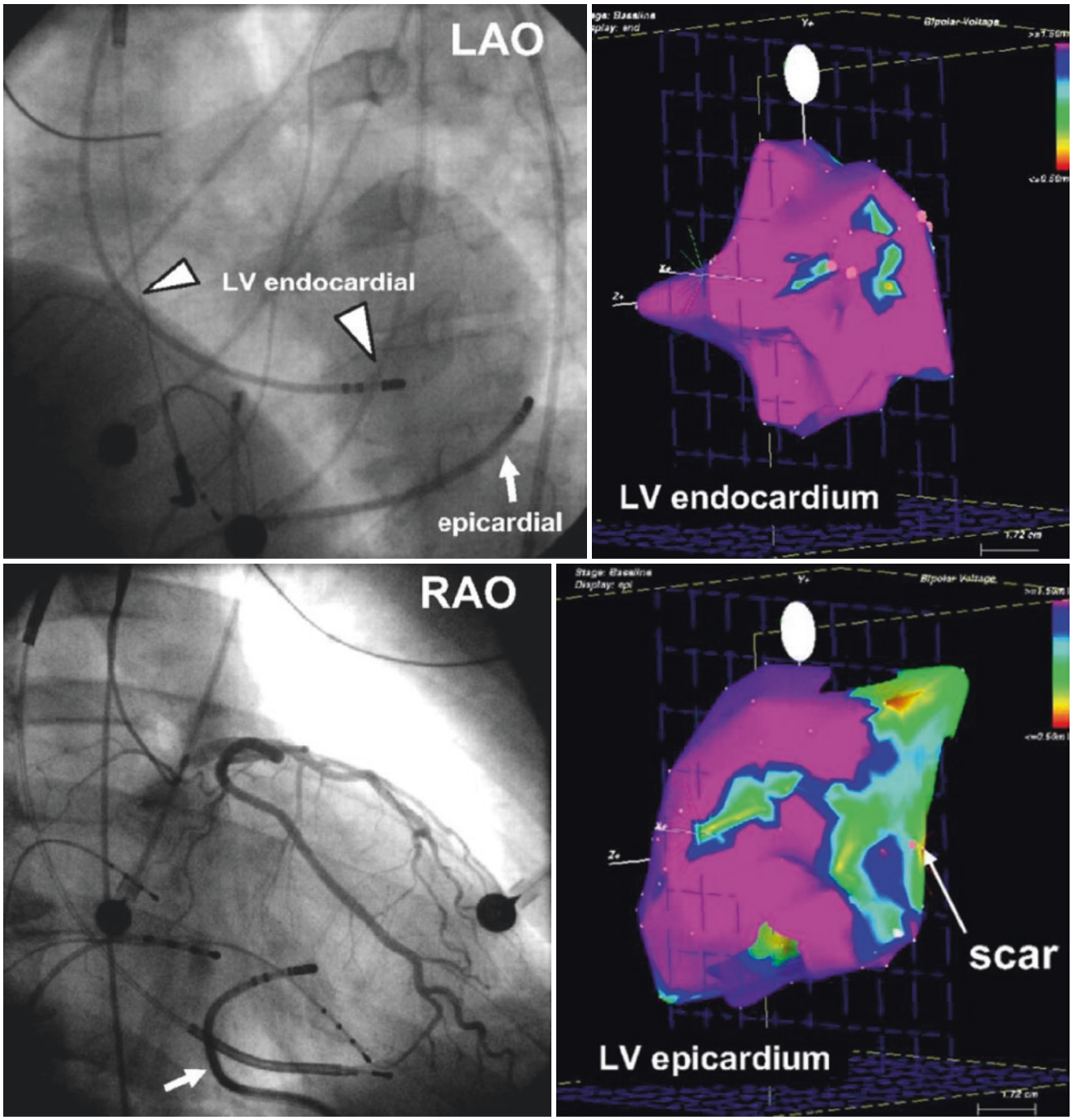


Fig. 20.1 Epicardial and endocardial mapping data from a patient with nonischemic cardiomyopathy are shown. *Top left*, left anterior oblique (LAO) fluoroscopic image of a mapping catheter placed retrograde through the aorta into the LV (*white triangles*) at the earliest endocardial site for VT. An epicardial catheter has been inserted by a subxiphoid puncture into the pericardial space (*arrows*). *Top right*, the LV endocardial voltage map viewed from a left posterior oblique position, showing relatively homogeneous normal voltage (*purple*) with no large areas of scar. *Bottom right*, the epicardial voltage map with a large low-amplitude region (*lighter color*) along the base of the LV. *Bottom left*, left coronary angiogram (right anterior oblique [RAO] projection) with the epicardial mapping catheter in the same location, revealing that no adjacent large coronary artery branches exist at risk of injury from ablation at that site. Ablation through the epicardial scar abolished the inducible VTs. (William G. Stevenson, and Kyoko Soejima: Circulation 115:2750, 2007)

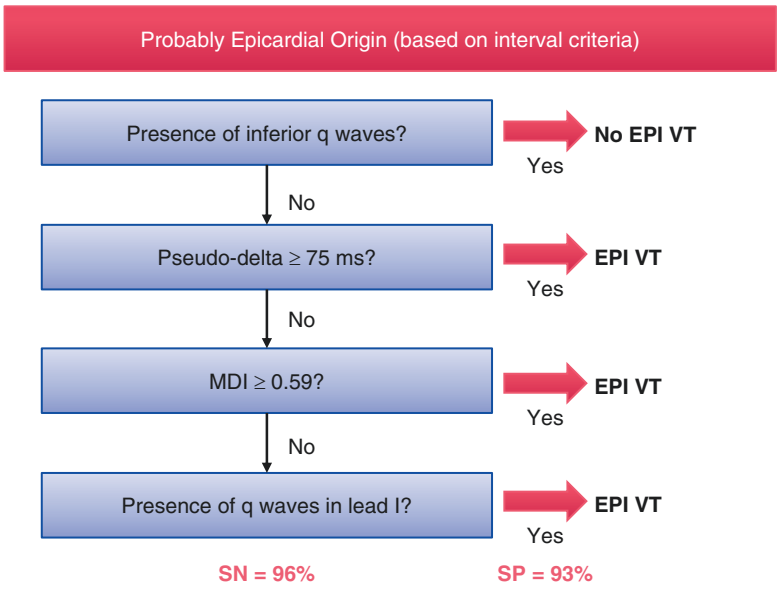


Fig. 20.2 Four-step algorithm for identifying EPI origin from basal superior and lateral LV in the setting of NICM. The three top steps have a high specificity and the last step is the most accurate. The total sensitivity and specificity of the algorithm in the study population for pace map localization reach 96 and 93%, respectively. (Ermengol Vallès et al.: Circ Arrhythm Electrophysiol 3:63, 2010)

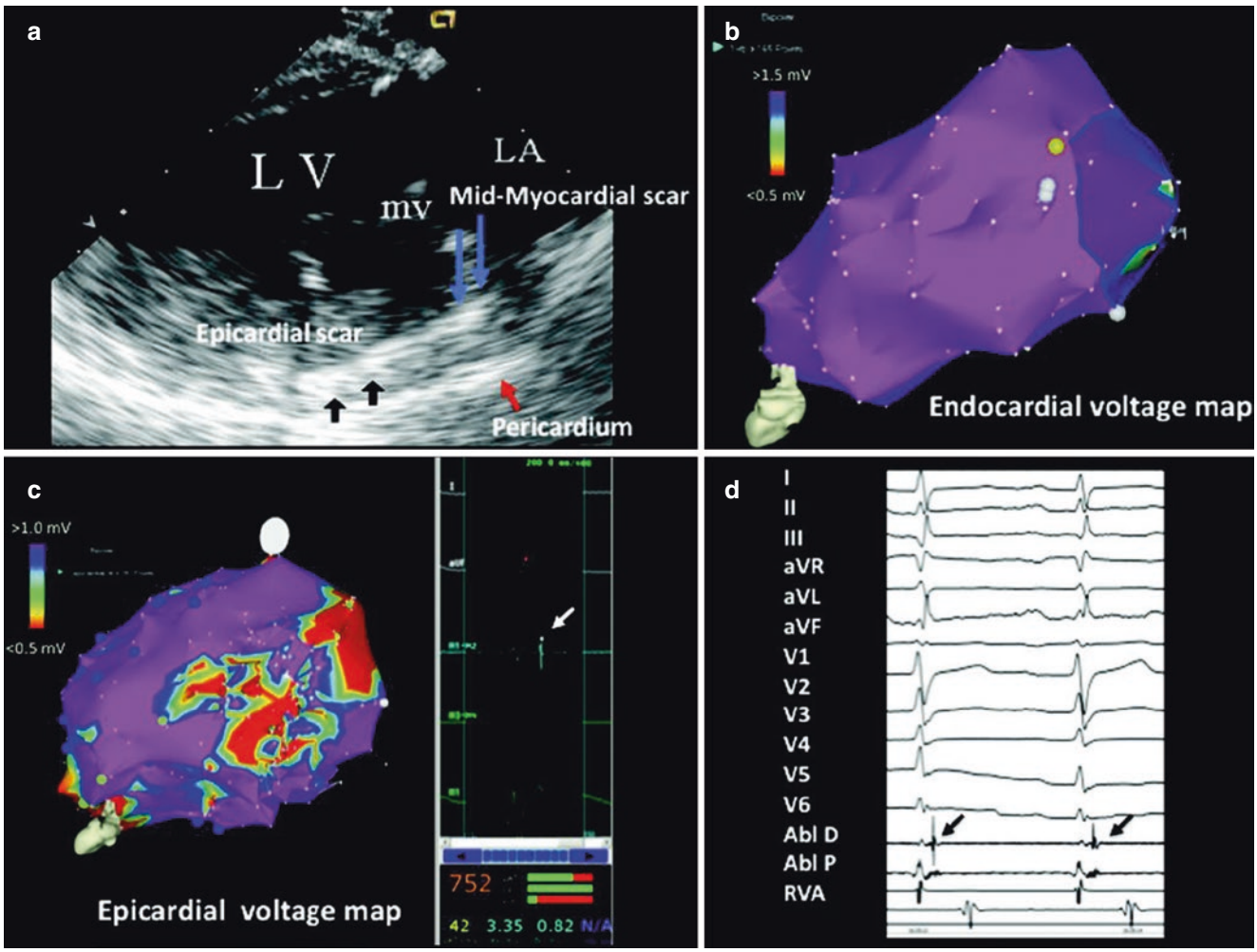


Fig. 20.3 (**a**), Intracardiac echocardiographic image with increased echogenicity in epicardium (*black arrows*) and midmyocardium (*blue arrows*) identified on the posterolateral wall. Pericardium is marked by the *red arrow*. (**b**), LV endocardial voltage map with normal voltage. (**c**), LV epicardial voltage map with area of low voltage on the posterolateral wall. The arrow points to a late potential identified in the epicardial scar. (**d**), Epicardial late potentials on Abl D (*arrows*). *Abl D* ablator distal; *Abl P* ablator proximal, *LA* left atrium, *LV* left ventricle, *mv* mitral valve, *RVA* right ventricular apex. (Rupa Bala et al.: Circ Arrhythm Electrophysiol 4:667, 2011)

ICDs have emerged as the major therapy for protecting patients from sudden death, but have created a cohort of patients with VT related shocks that reduce quality of life and are associated with increased mortality. Antiarrhythmic drug therapy only has been suboptimal. In view of these considerations, catheter ablation, performed in an experienced centre, should be considered early in the management of patients with heart disease who suffer recurrent symptomatic monomorphic VT.

Hypertrophic Cardiomyopathy

The identification of patients with hypertrophic cardiomyopathy (HCM) who are at risk of SCD has been challenging because of the relatively low disease prevalence and the low annual sudden death rates. ICDs are the mainstay of therapy for prophylaxis against sudden cardiac death. Although the occurrence of monomorphic ventricular tachycardia (VT) is rare in these patients, the mechanism of sudden death is more commonly ventricular fibrillation and polymorphic VT. There are multiple genetic variants that cause pleomorphic disease characterized by myocardial disarray and myocardial hypertrophy. Throughout the history of understanding this disease, we have come to learn that these patients are at an increased risk of atrial and ventricular arrhythmias and these contribute to the prognosis and mortality of the disease [21]. The mechanism of sudden death in HCM is ventricular tachyarrhythmia emanating from a structurally abnormal myocardium, which often includes areas of fibrosis [22].

Five risk factors have been found to be associated with SCD: family history of sudden death, history of recent syncope, massive wall thickness,(>30 mms NSVT during Holter monitoring, and abnormal blood pressure response to exercise [23]. In addition, the same risk factors were found to be important even in a community-based cohort [24].

Family history of sudden death was found as a significant risk factor for sudden death in patients with HCM. Alone, family history has a 1.9 (95% CI 0.8–4.5; P = 0.15) risk ratio. However, when taken with history of syncope, the combined risk ratio is 5.3 (95% CI 1.9–14.9; P = 0.002) [25]. Patients receiving ICDs for primary prevention because of a family history of HOCM related sudden death, whether as an isolated risk factor or combined with other markers, experienced rates of appropriate ICD discharge comparable to that of other patient subsets with increased risk [26]. Syncope is found in approximately 14% to 35% of patients suffering from HCM. Unexplained syncope is consistently found to be a predictor of SCD [27]. No increased risk is seen in patients older than 40 years with distant episodes of syncope or with neurally mediated (vasovagal) syncope [27].

Maximum LV thickness ≥30 mm in young patients has been highly predictive of SCD [28, 29]. Maximum LV thickness <15 mm has consistently shown very low rates of SCD [28]. A more recent study including 157 patients with HCM undergoing 2D echocardiography evaluated the ventricular arrhythmia events over a median of 3.7 years. The study looked at maximal LV wall hypertrophy as well as regional hypertrophy such as basal anterior and equatorial inferior wall thickness. Maximal ventricular wall thickness and basal anterior thickness more than 15 mm was associated with a 4.5-fold increase in relative risk of ventricular arrhythmias. In addition, equatorial inferior thicknesses more than 19 mm had a 5.9-fold increase in relative risk. The two regional measures (basal and equatorial) were independently associated with arrhythmic risk [30].

Premature ventricular contractions occur in 80%–90% of patients, ventricular couplets in 30%–40%, and nonsustained ventricular tachycardia (NSVT) in 20–25%. While NSVT is common, the number of episodes is low in most (1–3 runs in 24 h), bursts are usually short (3–5 beats), and episodes are typically asymptomatic [31]. Although a number of studies have reported an association between non-sustained ventricular tachycardia (NSVT) and the risk of SCD in patients with HCM, its utility as a clinical risk marker remains controversial [31–36].

Emerging evidence suggests that contrast-enhanced magnetic resonance imaging may be a useful risk stratification tool for SCD in HCM [37, 38]. Late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) represents areas of increased collagen deposition and myocardial fibrosis [39].

Multiple studies have found associations between the percentage of myocardial fibrosis/scarring as seen by LGE and ventricular tachyarrhythmias [40–44] (Fig. 20.4). In the largest study of 1293 patients undergoing CMR, fibrosis as found by LGE correlated linearly with risk of ventricular arrhythmias [45]. LGE of 15% or greater of LV mass showed a twofold increase in SCD event risk. In addition, certain locations of scarring may be at an increased likelihood of ventricular arrhythmias. Patients with basal septal scarring on CMR were shown to have higher VT frequency than those patients without (27% vs. 5%, $p = 0.03$). Another study looking at signal intensities of LGE found that intermediate signal intensity was a better predictor of ventricular tachyarrhythmias, including NSVT, ventricular couplets, and PVCs, compared with high-intensity LGE [46]. Late enhancement is associated with other risk factors for sudden death, greatest in patients [38]. Asymptomatic or mildly symptomatic patients with late enhancement had a sevenfold higher risk of NSVT [47]. A recent study with a larger cohort of HCM patients and longer follow-up found late enhancement to be significantly associated with sudden cardiac death and

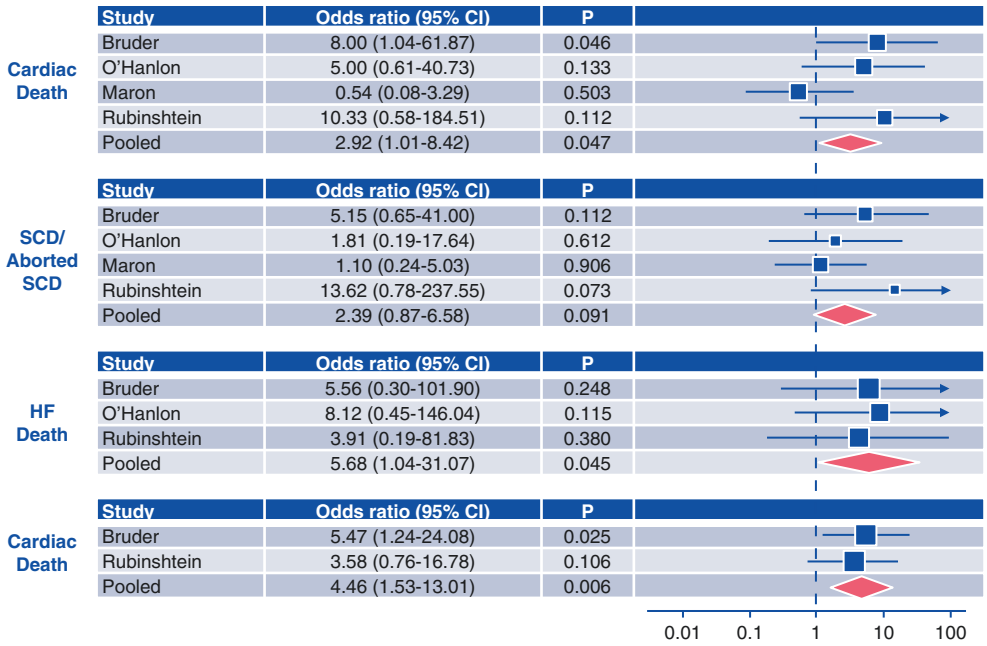


Fig. 20.4 Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy (J Am Coll Cardiol Img 5(4):370, 2012)

appropriate ICD discharges, even after controlling for traditional risk factors [48].

Surface electrocardiographic (ECG) findings have been evaluated to assess risk for future arrhythmic events. Using appropriate ICD therapies as a surrogate, fragmented QRS (fQRS) as seen on surface ECG at ICD implant was found to predict arrhythmic events in patients with HCM along with history of VT/VF. fQRS in the lateral location increased the risk of appropriate ICD therapy ($P < 0.0001$) [49].

Medical management of HCM patients at high risk for SCD with antiarrhythmic agents has not been supported in the recent literature. Before the introduction of ICDs, drugs including amiodarone, β-Blockers, calcium antagonists, and type I-A antiarrhythmic agents were used prophylactically [50]. Although early reports suggested amiodarone as potentially protective, it is clear that amiodarone does not provide protection from sudden death in patients with HCM [51]. In addition, amiodarone is associated with significant cumulative toxicity, making it unsuitable for use in young patients [50].

ICD placement is recommended (class I recommendation) for patients with HCM and prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant ventricular tachycardia [52]. For primary prevention of SCD in patients with HCM, the guidelines states that it is reasonable to recommend (class IIa recommendation) an ICD for patients with HCM with SCD presumably related to HCM in ≥1 first-degree relatives, or a maximum left ventricular wall thickness ≥30 mm, or ≥1 recent unexplained syncopal episodes. An ICD can be useful in select patients with nonsustained ventricular tachycardia in the presence of other SCD risk factors or modifiers or with an abnormal blood pressure response to exercise in the presence of other SCD risk factors or modifiers. It is reasonable to recommend an ICD for high-risk children with HCM, based on unexplained syncope, massive left ventricular hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation [52] (Fig. 20.5).

A simplified risk score has been developed to predict risk of sudden cardiac death [21]. However this has had mixed results to identify high risk cohort when independently applied in a retrospective cohort [53].

High risk patients with ICDs placed for primary or secondary prevention experience annual appropriate discharge rates for ventricular arrhythmias of 4–7%/year, with appropriate treatment occurring more frequently when placed for secondary prevention (7–11%/year) compared with primary prevention (3–5%/year) [54–57]. Unfortunately, inappropriate discharges are also common in HCM patients, with up to 25% receiving inappropriate shocks [56, 58]. Inappropriate discharge due to sinus tachycardia, AF, T wave oversensing or lead malfunction are the most common ICD complications in HCM, followed by infection, hemorrhage/thrombosis, lead fracture, dislodgement, and oversensing, which are found at rates similar to the general population of patients with pacemakers and ICDs [58]. The psychological and behavioral aspects of ICD therapy in patients with HCM warrants more investigation as many patients with HCM considered for ICD therapy are otherwise healthy and often asymptomatic young individuals. There have been recent optimistic reports on use of subcutaneous ICD in the patients with HCM [59].

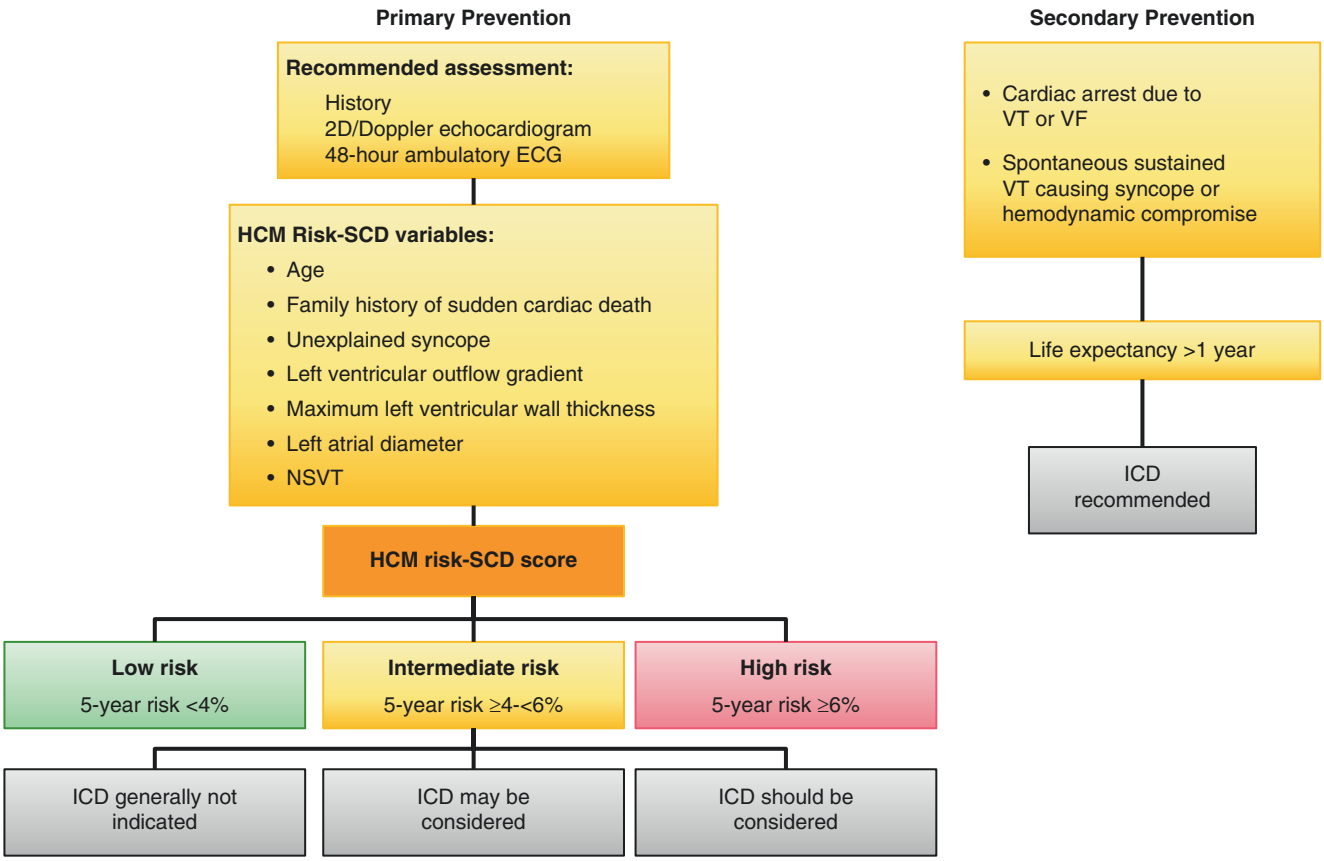


Fig. 20.5 Flow chart for ICD implantation. (N Engl J Med 364(26):2011)

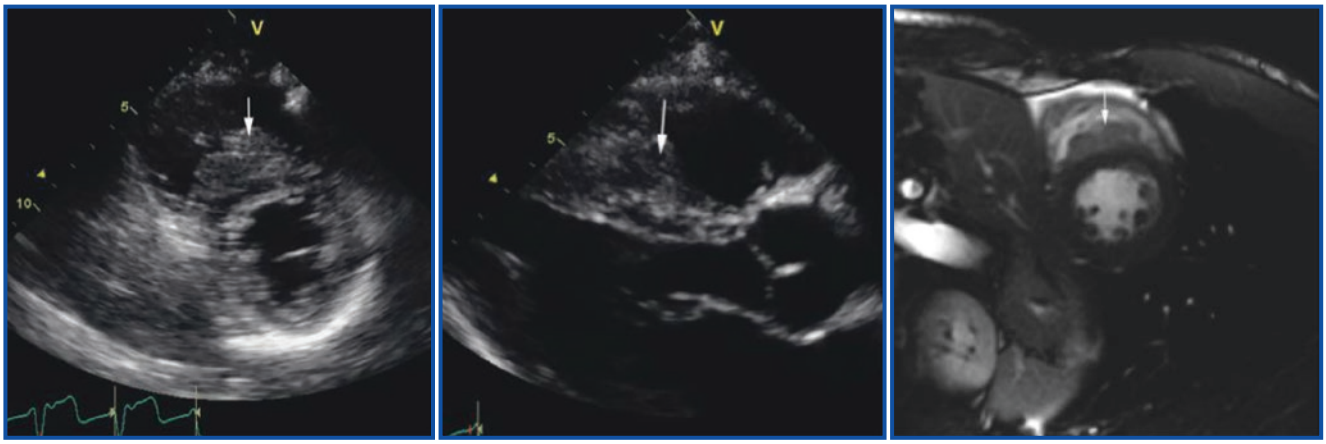
Radiofrequency catheter ablation (RFCA) may be a suitable treatment strategy for selected HCM patients with VT, especially for those with VTs arising from an LV apical aneurysm [60–65]. A recent multi center experience suggests catheter ablation of VTs in patients with hypertrophic cardiomyopathy refractory to medical therapy is safe, feasible, and successful in eliminating VT. Epicardial VT mapping and ablation should be considered as an important access option for the treatment of these patients to increase the success rate [66]. Thick ventricular wall and difficulty in catheter manipulation, septal circuits could be a plausible reason for inability to account for all the circuits.

Most people with HCM lead normal lives, but a small number experience significant symptoms and are at risk of disease-related complications and sudden cardiac death. Symptoms alleviation and prevention of sudden death remains the cornerstone for management.

Sarcoidosis

There has been considerable interest in extrapulmonary involvement of sarcoidosis. Cardiac involvement has been noted in at least 2–7% of patients with sarcoidosis but occult involvement is much higher (>20%) [67]. Early autopsy studies suggest up to 25% of patients with sarcoidosis have myocardial involvement [68]. Cardiac involvement can present with conduction abnormalities, ventricular arrhythmias, or heart failure. Initial presentation of cardiac sarcoidosis (CS) could be sudden death due to ventricular tachyarrhythmias or bradyarrhythmias [69]. Patients with CS causing sudden death show extensive myocardial granulomas with a predilection for the subepicardium and ventricular septum [70]. The frequent absence of specific symptoms and lack of a diagnostic 'gold standard' pose challenges in the diagnosis of CS. Endomyocardial biopsy, although specific, has an unacceptably low sensitivity. There has been growing interest in voltage mapping guided biopsy [71].

Multiple criteria's have been proposed for diagnosis and risk stratification of CS [72]. A recent survey however underscored the lack of agreement for criteria for diagnosis or optimal treatment of CS [73]. Granulomatous inflammation, the hallmark of sarcoidosis, may involve myocardium, endocardium, or pericardium. Nonnecrotizing granulomas, epithelioid histiocytes, multinucleated giant cells, Schaumann bodies or asteroid bodies, patchy fibrosis, and lymphocytic infiltration may be observed [74]. The areas of involvement in descending order of frequency are the left ventricular free



Parasternal short-axis echocardiogram showing right ventricular mass on interventricular septum

Parasternal long-axis echocardiogram showing right ventricular mass on interventricular septum

Cardiac magnetic resonance imaging bright blood sequence showed hyperintense soft tissue mass on the right ventricular side of interventrcular septum (mirror image of parasternal short-axis echocardiogram)

Fig. 20.6 Large granuloma on the interventricular septum (N Engl J Med 364(26):2011)

wall, interventricular septum (IVS), papillary muscles, right ventricle (RV), and atria [68, 70] (Fig. 20.6). In the series reported by Roberts et al., the following electrocardiogram (ECG) abnormalities were cited: complete heart block (22%); complete BBB (22%); VT (17%); PVCs (29%); and atrial arrhythmias (16%) [75]. Heart block of any degree can occur in cardiac sarcoidosis due to the predilection of granulomas for the interventricular septum where the conduction system resides.

In general, the ACC/AHA/HRS 2012 guidelines for permanent pacing apply to patients with CS and high degree AV block [20]. The consensus document on sarcoid suggests, device implantation can be useful in CS patients with an indication for pacing even if the AV block reverses. Permanent pacing is recommended because CS may have an unpredictable course, and AV block that reverses with immunosuppression may recur. In a recent systematic review, 27 of 57 CS patients (47.4%) treated with steroids had improvement in AV conduction [76]. ICD implantation can be useful in patients with CS and an indication for permanent pacemaker implantation. CS patients with significant granulomatous burden to have high degree AV block necessitating permanent pacing likely have the substrate for reentrant ventricular arrhythmias and therefore should have a device for brady and tachy therapies. There are little data regarding cardiac resynchronization in CS patients and general device selection recommendations apply to CS.

Ventricular arrhythmias (VA) in CS are most commonly due to macroreentry around granulomas; however, triggered activity and automaticity can also play a role. Treatment of VT can involve a stepwise escalation of therapy starting with immunosuppression, followed by antiarrhythmic drug therapy, and finally catheter ablation if immunosuppression and antiarrhythmic therapy have been unsuccessful [77].

The predictive value of programmed electrical stimulation-induced VA and guided antiarrhythmic medical therapy is limited in cardiac sarcoidosis. In one study, programmed ventricular stimulation was performed in 32 consecutive patients with cardiac sarcoidosis. ICDs were placed in all 12 patients with spontaneous or inducible sustained VT; the other 20 did not receive ICD. All 32 patients were followed up for the combined arrhythmic event end point of appropriate ICD therapies or sudden death. Mean length of follow-up to sustained VA or sudden death was 32 ± 3 months. Five of six patients with spontaneous sustained VA and four of six patients without spontaneous but with inducible sustained VA received appropriate ICD therapy. Importantly, no patient with an ICD died of a primary VA. Among patients with spontaneous or inducible sustained VA, mean survival from first appropriate ICD therapy or death or cardiac transplant was 60 ± 46 months; only 2 of 12 patients with ICD died or required cardiac transplant at study end. Unfortunately, 2 of 20 patients (10%) with neither spontaneous nor inducible sustained VA who did not receive ICD experienced sustained VA or sudden death. Currently, Society Guidelines cited primary prevention ICD implantation as a class IIA recommendation (level C) for patients with cardiac sarcoidosis [20]. In another study of 45 patients with cardiac sarcoidosis, the incidence of VA requiring ICD therapy was approximately

15% per year. Longer follow-up, LV systolic dysfunction, and complete heart block were associated with serious VA. A recent multicenter study (13 sites) followed 235 patients with cardiac sarcoidosis post-ICD placement. Overall, 85 of 234 (36.2%) patients received an appropriate ICD therapy (shocks and/or antitachycardia pacing) and 67 of 226 (29.7%) received an appropriate shock at 4.2 ± 4.0 years. However, 57 patients (24.3%) received a total of 222 inappropriate shocks; further, 46 AE occurred in 41 patients (17.4%). Thus, patients with cardiac sarcoidosis and ICDs are a high risk for VA, but the rate of inappropriate shocks and device complications is not trivial [78].

Catheter ablation may be efficacious in patients with persistent VT despite medical therapy [77]. In one study of 42 patients with cardiac sarcoidosis, VT was not controlled despite medical therapy (CS, antiarrhythmics) and ICD in 9 patients [77]. Endocardial or epicardial radiofrequency ablation resulted in decreased (n = 4) or complete elimination (n = 5) of VT in all patients. Arrhythmic events decreased from a mean of 271 ± 363 episodes preablation to 4.0 ± 9.7 postablation. However, radiofrequency ablation is not consistently effective. Thachil et al. reported 14 patients with sustained monomorphic VT (SMVT), mediastinal adenopathy, and abnormalities on PET-CT in the mid-myocardium consistent with scar ± inflammation [79]. Mediastinal lymph node biopsies revealed nonnecrotizing granulomas in all 14 patients; 11 (79%) had TB (79%). All patients were treated with antiarrhythmics ± radiofrequency ablation, yet VT recurred in 92%. The addition of disease-specific therapy (for TB or sarcoidosis) ended further recurrences in 64%. The reduction/disappearance of VT correlated with resolution of myocardial inflammation on serial PET/CT scans. A recent report from Stevenson et al. suggests a mechanism consistent with scar-mediated re-entry in all VTs. Voltage maps showed widespread and confluent right ventricular scarring. Left ventricular scarring was patchy with a predilection for the basal septum, anterior wall, and perivalvular regions. Elimination of all inducible VTs was difficult to achieve because of diffuse and heterogeneous RV involvement, intramural scarring, or close proximity to critical epicardial structures, such as the coronary arteries prohibiting ablation. The inability to abolish all inducible VTs, as well as the high risk of recurrence, death, or cardiac transplant emphasizes the need for better treatment options including the ICD in this high-risk group [80].

Cardiac Sarcoidosis Consortium (CSC) has been created to form international relationships with the unifying purpose of understanding more about cardiac sarcoidosis. Currently, there are more than 25 centers enrolled from the United States, Europe, India, and Japan. Long-term goals include creating a large prospective database and more collaboration to understand and treat the disease more effectively.

Chagas Disease

Chagas disease (ChD) is a major healthcare issue in Latin America and affects 8–10 million people. More recently, with increased migration, it has also become a problem for developed countries, which now have hundreds of thousands of patients with this disease [81]. The US Centers for Disease Control and Prevention have reported more than 300,000 immigrants living in the United States infected with T cruzi. ChD is a chronic parasitosis that affects the heart and other organs and is caused by the protozoan parasite Trypanosoma cruzi. T cruzi is transmitted to humans mainly through parasite-laden feces from a hematophagous insect vector (Triatoma infestans in South American Countries and Rhodnius prolixus in the Andean region and Central America). The triatomine vectors are only found in the South American continent, where the disease in considered endemic (also called American trypanosomiasis). The triatomine vectors live in the walls and roofs of houses built with vegetable materials, a practice that is common many poor, rural areas of Latin America. It is common for patients infected during childhood before moving from an endemic area to present as adults with clinical manifestations of the disease in nonendemic areas, leading to delays in timely diagnosis and treatment [82]. Most of the acute infections are subclinical with either no symptoms or a relatively mild and nonspecific febrile illness that resolves spontaneously in 4–8 weeks. Most patients remain asymptomatic for lasting from several months to their entire lifetime [83].

The pathogenesis of cardiac injury is unclear. Potential mechanisms include: cardiac parasympathetic neuronal damage, immune-mediated myocardial injury, parasite persistence in cardiac tissue with secondary antigenic stimulation, and coronary microvascular abnormalities causing myocardial ischemia [84] (Figs. 20.7 and 20.8). The main arrhythmogenic substrates are necrotic and fibrotic lesions due to inflammation. The lesions are also associated with blood flow impairment secondary to microvascular lesions or autonomic changes that regulate blood perfusion of the injured myocardium. The lesions caused by inflammatory processes damage the intercellular junctions that are associated with changes in electrical potential and hamper conduction between cells. These changes cause electrical uncoupling those results in the slow conduction of stimuli and unidirectional block. This process, coupled with the fibrotic areas, forms the reentrant circuit that causes VAs. It is postulated that cardiac dysautonomia, a typical finding in Chagas disease, may be related to the pathogenesis of and risk associated with ventricular arrhythmias in ChD [85]. The prevalence and severity of chagasic VAs correlates with the severity of the cardiomyopathy but can occur in patients with preserved LVEF. Frequent monomorphic or polymorphic

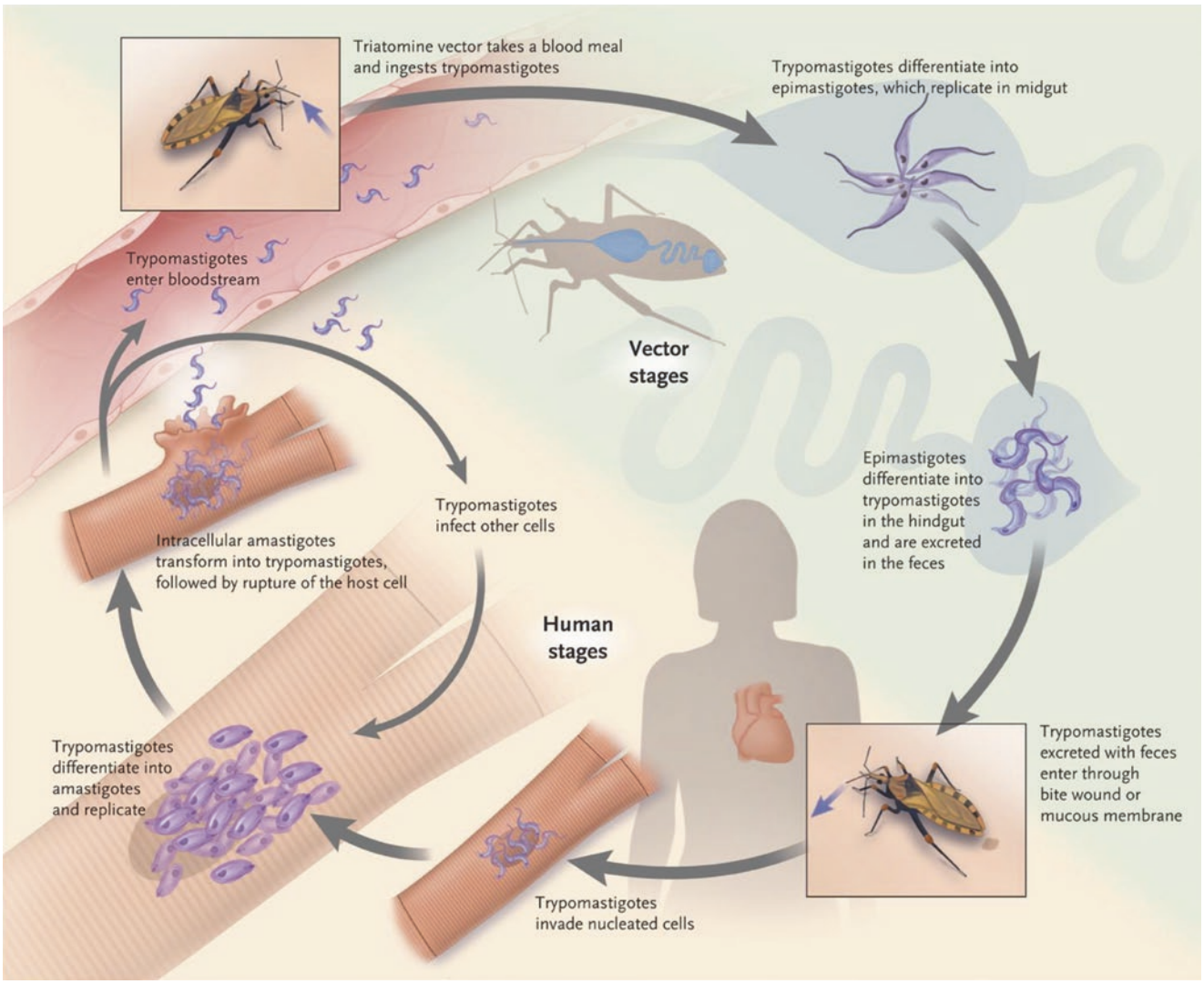


Fig. 20.7 The Life Cycle of *Trypanosoma cruzi*. The triatomine vector ingests circulating trypomastigotes in a blood meal from an infected mammalian host. Trypomastigotes differentiate into epimastigotes, which replicate in the vector midgut. The epimastigotes then migrate to the hindgut and differentiate into infective metacyclic trypomastigotes, which are excreted with the feces of the vector. Metacyclic trypomastigotes enter through a bite wound or an intact mucous membrane of the mammalian host and invade many types of nucleated cells. In the cytoplasm, trypomastigotes differentiate into the intracellular amastigote form, which replicates, with a doubling time of about 12 h, over a period of 4–5 days. At the end of this period, the amastigotes are transformed into trypomastigotes, the host cell ruptures, and the trypomastigotes are released into the circulation. The circulating parasites can then invade new cells and initiate new replicative cycles, and they are available to infect vectors that feed on the host. (Bern C: N Engl J Med 364:2527, 2011)

premature ventricular contractions (PVCs), couplets, and salvos of nonsustained VT (NSVT) are common on Holter monitoring in ChD. Sustained VT is considered a hallmark of ChD, the main cause of SCD, and the most frequently observed life-threatening ventricular arrhythmia in chagasic patients with ICDs [86].

SCD is most common cause of death in ChD (55%–65%), followed by CHF in 25–30% and cerebral or pulmonary embolism in 10% to 15% [87–89]. Most SCD cases are in patients with manifest chagasic cardiomyopathy and mainly between 30 and 50 years of age, being rare after the sixth decade of life. This wide range of presentations implies that the risk of SCD is not similar for every patient and thus identifying factors that increase risk becomes extremely important.

Rassi and colleagues developed and validated a risk score for predicting death in ChD based on a retrospective evaluation of 424 outpatients who underwent routine noninvasive tests and were followed for a mean of 7.9 years [90]. They identified six independent prognostic factors: NYHA class III or IV (5 points), cardiomegaly on chest radiography (5 points), segmental or global wall motion abnormality on echocardiogram (3 points), NSVT on Holter monitoring (3 points), low QRS voltage (2 points), and male sex (2 points).

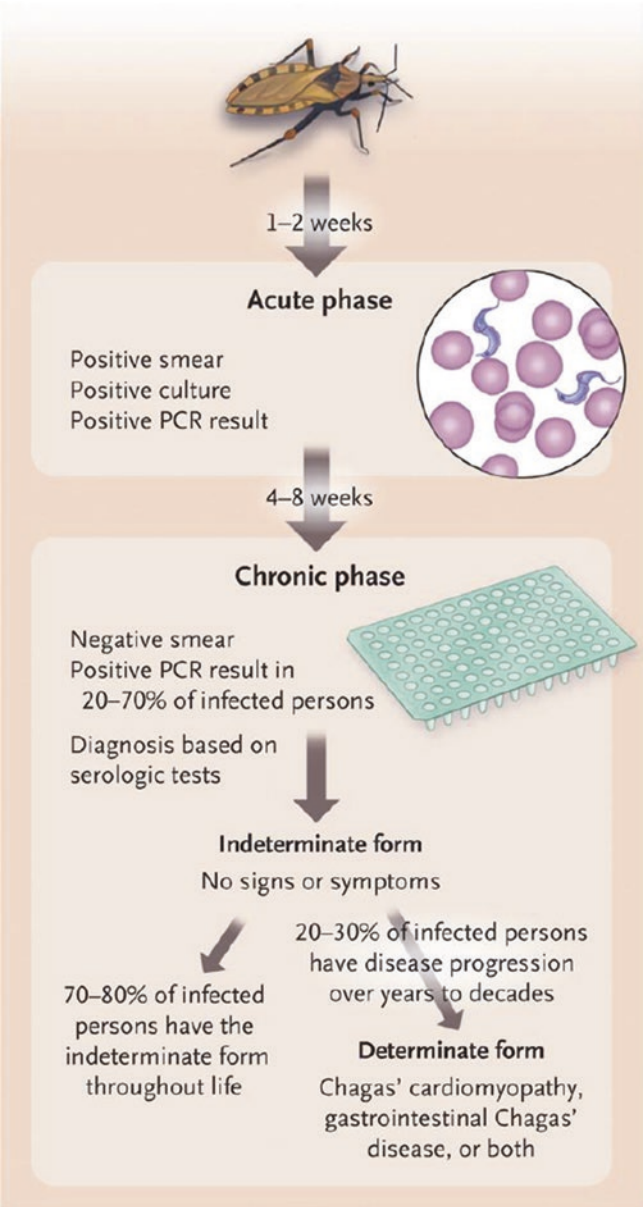


Fig. 20.8 Phases and Forms of *Trypanosoma cruzi* Infection. The acute phase of *Trypanosoma cruzi* infection is characterized by microscopically detectable parasitemia and lasts 4–8 weeks. Diagnosis during the chronic phase of infection is based on serologic assays. Persons with chronic *T. cruzi* infection but without signs or symptoms of Chagas' disease are considered to have the indeterminate form of the disease. An estimated 20–30% of people with the indeterminate form of Chagas' disease have progression to clinically evident cardiac disease, gastrointestinal disease, or both over a period of years to decades. PCR denotes polymerase chain reaction. (Bern C: N Engl J Med 364:2527, 2011)

This score classifies chagasic patients into 3 groups: low (0–6 points), intermediate (7–11 points), and high risk (12–20 points), with 10-year mortalities of 10%, 44%, and 84%, respectively. Conveniently, the score is based on noninvasive clinical variables that are easy to use and inexpensive. In addition, this score identifies chagasic patients with increased risk who could potentially benefit from a more aggressive therapeutic approach (Fig. 20.9).

The most frequent VAs in patients with Chagas disease are ventricular, isolated and repetitive ectopic beats. Antiarrhythmic treatment is not required in asymptomatic patients with preserved ventricular function. In patients with ChD with LV dysfunction and frequent PVCs/nonsustained VT, the guidelines recommend amiodarone as the only safe drug available. However, there are no clinical trials supporting a role for amiodarone to reduce the risk for SCD and total mortality in this context. Scanavacca and colleagues reported the results of amiodarone used in 35 chagasic patients with sustained VT and a mean LVEF of 56% ± 14% [91]. After 27 ± 20 months of follow-up, the probability of suppressing sustained VT was 0.62 at 12 months, 0.56 at 24 months, and 0.44 at 36 months. Importantly, all patients in functional class III or IV and with LVEF less than 30% had recurrence of sustained VT. Thus, amiodarone seems to have limited efficacy to prevent sustained VT recurrence in patients with ChD, especially in patients with LV dysfunction and significantly reduced functional class. Parasite persistence likely contributes to the pathogenesis of chagasic cardiomyopathy, which suggests that trypanocidal therapy may have a positive impact on the clinical course of patients with ChD. However, the currently available experimental and clinical evidence is insufficient to support the routine use of treatment in these patients. The results of the BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) trial were expected to provide more insight [92]. Recently reported, they suggest reduced serum parasite detection but did not significantly reduce cardiac clinical deterioration through 5 years of follow-up [93].

The use of ICDs appears to provide effective protection for Chagas patients and constitutes a safe procedure with low frequencies of inappropriate therapy and complications, despite having been assessed in only a few prospective and retrospective observational studies that examined limited numbers of patients. The guidelines for diagnosis and treatment of ChD do not define recommendations about ICD implantation for primary prevention, reflecting the lack of clinical trials and observational studies in this area. Barbosa et al. and the ICD registry for patients with Chagas disease in Latin America found differences between the chagasic and non-chagasic populations. ChD groups had higher numbers of ventricular arrhythmias, a higher percentage of patients receiving appropriate therapy and increased numbers of shocks overall [94–97]. The groups did not differ in the outcomes for mortality and the number of inappropriate shocks.

A recent study by Gali et al. [59] compared the outcomes of ChD patients with life-threatening ventricular arrhythmias who were treated either with ICD implantation plus amiodarone or with amiodarone alone [98]. Therapy with ICD plus

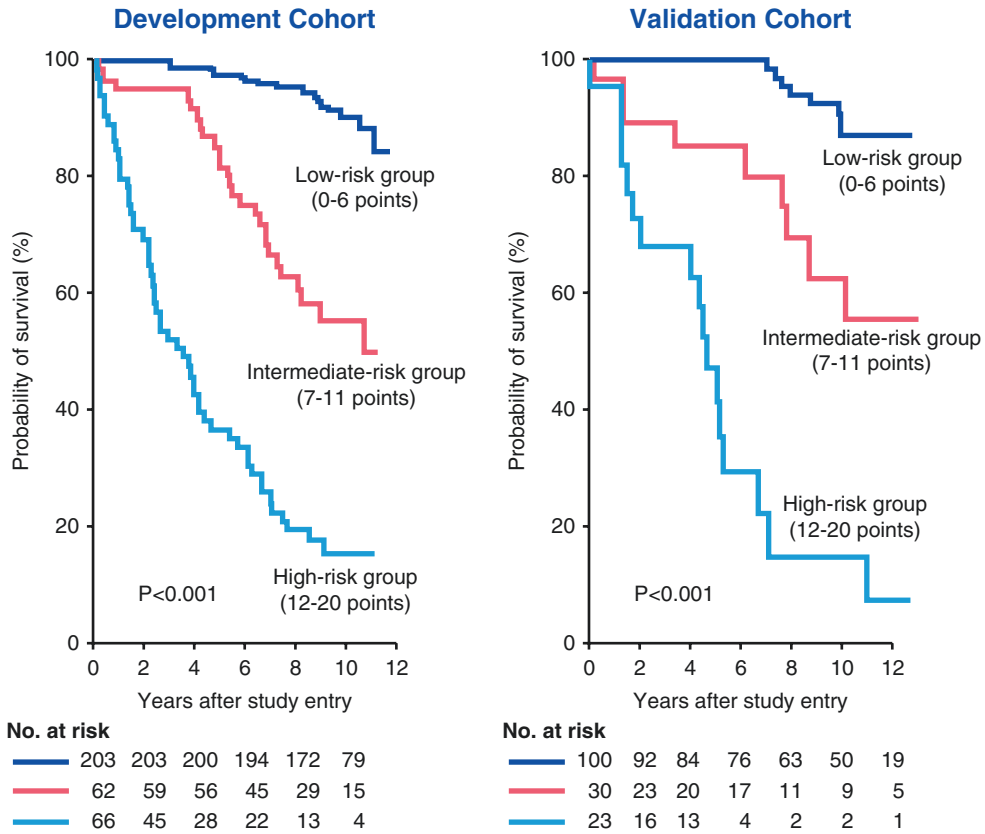


Fig. 20.9 Kaplan–Meier Survival Curves for the Development Cohort (Panel (**a**)) and the Validation Cohort (Panel (**b**)), According to the Prognostic Classification. Because data for some variables were missing for some patients, the prognostic classification of the development cohort was based on a total of 331 patients rather than 424. Risk categories were determined by adding up the points for each of the following risk factors: male sex (two points), low QRS voltage on electrocardiography (two points), nonsustained ventricular tachycardia on 24-hour Holter monitoring (three points), segmental or global wall-motion abnormality on echocardiography (three points), cardiomegaly on chest radiography (five points), and NYHA class III or IV (five points). (Rassi A Jr. et al.: N Engl J Med 355:799, 2006)

amiodarone resulted in a 72% reduced risk of all-cause mortality (p = 0.007) and a 95% reduced risk of sudden death (p = 0.006) compared with amiodarone-only therapy. The survival benefit associated with ICD was greatest in patients with LVEF <40% (p = 0.01) and was not significant in those with LVEF ≥40% (p = 0.15). Appropriate ICD therapies occurred in 72% of patients, and the rates of interventions were similar across patients with LVEF <40% and those with LVEF ≥40%.

VT ablation in Chd poses unique issues and challenges. The reentrant circuit responsible for scar-related VT in these patients may be subendocardial, subepicardial, or intramyocardial. Occasionally, these circuits exist in areas of the heart with thin walls and radiofrequency ablation may result in transmural injury effectively treating all portions of the myocardium involved in the arrhythmia circuit. However, scar commonly exists intramyocardially and/or subepicardially in an area with an associated thick layer of subendocardial myocardium. In these instances, endocardial radiofrequency ablation may not effectively treat all of the involved myocardium. The initial attempts at endocardial ablation were associated with disappointing results. D'Avila reported on a series of 24 consecutive patients who underwent endocardial ablation between 1991 an1996. After an average of 26 months of follow-up, only 17% of patients remained VT-free [99]. One of the biggest lessons learnt from Chagas cardiomyopathy has been opening our horizon for epicardial access. In 1996 Sosa et al. pioneered the technique of percutaneous epicardial access and catheter ablation in patients with Chagas cardiomyopathy; 2 years later the same group described the results of a combined endocardial and epicardial mapping and ablation approach in ten patients with Chagas disease and recurrent VT [100, 101]. The epicardial surface presents three major anatomic challenges that may affect the efficiency and safety of ablation: epicardial coronary arteries, thick epicardial fat, and potential injury to surrounding structures (phrenic nerve). To understand the utility and risks of epicardial access for the ablation of sustained VT in chagasic cardiomyopathy, prospective randomized studies are needed. In a subset of patient for whom catheter ablation can be useful; clinical outcomes are favorable at short-term (83% acute success) and medium-term follow-up [102].

The use of surgical resection (aneurysmectomy) for the treatment of recurrent ventricular arrhythmias in ChD has been described [103]. In one report, electrophysiologic mapping was performed of the area adjacent to the aneurysm to identify abnormal potentials. These areas were excised along with the aneurysm. Pathologic examination revealed a chronic inflammatory reaction, myocytolysis, and fibrosis. In addition, interlaced fronts of healthy (normally conducting) and damaged (slowly conducting) myocytes were observed, resulting in an ideal configuration for reentry [104].

The development of a collaborative approach to accurately predict which patients are at a high risk of presenting with malignant cardiac arrhythmia would allow effective preventive actions and a more rational use of available funds for the treatment of Chagas cardiomyopathy especially in the developing world.

Left Ventricular Non-compaction Cardiomyopathy

Left ventricular non-compaction cardiomyopathy (LVNC), which was first described by Grant in 1926, is a heterogeneous myocardial disorder characterized by prominent trabeculae, intratrabecular recesses, and a left ventricular myocardium with two distinct layers: compacted and noncompacted [105]. Although LVNC mainly affects the left ventricle, isolated right ventricular and biventricular noncompaction also occur. The American Heart Association formally classified LVNC as a distinct cardiomyopathy in 2006.

During embryogenesis, the myocardium consists of a loose network of interwoven fibers separated by deep intertrabecular recesses linking the myocardium with the left ventricular cavity. Between the fifth and eighth weeks of embryonic development, this meshwork compacts, proceeding from the epicardium to the endocardium and from the base of the heart to the apex. Ventricular noncompaction results from intrauterine arrest of this process, due to pressure overload or myocardial ischemia preventing the normal compaction process and regression of the myocardial sinusoids [106].

The clinical manifestations of LVNC are highly variable, ranging from asymptomatic to progressive heart failure and recurrent or life-threatening arrhythmias. Therefore, great interest has developed in characterizing the natural history of this disease and its associated arrhythmias, in order to help guide the counseling and management of this heterogeneous patient population.

Early descriptions of LVNC point to three major clinical manifestations of the disease, including heart failure, embolic events, and arrhythmias [106]. It is commonly discovered through screening of family members of affected patients during early, nonsymptomatic stages [107].

Supraventricular and ventricular arrhythmias, and bradyarrhythmias, many of which are life threatening, occur frequently in LVNC. The LVNC subtype associated with early-onset rhythm abnormalities generally has a substantial risk of sudden death. ICDs are highly effective for the prevention of sudden arrhythmic death in patients with LVNC, including those with severe left ventricular dysfunction, a previous history of sustained VT or VF, recurrent syncope of unknown cause, or a family history of sudden cardiac death. Ventricular tachyarrhythmias, including those in patients in whom ventricular fibrillation causes cardiac arrest, are reported in 38–47% of adult patients with LVNC and in 13–18% of those who die suddenly [107]. A recent systematic overview of literature by Bhatia and colleagues, including over 200 adults, found the prevalence of VT (both sustained and nonsustained) to be 38% [108]. This finding was thought to merit special attention because SCD accounted for greater than 55% of all LVNC-related mortality in their analysis. The key in the management of these patients is the EF and the indications for the ICD are similar to those in other patients with CHF in regard to the ED criteria.

Although the primary form of ventricular arrhythmia reported in studies remains sustained or nonsustained monomorphic VT, specific morphologic descriptions have not been carried out and series to date have emphasized the broad spectrum of presentation. Indeed, case reports have found a variety of ventricular arrhythmias in association with LVNC, including bundle branch reentry, right ventricular outflow tract (RVOT) origin, apparent idiopathic VT, left bundle branch and right bundle branch morphologies, fascicular VT, bidirectional VT, polymorphic VT, and VF [109]. The precise mechanism for ventricular arrhythmias in patients with LVNC is not delineated. However, it is postulated that developmental arrest of conduction and the presence of intratrabecular crypts may create pathways for reentrant circuits. In addition, relatively decreased perfusion and ischemia-related fibrosis at subendocardial noncompacted regions can cause electrical inhomogeneity and microreentry resulting in ventricular arrhythmias.

There have been no controlled studies to determine efficacy of antiarrhythmic treatment of ventricular tachyarrhythmias in LVNC. β-Blockade as a single agent for nonsustained VT has been used; however, most reports suggest that combination therapy or more potent antiarrhythmics may be necessary, with amiodarone being the most frequently used medication among adults and in those with severely depressed function. Amiodarone seems to have good efficacy in this scenario; however, incomplete control has also been described [110].

Small studies have demonstrated appropriate shocks in both secondary and primary prevention, suggesting the potential utility of ICDs in this cohort. Conversely, inappropriate

shock rates in this population have been reported to be 13% to 20%.Therefore, because of the high prevalence of supraventricular arrhythmias in this cohort of patients, dual-chamber devices with enhanced detection and discrimination algorithms should be considered [111–114].

Monomorphic ventricular arrhythmias, particularly those that are sustained, have been successfully mapped and ablated using radiofrequency energy in patients with LVNC [109, 115]. Information and long-term follow-up of left cardiac sympathetic denervation in patients with LVNC is lacking. Based on short-term follow-up, sympathetic denervation may be an adjunct therapy if there are poorly controlled ventricular arrhythmias; however, further studies are needed [116].

Peripartum Cardiomyopathy (PPCM)

PPCM is diagnosed when a woman develops heart failure in the last month of pregnancy or up to 5 months postpartum, with a left ventricular (LV) ejection fraction less than 45% and no other identifiable cause of heart failure [117, 118]. Data on arrhythmia associated specifically with PPCM are sparse, and underlying mechanisms are unclear. In a series of 19 patients in Senegal with PPCM who underwent 24-h continuous electrocardiographic monitoring, 89% had sinus tachycardia, 37% had premature ventricular contractions, 21% had nonsustained ventricular tachycardia (VT), and 1 patient had first-degree atrioventricular block [119].

A recent study reported that 2.1% of women with PPCM in the United States suffered cardiac arrest in the period 2004–2011 [120]. Some women who develop arrhythmias secondary to PPCM may require intravenous antiarrhythmic drugs (AADs) in the acute setting or oral AADs for chronic management. In women requiring AADs prior to delivery, consideration must be given to the effects of AADs on fetal heart rhythm, fetal growth, and uterine activity [121]. In a prospective cohort with PPCM, most women recovered; however, 13% had major events or persistent severe cardiomyopathy. Black women had more LV dysfunction at presentation and at 6 and 12 months post-partum. Severe LV dysfunction and greater remodeling at study entry were associated with less recovery [122].

There is lack of data on catheter ablation of arrhythmias associated with PPCM. One recent report described successful mapping and ablation of sustained, unstable VT in a patient with PPCM [123]. Patients with PPCM are at risk for SCD, and, as with other cardiomyopathies, this risk is increased in patients with lower ejection fractions. Given that approximately half of women do not recover LV function, these data suggest that ICDs are underutilized in women with PPCM. In a series of 100 US women, 53 patients who did not recover LV function qualified for an ICD based on LV ejection fraction less than or equal to 35%, but only 7 women (13%) in this group received an ICD [124]. The European Society of Cardiology guidelines advise that for women presenting with symptoms and severe LV dysfunction 6 months after initial presentation, despite optimal medical therapy and QRS duration greater than 120 ms, cardiac resynchronization therapy or ICD treatment should be strongly considered. The guidelines do not comment on prevention of SCD or the use of devices in the first 6 months after diagnosis [125].

Because some PPCM patients with depressed ejection fraction ultimately recover LV function, it is reasonable to consider Wearable cardioverter-defibrillators (WCD) as a bridge to LV recovery or to ICD [118]. Only two studies to date have examined WCDs in patients with PPCM; no patients died while using a WCD in either study [126, 127]. In the other study, 107 women with PPCM were followed for an average of 3 years; mortality in this cohort was low (2.8%), despite a mean baseline LV ejection fraction of 21%. No women with PPCM, however, received any appropriate or inappropriate shocks [126]. Further research is needed to elucidate the prevalence, underlying mechanism, and natural history of arrhythmias in this condition.

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TCM) is a distinct, usually reversible, form of myocardial stunning occurring in the setting of severe emotional or physical stress and is related to catecholamine-mediated myocardial toxicity [128]. Oxidative stress leading to dysregulation of calcium homeostasis is also thought to contribute to myocyte dysfunction in addition to cardiac arrhythmias [129]. Despite the severe repolarization abnormalities observed in TCM and the heightened adrenergic milieu, the reported arrhythmic risk is surprisingly low. In a comprehensive literature review encompassing 816 cases, Syed and colleagues reported a range of arrhythmias including atrial fibrillation (4.7% of cases), sinus node dysfunction (1.3% of cases), and atrioventricular nodal dysfunction (including heart block in 2.9% of cases) [130]. The frequency of life-threatening ventricular arrhythmias, including VF or sustained ventricular tachycardia (VT), was 3.4% (28 of 816 cases). Analysis of data from 16,450 patients with TCM in the Nationwide Inpatient Sample database established an overall arrhythmic burden of 26% [131]. A QTc interval of greater than 500 milliseconds should alert physicians to arrhythmic risk, and has been demonstrated to have sensitivity of 82% and specificity of 85% for the risk of TdP [132, 133]. Indications for ICD are controversial and should be based on clinical judgment in the absence of class I indications, such as SCD. Life vest has also emerged as an attractive option [134].

Fabry's Disease

Anderson-Fabry disease (FD) is a multisystem disorder caused by the deficiency of α-galactosidase A, which leads to abnormal lysosomal accumulation of glycolipids. Life expectancy is decreased by 20 years in men and 10 to 15 years in women, and the principal cause of death is renal failure followed by cardiac and cerebrovascular causes [135]. Left ventricular hypertrophy is the most common cardiac manifestation related to abnormal lysosomal storage and is implicated arrythmogenesis [136]. Smaller holter studies in patients with FD showed 3.9% had persistent atrial fibrillation, 13.3% had paroxysmal atrial fibrillation, and 8.3% had nonsustained ventricular tachycardia [137].

A review of the 1448 untreated patients with FD showed a 13% incidence of ventricular arrhythmias in men and 20% in women, highlighting the significant arrhythmic risk in women [138]. The major mechanism of sustained VT in FD appears to be reentry related to myocardial fibrosis. Although diffuse myocardial hypertrophy is the characteristic finding in FD, localized thinning and fibrosis, typically of the basal posterior or lateral wall, has been described [139]. There are no international guidelines for device therapy specific to FD. The European Society of Cardiology Guidelines for Hypertrophic Cardiomyopathy include FD, with the explicitly stated caveat that there are no randomized trials or validated prediction models to guide ICD implantation [21].

Arrhythmogenic Right Ventricular Dysplasia

VT management in Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) has remained a significant challenge since initial description in 1728. It is the current paradigm that ARVC results from gene mutations that encode desmosomal proteins, the organelle responsible for cell-cell adhesion. Desmosomal dysfunction results in inadequate cell adhesion and subsequent myocyte detachment and apoptosis [140]. ARVC is a leading cause of sudden cardiac death (SCD) in young people, accounting for up to 10% of deaths from undiagnosed cardiac disease in patients less than 65 years old. The three most common locations of the disease are: the anterior infundibulum, RV apex and subtricuspid infero-basal aspect of the RV, comprising the so-called "triangle of dysplasia", considered a hallmark of ARVC [141]. ARVC leads to RV dilatation or aneurysms (Fig. 20.10). With disease progression, further involvement of the RV free wall, and left ventricular (LV) involvement and atrium can occur.

Clinical presentation is characterized by arrhythmias of right ventricular origin ranging from premature beats to sustained VT or VF resulting in sudden death [142].

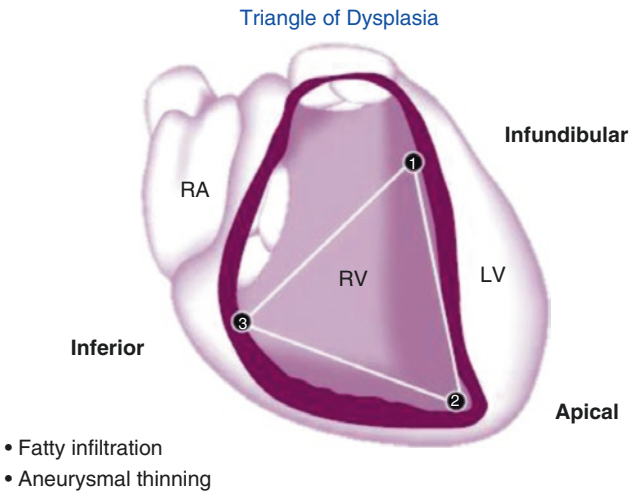


Fig. 20.10 Triangle of dysplasia

The natural history of ARVC, in its classic form, has been classified into four distinct phases with progressive development of symptoms and structural abnormalities [1]. Concealed phase: a subclinical asymptomatic phase with mild or absence of identifiable structural RV abnormalities, however sudden death is still possible [2] overt electrical disorder: with palpitations, syncope and typically with symptomatic ventricular arrhythmias of RV origin usually triggered by exertion [3]. RV failure: progressive loss of RV myocardium due to fibrofatty replacement impairs RV function and may result in pump failure; and [4] biventricular failure: an advanced stage with involvement of the interventricular septum and LV causing congestive heart failure (HF). Endocavitary mural thrombosis may occur, especially within RV aneurysm or in the atria if atrial fibrillation is present.

The revised diagnostic criteria for ARVC are noted in Fig. 20.11.

Assessment of substrate: Advances in 3D electroanatomic mapping (EAM) enabled a more thorough understanding of the complex electrophysiologic substrate in patients with ARVD and VT. Abnormal RV endocardial regions can be localized with EAM by identifying regions of low bipolar RV endocardial voltage (< 1.5 mV) and long duration, low-amplitude, fractionated potentials. These areas have been correlated to relevant histopathologic findings (myocyte loss with fibrofatty replacement) and critical VT circuits confirming the involvement of these areas in the arrhythmogenesis. LV abnormalities have been documented with EAM and typically involve the basal perivalvular region, which is characteristic of other non-infarct related cardiomyopathies. Consideration of endocardial LV involvement is of particular importance if right bundle branch block VTs with positive R waves in the precordial leads are seen as this suggests an LV VT exit site of interest.

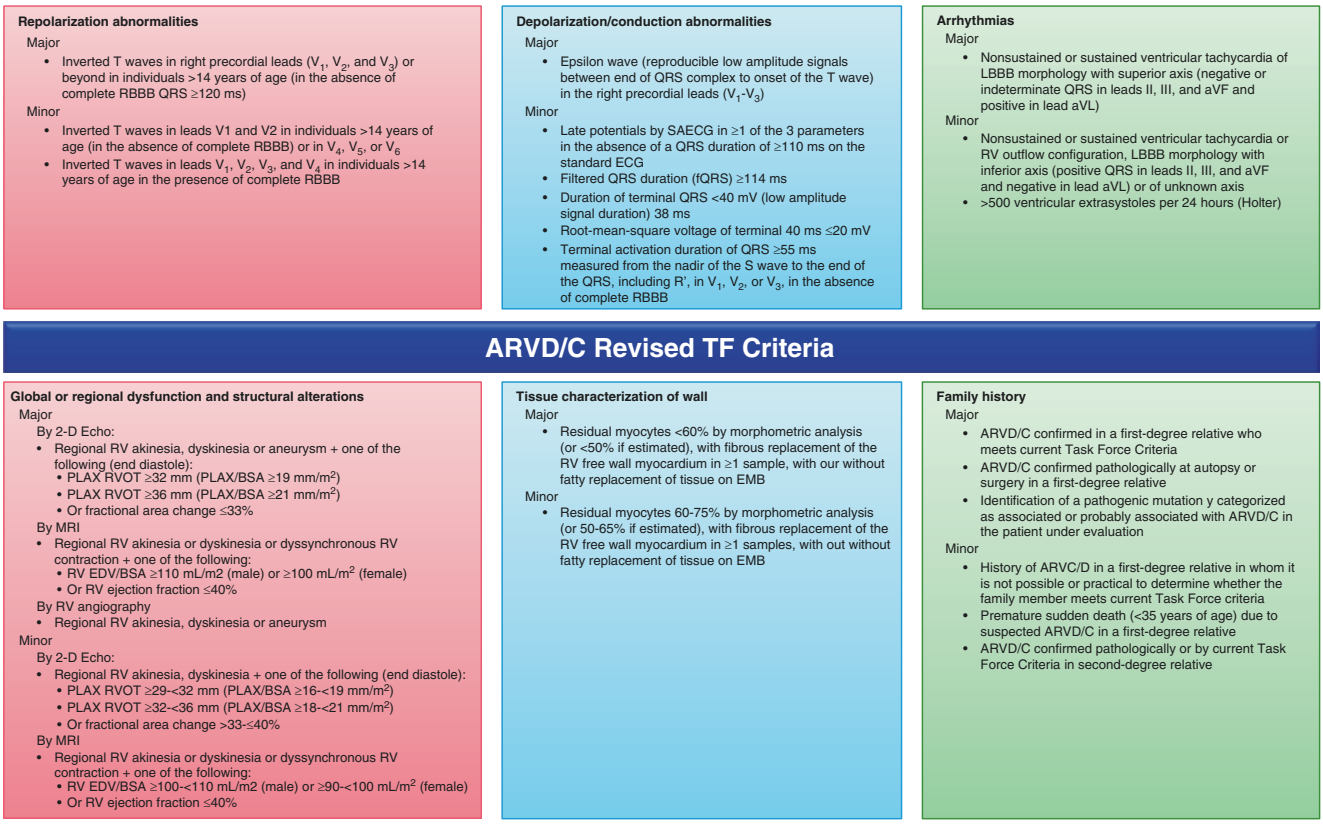


Fig. 20.11 ARVC revised taskforce criteria

The endocardial ablation approach provides modest long-term arrhythmia freedom. The epicardial to endocardial scarring process associated with ARVD often results in a more extensive abnormal epicardial substrate that may not be amendable to endocardial ablation alone. Insights from percutaneous epicardial mapping and ablation procedures in patients with ARVD and VT have demonstrated the important role of the epicardium. Abnormal epicardial low-voltage areas are typically much larger than the corresponding endocardial region [143–145]. Assessment of the epicardial voltage map should be performed with voltage threshold set to 1.5 mV to identify abnormalities consistent with scar as opposed to epicardial fat. In addition, the dense mid-myocardial/sub epicardial fibrosis can create an effective barrier for endocardial to epicardial spread of activation. The resultant delayed epicardium to endocardium activation of the substrate predisposes to isolated VT circuit entirely constrained to the epicardium and requiring epicardial access and direct ablation for elimination. For these reasons, the operator should always anticipate a high likelihood of needing epicardial access for mapping and ablation to achieve a successful outcome [143]. Although identification of abnormal epicardial substrate is best achieved through a percutaneous pericardial puncture, analysis of unipolar endocardial voltage maps with the associated larger field-of-view, may suggest degree of epicardial abnormality present. Unipolar voltage abnormalities (< 5.5 mv) identified during RV endocardial mapping that far exceed the bipolar endocardial substrate is highly suggestive of a more extensive epicardial > endocardial substrate Additional clues to the requirement for epicardial mapping and ablation include surface ECG, presence of isolated epicardial scar on magnetic resonance or intracardiac echo imaging, and/or prior failed endocardial ablation.

Risk Stratification

Poor outcome of ARVD patients were driven by referral bias [146] Data from autopsy series and observational clinical studies on ARVD have provided clinical predictors of adverse events and death. Apart from sustained VT or VF, other independent risk factors include nonsustained VT on 24-h Holter monitoring, dilation/dysfunction of RV, left ventricle (LV), or both, male gender; compound and digenic heterozygosity of desmosomal-gene mutations; young age at

the time of diagnosis; proband status; inducibility at programmed ventricular stimulation; scar burden, extent of T-wave inversion across precordial and inferior leads; low QRS amplitude and QRS fragmentation [146].

The role of EP study for inducibility of sustained VT or VF for prediction of long-term arrhythmic outcome in ARVC/D patients is nebulous [147].

The aim of antiarrhythmic drug (AAD) therapy in patients with ARVC/D is to improve the quality of life by preventing symptomatic ventricular arrhythmias. There are no prospective and randomized trials on AAD therapy in ARVC/D and systematic comparison of treatment strategies. At best currently they are used as an adjunct along with ablation therapy and ICD.

ICD therapy is the most important therapeutic strategy for patients with ARVD, because the natural history is primarily characterized by the risk of SCD. Prospective randomized trials are unlikely to be performed for ethical reasons and because of practical limitations predominantly linked to relatively low disease prevalence and low event rate. Implantation of an ICD is recommended in ARVD patients who have experienced ≥1 episodes of hemodynamically unstable, sustained VT or VF and in patients with severe systolic dysfunction of the RV, LV, or both, irrespective of arrhythmias (class I). Other considerations include ICD in patients who have experienced ≥1 episodes of haemodynamically stable, sustained VT, patients who have 'major' risk factors such as unexplained syncope, moderate ventricular dysfunction, or NSVT (class IIa). Prophylactic ICD implantation is not recommended in asymptomatic ARVD patients with no risk factors or healthy gene carriers (class III) (Fig. 20.12).

Catheter ablation is an important therapeutic option for ARVC/D patients who have VT It is recommended in ARVC/D patients with incessant VT or frequent appropriate ICD interventions on VT despite maximal pharmacological therapy, including amiodarone (class I). An epicardial approach to VT ablation is recommended in patients who fail one or more attempts of endocardial VT ablation (class I). A combined endocardial/epicardial VT ablation approach as an initial ablation strategy should be considered, provided that the operator and electrophysiological laboratory are experienced performing epicardial VT ablation in patients with ARVC/D (class IIa).

Reviewing the literature, the outcome of ablation in ARVDC has been studied with heterogeneous results, which were mostly explained by limited case numbers, the different ablation strategies, distinct disease stages, and variable follow-up duration. Generally, in the era of endocardial ablation, the long-term efficacy in prevention of VT recurrence could be achieved in only 25–53% of cases. Recent studies demonstrated a significant benefit of freedom from ventricular tachyarrhythmias or ICD therapy by 45–84.6% with the combination of endocardial and epicardial ablation. Current therapeutic and preventive measures are at best palliative, not curative.

PVC Mediated Cardiomyopathy

The significance of premature ventricular contractions (PVCs) has been a controversial and conflicting topic for the last 50 years. However, there has been a resurgent interest in frequent PVCs led by the novel concept that they may be a potential cause of, or at least contribute to, cardiomyopathy. Although rare in the general population, frequent PVCs are more common among patients with left ventricular (LV) dysfunction and CHF. This growing interest in PVCs was instigated by Duffee and colleagues, who described significant improvement in cardiac function among five patients with frequent PVCs (>20,000/24 h) and LV dysfunction, who had suppression of PVCs with amiodarone. This suggested, for

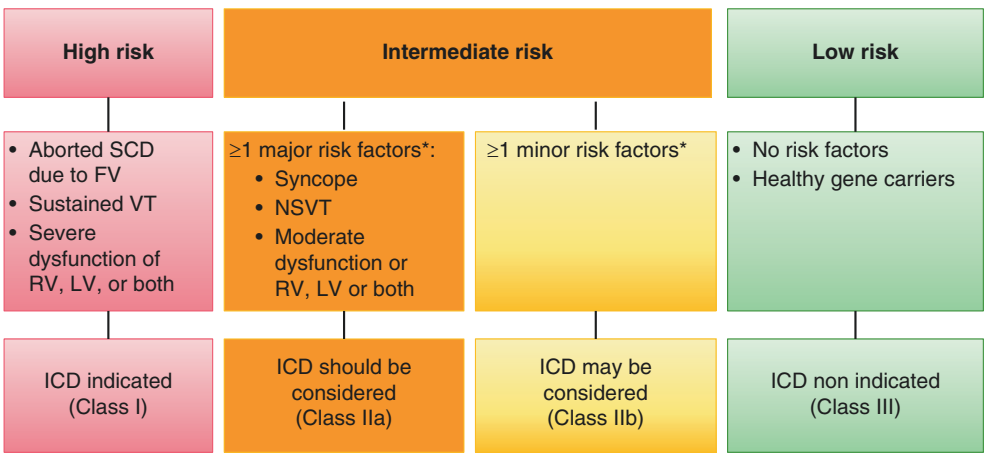


Fig. 20.12 Flow chart for ICD implantation

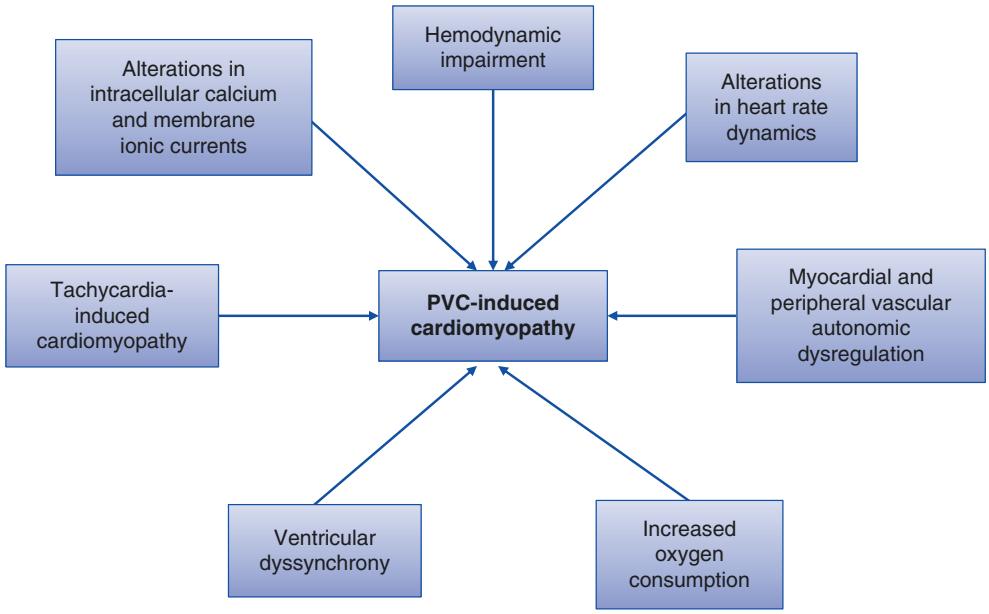


Fig. 20.13 Putative mechanisms of premature ventricular contraction (PVC)-induced cardiomyopathy. (Yong-Mei Cha et al.: Circ Arrhythm Electrophysiol 5:229, 2012)

the first time, that frequent PVCs might result in reversible LV dysfunction termed 'PVC-induced cardiomyopathy' [148]. PVC-induced cardiomyopathy was originally thought to be a type of tachycardia-induced cardiomyopathy, a phenomenon that has been well described in the context of atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia. However, this concept has been called into question because patients with frequent PVCs have overall heart rates similar to those of their normal counterparts on Holter monitoring. The cellular mechanisms of PVC-induced cardiomyopathy have as yet not been elucidated. Bogun postulated that ventricular dyssynchrony and increased oxygen consumption may be possible pathogenic mechanism. Ventricular dyssynchrony results in compromised global cardiac mechanical efficiency, asymmetrically increased wall thickness in the late-activated regions, altered myocardial blood flow, and local changes in myocardial protein expression [149] (Fig. 20.13).

Approximately two thirds of idiopathic PVCs originate from the ventricular outflow tracts, primarily the right ventricular outflow tract. The ventricular outflow tract musculature, and hence the anatomic source of the PVCs, may extend above the pulmonary or aortic valves. The remaining third of PVCs may have various ventricular origins, including the ventricular free walls, LV fascicles, septum, and papillary muscles. Several studies have shown that the frequency of PVCs correlates at least modestly with the extent of LV dysfunction and ventricular dilation at the time of initial clinical presentation. Patients with decreased LVEF had a higher mean PVC burden than their counterparts with normal LV function However, there are no clear-cut points that mark the frequency at which cardiomyopathy is unavoidable. Baman suggested that a PVC burden of >24% had a sensitivity and specificity of 79% and 78%, respectively, in separating the patient populations with impaired versus preserved LV function [150]. Nevertheless, the majority of patients presenting with frequent PVCs had preserved LVEF. Therefore, although significant, the PVC burden is not the only factor contributing to impairment of LV systolic function. The workup, treatment, and follow-up of patients with frequent PVCs are summarized in (Fig. 20.14). Catheter ablation is pursued with the intention of cure . However use of catheter ablation has brought to light some unique anatomical, imaging, ablation and mechanistic insights. A number of randomized trials are currently in the design or recruitment phase and aim to establish whether therapy for frequent PVCs in patients with idiopathic LV dysfunction will alter clinical outcomes. NCT01757067 [Early Elimination of Premature Ventricular Contractions in Heart Failure (EVAC-HF)] is a prospective, randomized study that will compare the effects on LVEF in patients with nonischemic cardiomyopathy with LVEF <= 45% and >20% PVCs following ablation or optimal medical therapy. These will undoubtedly help inform the optimal care for patients with frequent PVCs.

Management of constellation of non ischemic cardiomyopathies is complex. Complexity is increased by variable substrates, thus "all size fits all" approach is not likely to be successful. The overall improvement in survival is encouraging with ICD therapy and improvement in arrhythmia burden by ablation. However still key fundamentals gaps in knowledge exits in understanding of the substrate and methods to modify it to achieve more long lasting success. With improvement in imaging and mapping along with improvement in energy delivery will probably help to overcome some of these impediments.

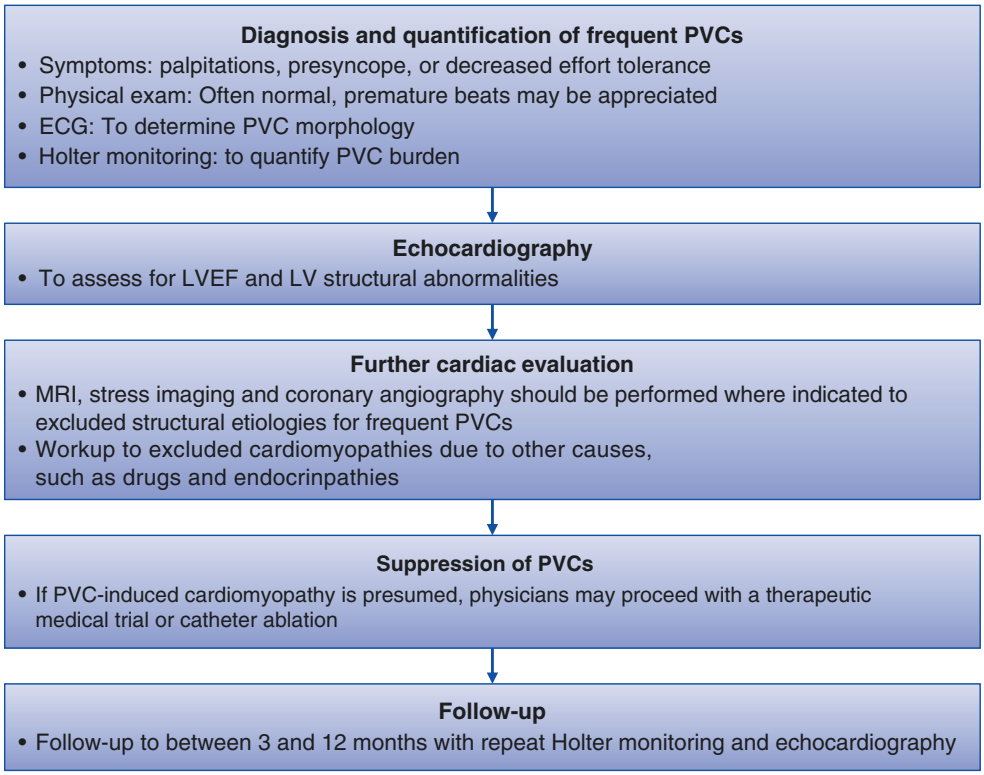


Fig. 20.14 Flow chart for the diagnosis, treatment and follow-up of patients presenting frequent premature ventricular contractions (PVCs). Electrocardiography indicates electrocardiography. *LV* left ventricular, *LVEF* left ventricular ejection fraction, *PVC* premature ventricular contraction. (Yong-Mei Cha et al.: Circ Arrhythm Electrophysiol 5:229, 2012)

References

1. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, et al. Trends in heart failure incidence and survival in a community-based population. JAMA. 2004;292(3):344–50.
2. Kawara T, Derksen R, de Groot JR, Coronel R, Tasseron S, Linnenbank AC, et al. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. Circulation. 2001;104(25):3069–75.
3. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. J Am Coll Cardiol. 2006;48(10):1977–85.
4. Anderson KP, Walker R, Urie P, Ershler PR. Lux RL, Karwandee SV. Myocardial electrical propagation in patients with idiopathic dilated cardiomyopathy. J Clin Invest. 1993;92(1):122–40.
5. Hsia HH, Callans DJ, Marchlinski FE. Characterization of endocardial electrophysiological substrate in patients with nonischemic cardiomyopathy and monomorphic ventricular tachycardia. Circulation. 2003;108(6):704–10.
6. Soejima K, Stevenson WG, Sapp JL, Selwyn AP, Couper G, Epstein LM. Endocardial and epicardial radiofrequency ablation of ventricular tachycardia associated with dilated cardiomyopathy: the importance of low-voltage scars. J Am Coll Cardiol. 2004;43(10):1834–42.
7. Haqqani HM, Tschabrunn CM, Tzou WS, Dixit S, Cooper JM, Riley MP, et al. Isolated septal substrate for ventricular tachycardia in nonischemic dilated cardiomyopathy: incidence, characterization, and implications. Heart Rhythm. 2011;8(8):1169–76.
8. Cano O, Hutchinson M, Lin D, Garcia F, Zado E, Bala R, et al. Electroanatomic substrate and ablation outcome for suspected epicardial ventricular tachycardia in left ventricular nonischemic cardiomyopathy. J Am Coll Cardiol. 2009;54(9):799–808.
9. Tzou WS, Zado ES, Lin D, Callans DJ, Dixit S, Cooper JM, et al. Sinus rhythm ECG criteria associated with basal-lateral ventricular tachycardia substrate in patients with nonischemic cardiomyopathy. J Cardiovasc Electrophysiol. 2011;22(12):1351–8.
10. Valles E, Bazan V, Marchlinski FEECG. criteria to identify epicardial ventricular tachycardia in nonischemic cardiomyopathy. Circ Arrhythm Electrophysiol. 2010;3(1):63–71.
11. Hutchinson MD, Gerstenfeld EP, Desjardins B, Bala R, Riley MP, Garcia FC, et al. Endocardial unipolar voltage mapping to detect epicardial ventricular tachycardia substrate in patients with nonischemic left ventricular cardiomyopathy. Circ Arrhythm Electrophysiol. 2011;4(1):49–55.
12. Wissner E, Stevenson WG, Kuck KH. Catheter ablation of ventricular tachycardia in ischaemic and non-ischaemic cardiomyopathy: where are we today? A clinical review. Eur Heart J. 2012;33(12):1440–50.
13. Kottkamp H, Hindricks G, Chen X, Brunn J, Willems S, Haverkamp W, et al. Radiofrequency catheter ablation of sustained ventricular tachycardia in idiopathic dilated cardiomyopathy. Circulation. 1995;92(5):1159–68.
14. Dinov B, Fiedler L, Schonbauer R, Bollmann A, Rolf S, Piorkowski C, et al. Outcomes in catheter ablation of ventricular tachycardia in dilated nonischemic cardiomyopathy compared with ischemic cardiomyopathy: results from the Prospective Heart Centre of Leipzig VT (HELP-VT) Study. Circulation. 2014;129(7):728–36.
15. Dinov B, Arya A, Schratter A, Schirripa V, Fiedler L, Sommer P, et al. Catheter ablation of ventricular tachycardia and mortality in patients with nonischemic dilated cardiomyopathy: can noninducibility after ablation be a predictor for reduced mortality? Circ Arrhythm Electrophysiol. 2015;8(3):598–605.

16. Tokuda M, Tedrow UB, Kojodjojo P, Inada K, Koplan BA, Michaud GF, et al. Catheter ablation of ventricular tachycardia in nonischemic heart disease. Circ Arrhythm Electrophysiol. 2012;5(5):992–1000.
17. Kumar S, Stevenson WG, John RM. Arrhythmias in dilated cardiomyopathy. Card Electrophysiol Clin. 2015;7(2):221–33.
18. Natale A, Raviele A, Al-Ahmad A, Alfieri O, Aliot E, Almendral J, et al. Venice Chart International Consensus document on ventricular tachycardia/ventricular fibrillation ablation. J Cardiovasc Electrophysiol. 2010;21(3):339–79.
19. Cevik C, Nugent K, Perez-Verdia A, Fish RD. Prophylactic implantation of cardioverter defibrillators in idiopathic nonischemic cardiomyopathy for the primary prevention of death: a narrative review. Clin Cardiol. 2010;33(5):254–60.
20. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2013;127(3):e283–352.
21. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733–79.
22. Varnava AM, Elliott PM, Baboonian C, Davison F, Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: histopathological features of sudden death in cardiac troponin T disease. Circulation. 2001;104(12):1380–4.
23. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J. 2014;35(30):2010–20.
24. Anastasakis A, Theopistou A, Rigopoulos A, Kotsiopoulou C, Georgopoulos S, Fragakis K, et al. Sudden cardiac death: investigation of the classical risk factors in a community-based hypertrophic cardiomyopathy cohort. Hell J Cardiol. 2013;54(4):281–8.
25. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36(7):2212–8.
26. Bos JM, Maron BJ, Ackerman MJ, Haas TS, Sorajja P, Nishimura RA, et al. Role of family history of sudden death in risk stratification and prevention of sudden death with implantable defibrillators in hypertrophic cardiomyopathy. Am J Cardiol. 2010;106(10):1481–6.
27. Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, et al. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119(13):1703–10.
28. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med. 2000;342(24):1778–85.
29. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet. 2001;357(9254):420–4.
30. Puntmann VO, Yap YG, McKenna W, Camm AJ. Significance of maximal and regional left ventricular wall thickness in association with arrhythmic events in patients with hypertrophic cardiomyopathy. Circ J. 2010;74(3):531–7.
31. Spirito P, Rapezzi C, Autore C, Bruzzi P, Bellone P, Ortolani P, et al. Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia. Circulation. 1994;90(6):2743–7.
32. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol. 2003;42(5):873–9.
33. Cecchi F, Olivotto I, Montereggi A, Squillatini G, Dolara A, Maron BJ. Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy: assessment in an unselected non-referral based patient population. Heart. 1998;79(4):331–6.
34. Giorgberidze I, Saksena S, Krol RB, Munsif AN, Kolettis T, Mathew P, et al. Risk stratification and clinical outcome of minimally symptomatic and asymptomatic patients with nonsustained ventricular tachycardia and coronary disease: a prospective single-center study. Am J Cardiol. 1997;80(5B):3F–9F.
35. Fananapazir L, Chang AC, Epstein SE, McAreavey D. Prognostic determinants in hypertrophic cardiomyopathy. Prospective evaluation of a therapeutic strategy based on clinical, Holter, hemodynamic, and electrophysiological findings. Circulation. 1992;86(3):730–40.
36. Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol. 1981;48(2):252–7.
37. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2012;5(4):370–7.
38. Moon JC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. J Am Coll Cardiol. 2003;41(9):1561–7.
39. Moon JC, Reed E, Sheppard MN, Elkington AG, Ho SY, Burke M, et al. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;43(12):2260–4.
40. Petkow-Dimitrow P, Klimeczek P, Vliegenthart R, Pasowicz M, Miszalski-Jamka T, Oudkerk M, et al. Late gadolinium enhancement in cardiovascular magnetic resonance in patients with hypertrophic cardiomyopathy complicated by life-threatening ventricular tachyarrhythmia. Kardiol Pol. 2009;67(8A):964–9.
41. Kwon DH, Smedira NG, Rodriguez ER, Tan C, Setser R, Thamilarasan M, et al. Cardiac magnetic resonance detection of myocardial scarring in hypertrophic cardiomyopathy: correlation with histopathology and prevalence of ventricular tachycardia. J Am Coll Cardiol. 2009;54(3):242–9.
42. Suk T, Edwards C, Hart H, Christiansen JP. Myocardial scar detected by contrast-enhanced cardiac magnetic resonance imaging is associated with ventricular tachycardia in hypertrophic cardiomyopathy patients. Heart Lung Circ. 2008;17(5):370–4.
43. Kwon DH, Setser RM, Popovic ZB, Thamilarasan M, Sola S, Schoenhagen P, et al. Association of myocardial fibrosis, electrocardiography and ventricular tachyarrhythmia in hypertrophic cardiomyopathy: a delayed contrast enhanced MRI study. Int J Cardiovasc Imaging. 2008;24(6):617–25.
44. Dimitrow PP, Klimeczek P, Vliegenthart R, Pasowicz M, Oudkerk M, Podolec P, et al. Late hyperenhancement in gadolinium-enhanced magnetic resonance imaging: comparison of hypertrophic cardiomyopathy patients with and without nonsustained ventricular tachycardia. Int J Cardiovasc Imaging. 2008;24(1):77–83. discussion 5-7
45. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation. 2014;130(6):484–95.
46. Appelbaum E, Maron BJ, Adabag S, Hauser TH, Lesser JR, Haas TS, et al. Intermediate-signal-intensity late gadolinium

enhancement predicts ventricular tachyarrhythmias in patients with hypertrophic cardiomyopathy. Circ Cardiovasc Imaging. 2012;5(1):78–85.
47. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51(14):1369–74.
48. Rubinshtein R, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajja P, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3(1):51–8.
49. Femenia F, Arce M, Van Grieken J, Trucco E, Mont L, Abello M, et al. Fragmented QRS as a predictor of arrhythmic events in patients with hypertrophic obstructive cardiomyopathy. J Interv Card Electrophysiol. 2013;38(3):159–65.
50. Maron BJ, Estes NA III, Maron MS, Almquist AK, Link MS, Udelson JE. Primary prevention of sudden death as a novel treatment strategy in hypertrophic cardiomyopathy. Circulation. 2003;107(23):2872–5.
51. Spoladore R, Maron MS, D'Amato R, Camici PG, Olivotto I. Pharmacological treatment options for hypertrophic cardiomyopathy: high time for evidence. Eur Heart J. 2012;33(14):1724–33.
52. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58(25):e212–60.
53. Maron BJ, Casey SA, Chan RH, Garberich RF, Rowin EJ, Maron MS. Independent assessment of the European society of cardiology sudden death risk model for hypertrophic cardiomyopathy. Am J Cardiol. 2015;116(5):757–64.
54. Begley DA, Mohiddin SA, Tripodi D, Winkler JB, Fananapazir L. Efficacy of implantable cardioverter defibrillator therapy for primary and secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Pacing Clin Electrophysiol. 2003;26(9):1887–96.
55. Maron BJ, Spirito P, Ackerman MJ, Casey SA, Semsarian C, Estes NA III, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;61(14):1527–35.
56. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298(4):405–12.
57. You JJ, Woo A, Ko DT, Cameron DA, Mihailovic A, Krahn M. Life expectancy gains and cost-effectiveness of implantable cardioverter/defibrillators for the primary prevention of sudden cardiac death in patients with hypertrophic cardiomyopathy. Am Heart J. 2007;154(5):899–907.
58. Lin G, Nishimura RA, Gersh BJ, Phil D, Ommen SR, Ackerman MJ, et al. Device complications and inappropriate implantable cardioverter defibrillator shocks in patients with hypertrophic cardiomyopathy. Heart. 2009;95(9):709–14.
59. Francia P, Adduci C, Palano F, Semprini L, Serdoz A, Montesanti D, et al. Eligibility for the subcutaneous implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2015;26(8):893–9.
60. Casella M, Dello Russo A, Pelargonio G, Tondo C. Sustained right ventricular tachycardia originating close to defibrillator lead tip in hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2007;18(9):994–7.
61. Okumura Y, Watanabe I, Ohkubo K, Saito S. Successful catheter ablation for incessant ventricular tachycardia in a patient with hypertrophic cardiomyopathy. Circ J. 2007;71(7):1164–8.
62. Rodriguez LM, Smeets JL, Timmermans C, Blommaert D, van Dantzig JM, de Muinck EB, et al. Radiofrequency catheter ablation of sustained monomorphic ventricular tachycardia in hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 1997;8(7):803–6.
63. Lim KK, Maron BJ, Knight BP. Successful catheter ablation of hemodynamically unstable monomorphic ventricular tachycardia in a patient with hypertrophic cardiomyopathy and apical aneurysm. J Cardiovasc Electrophysiol. 2009;20(4):445–7.
64. Inada K, Seiler J, Roberts-Thomson KC, Steven D, Rosman J, John RM, et al. Substrate characterization and catheter ablation for monomorphic ventricular tachycardia in patients with apical hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2011;22(1):41–8.
65. Bordignon S, Chun KR, Schmidt B. Epicardial ablation of monomorphic ventricular tachycardia storm in hypertrophic cardiomyopathy. Europace. 2013;15(3):346.
66. Santangeli P, Di Biase L, Lakkireddy D, Burkhardt JD, Pillarisetti J, Michowitz Y, et al. Radiofrequency catheter ablation of ventricular arrhythmias in patients with hypertrophic cardiomyopathy: safety and feasibility. Heart Rhythm. 2010;7(8):1036–42.
67. Lynch JP III, Hwang J, Bradfield J, Fishbein M, Shivkumar K, Tung R. Cardiac involvement in sarcoidosis: evolving concepts in diagnosis and treatment. Semin Respir Crit Care Med. 2014;35(3):372–90.
68. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation. 1978;58(6):1204–11.
69. Deshmukh A, Sewani A, Sachdeva R. Cardiac sarcoidosis masquerading as syncope with right ventricular septal mass. J Invasive Cardiol. 2012;24(8):418–9.
70. Tavora F, Cresswell N, Li L, Ripple M, Solomon C, Burke A. Comparison of necropsy findings in patients with sarcoidosis dying suddenly from cardiac sarcoidosis versus dying suddenly from other causes. Am J Cardiol. 2009;104(4):571–7.
71. Liang JJ, Hebl VB, DeSimone CV, Madhavan M, Nanda S, Kapa S, et al. Electrogram guidance: a method to increase the precision and diagnostic yield of endomyocardial biopsy for suspected cardiac sarcoidosis and myocarditis. JACC Heart Fail. 2014;2(5):466–73.
72. Aggarwal NR, Snipelisky D, Young PM, Gersh BJ, Cooper LT, Chareonthaitawee P. Advances in imaging for diagnosis and management of cardiac sarcoidosis. Eur Heart J Cardiovasc Imaging. 2015;16(9):949–58.
73. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014;11(7):1305–23.
74. Rosen Y. Pathology of sarcoidosis. Semin Respir Crit Care Med. 2007;28(1):36–52.
75. Roberts WC, McAllister HA Jr, Ferrans VJ. Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy patients (group 11). Am J Med. 1977;63(1):86–108.
76. Sadek MM, Yung D, Birnie DH, Beanlands RS, Nery PB. Corticosteroid therapy for cardiac sarcoidosis: a systematic review. Can J Cardiol. 2013;29(9):1034–41.
77. Jefic D, Joel B, Good E, Morady F, Rosman H, Knight B, et al. Role of radiofrequency catheter ablation of ventricular tachycar-

dia in cardiac sarcoidosis: report from a multicenter registry. Heart Rhythm. 2009;6(2):189–95.
78. Kron J, Sauer W, Schuller J, Bogun F, Crawford T, Sarsam S, et al. Efficacy and safety of implantable cardiac defibrillators for treatment of ventricular arrhythmias in patients with cardiac sarcoidosis. Europace. 2013;15(3):347–54.
79. Thachil A, Christopher J, Sastry BK, Reddy KN, Tourani VK, Hassan A, et al. Monomorphic ventricular tachycardia and mediastinal adenopathy due to granulomatous infiltration in patients with preserved ventricular function. J Am Coll Cardiol. 2011;58(1):48–55.
80. Kumar S, Barbhaiya C, Nagashima K, Choi EK, Epstein LM, John RM, et al. Ventricular tachycardia in cardiac sarcoidosis: characterization of ventricular substrate and outcomes of catheter ablation. Circ Arrhythm Electrophysiol. 2015;8(1):87–93.
81. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MO. Diagnosis and management of Chagas disease and cardiomyopathy. Nat Rev Cardiol. 2012;9(10):576–89.
82. Bern C, Montgomery SP. An estimate of the burden of Chagas disease in the United States. Clin Infect Dis. 2009;49(5):e52–4.
83. Munoz-Saravia SG, Haberland A, Wallukat G, Schimke I. Chronic Chagas' heart disease: a disease on its way to becoming a worldwide health problem: epidemiology, etiopathology, treatment, pathogenesis and laboratory medicine. Heart Fail Rev. 2012;17(1):45–64.
84. Healy C, Viles-Gonzalez JF, Saenz LC, Soto M, Ramirez JD, d'Avila A. Arrhythmias in chagasic cardiomyopathy. Card Electrophysiol Clin. 2015;7(2):251–68.
85. Barbosa MP, Carmo AA, Rocha MO, Ribeiro AL. Ventricular arrhythmias in Chagas disease. Rev Soc Bras Med Trop. 2015;48(1):4–10.
86. Bestetti RB, Cardinalli-Neto A. Sudden cardiac death in Chagas' heart disease in the contemporary era. Int J Cardiol. 2008;131(1):9–17.
87. Bestetti RB, Cardinalli-Neto A. Device therapy in Chagas disease heart failure. Expert Rev Cardiovasc Ther. 2012;10(10):1307–17.
88. Biolo A, Ribeiro AL, Clausell N. Chagas cardiomyopathy—where do we stand after a hundred years? Prog Cardiovasc Dis. 2010;52(4):300–16.
89. Nunes MC, Dones W, Morillo CA, Encina JJ, Ribeiro AL. Chagas disease: an overview of clinical and epidemiological aspects. J Am Coll Cardiol. 2013;62(9):767–76.
90. Rassi A Jr, Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, et al. Development and validation of a risk score for predicting death in Chagas' heart disease. N Engl J Med. 2006;355(8):799–808.
91. Scanavacca MI, Sosa EA, Lee JH, Bellotti G, Pileggi F. Empiric therapy with amiodarone in patients with chronic Chagas cardiomyopathy and sustained ventricular tachycardia. Arq Bras Cardiol. 1990;54(6):367–71.
92. Marin-Neto JA, Rassi A Jr, Avezum A Jr, Mattos AC, Rassi A, Morillo CA, et al. The BENEFIT trial: testing the hypothesis that trypanocidal therapy is beneficial for patients with chronic Chagas heart disease. Mem Inst Oswaldo Cruz. 2009;104(Suppl 1):319–24.
93. Morillo CA, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi A Jr, Rosas F, et al. Randomized trial of benznidazole for chronic chagas' cardiomyopathy. N Engl J Med. 2015;373(14):1295–306.
94. Barbosa MP, da Costa Rocha MO, de Oliveira AB, Lombardi F, Ribeiro AL. Efficacy and safety of implantable cardioverter-defibrillators in patients with Chagas disease. Europace. 2013;15(7):957–62.
95. di Toro D, Muratore C, Aguinaga L, Batista L, Malan A, Greco O, et al. Predictors of all-cause 1-year mortality in implantable cardioverter defibrillator patients with chronic Chagas' cardiomyopathy. Pacing Clin Electrophysiol. 2011;34(9):1063–9.
96. Dubner S, Valero E, Pesce R, Zuelgaray JG, Mateos JC, Filho SG, et al. A Latin American registry of implantable cardioverter defibrillators: the ICD-LABOR study. Ann Noninvasive Electrocardiol. 2005;10(4):420–8.
97. Muratore CA, Batista Sa LA, Chiale PA, Eloy R, Tentori MC, Escudero J, et al. Implantable cardioverter defibrillators and Chagas' disease: results of the ICD Registry Latin America. Europace. 2009;11(2):164–8.
98. Gali WL, Sarabanda AV, Baggio JM, Ferreira LG, Gomes GG, Marin-Neto JA, et al. Implantable cardioverter-defibrillators for treatment of sustained ventricular arrhythmias in patients with Chagas' heart disease: comparison with a control group treated with amiodarone alone. Europace. 2014;16(5):674–80.
99. d'Avila A, Splinter R, Svenson RH, Scanavacca M, Pruitt E, Kasell J, et al. New perspectives on catheter-based ablation of ventricular tachycardia complicating Chagas' disease: experimental evidence of the efficacy of near infrared lasers for catheter ablation of Chagas' VT. J Interv Card Electrophysiol. 2002;7(1):23–38.
100. Sosa E, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. J Cardiovasc Electrophysiol. 1996;7(6):531–6.
101. Sosa E, Scanavacca M, D'Avila A, Piccioni J, Sanchez O, Velarde JL, et al. Endocardial and epicardial ablation guided by nonsurgical transthoracic epicardial mapping to treat recurrent ventricular tachycardia. J Cardiovasc Electrophysiol. 1998;9(3):229–39.
102. Henz BD, do Nascimento TA, Dietrich Cde O, Dalegrave C, Hernandes V, Mesas CE, et al. Simultaneous epicardial and endocardial substrate mapping and radiofrequency catheter ablation as first-line treatment for ventricular tachycardia and frequent ICD shocks in chronic chagasic cardiomyopathy. J Interv Card Electrophysiol. 2009;26(3):195–205.
103. Iturralde P, Barragan R, Araya V, Romero L, Ramirez S, Colin L, et al. Surgical resection of a focus of ventricular tachycardia guided by endocardial and epicardial mapping. Arch Inst Cardiol Mex. 1992;62(1):69–75.
104. Milei J, Pesce R, Valero E, Muratore C, Beigelman R, Ferrans VJ. Electrophysiologic-structural correlations in chagasic aneurysms causing malignant arrhythmias. Int J Cardiol. 1991;32(1):65–73.
105. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. Lancet. 2015;386(9995):813–25.
106. Hussein A, Karimianpour A, Collier P, Krasuski RA. Isolated Noncompaction of the Left Ventricle in Adults. J Am Coll Cardiol. 2015;66(5):578–85.
107. Lofiego C, Biagini E, Pasquale F, Ferlito M, Rocchi G, Perugini E, et al. Wide spectrum of presentation and variable outcomes of isolated left ventricular non-compaction. Heart. 2007;93(1):65–71.
108. Bhatia NL, Tajik AJ, Wilansky S, Steidley DE, Mookadam F. Isolated noncompaction of the left ventricular myocardium in adults: a systematic overview. J Card Fail. 2011;17(9):771–8.
109. Derval N, Jais P, O'Neill MD, Haissaguerre M. Apparent idiopathic ventricular tachycardia associated with isolated ventricular noncompaction. Heart Rhythm. 2009;6(3):385–8.
110. Celiker A, Ozkutlu S, Dilber E, Karagoz T. Rhythm abnormalities in children with isolated ventricular noncompaction. Pacing Clin Electrophysiol. 2005;28(11):1198–202.
111. Caliskan K, Szili-Torok T, Theuns DA, Kardos A, Geleijnse ML, Balk AH, et al. Indications and outcome of implantable cardioverter-defibrillators for primary and secondary prophylaxis in patients with noncompaction cardiomyopathy. J Cardiovasc Electrophysiol. 2011;22(8):898–904.
112. Kobza R, Steffel J, Erne P, Schoenenberger AW, Hurlimann D, Luscher TF, et al. Implantable cardioverter-defibrillator and cardiac resynchronization therapy in patients with left ventricular noncompaction. Heart Rhythm. 2010;7(11):1545–9.

113. Okubo K, Sato Y, Matsumoto N, Kunimasa T, Kasama S, Sano Y, et al. Cardiac resynchronization and cardioverter defibrillation therapy in a patient with isolated noncompaction of the ventricular myocardium. Int J Cardiol. 2009;136(3):e66–8.
114. Steffel J, Duru F. Rhythm disorders in isolated left ventricular noncompaction. Ann Med. 2012;44(2):101–8.
115. Fiala M, Januska J, Bulkova V, Pleva M. Septal ventricular tachycardia with alternating LBBB-RBBB morphology in isolated ventricular noncompaction. J Cardiovasc Electrophysiol. 2010;21(6):704–7.
116. Coleman MA, Bos JM, Johnson JN, Owen HJ, Deschamps C, Moir C, et al. Videoscopic left cardiac sympathetic denervation for patients with recurrent ventricular fibrillation/malignant ventricular arrhythmia syndromes besides congenital long-QT syndrome. Circ Arrhythm Electrophysiol. 2012;5(4):782–8.
117. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA. 2000;283(9):1183–8.
118. Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States: diagnosis, prognosis, and management. J Am Coll Cardiol. 2011;58(7):659–70.
119. Diao M, Diop IB, Kane A, Camara S, Sarr M, Ba SA, et al. Electrocardiographic recording of long duration (Holter) of 24 hours during idiopathic cardiomyopathy of the peripartum. Arch Mal Coeur Vaiss. 2004;97(1):25–30.
120. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. J Am Heart Assoc. 2014;3(3):e001056.
121. Enriquez AD, Economy KE, Tedrow UB. Contemporary management of arrhythmias during pregnancy. Circ Arrhythm Electrophysiol. 2014;7(5):961–7.
122. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, et al. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC Study (Investigations of Pregnancy-Associated Cardiomyopathy). J Am Coll Cardiol. 2015;66(8):905–14.
123. Tokuda M, Stevenson WG, Nagashima K, Rubin DA. Electrophysiological mapping and radiofrequency catheter ablation for ventricular tachycardia in a patient with peripartum cardiomyopathy. J Cardiovasc Electrophysiol. 2013;24(11):1299–301.
124. Pillarisetti J, Kondur A, Alani A, Reddy M, Vacek J, Weiner CP, et al. Peripartum cardiomyopathy: predictors of recovery and current state of implantable cardioverter-defibrillator use. J Am Coll Cardiol. 2014;63(25 Pt A):2831–9.
125. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147–97.
126. Saltzberg MT, Szymkiewicz S, Bianco NR. Characteristics and outcomes of peripartum versus nonperipartum cardiomyopathy in women using a wearable cardiac defibrillator. J Card Fail. 2012;18(1):21–7.
127. Duncker D, Haghikia A, Konig T, Hohmann S, Gutleben KJ, Westenfeld R, et al. Risk for ventricular fibrillation in peripartum cardiomyopathy with severely reduced left ventricular function-value of the wearable cardioverter/defibrillator. Eur J Heart Fail. 2014;16(12):1331–6.
128. Bennett J, Ferdinande B, Kayaert P, Wiyono S, Goetschalkx K, Dubois C, et al. Time course of electrocardiographic changes in transient left ventricular ballooning syndrome. Int J Cardiol. 2013;169(4):276–80.
129. Wright PT, Tranter MH, Morley-Smith AC, Lyon AR. Pathophysiology of takotsubo syndrome: temporal phases of cardiovascular responses to extreme stress. Circ J. 2014;78(7):1550–8.
130. Syed FF, Asirvatham SJ, Francis J. Arrhythmia occurrence with takotsubo cardiomyopathy: a literature review. Europace. 2011;13(6):780–8.
131. Pant S, Deshmukh A, Mehta K, Badheka AO, Tuliani T, Patel NJ, et al. Burden of arrhythmias in patients with Takotsubo cardiomyopathy (apical ballooning syndrome). Int J Cardiol. 2013;170(1):64–8.
132. Behr ER, Mahida S. Takotsubo cardiomyopathy and the long-QT syndrome: an insult to repolarization reserve. Europace. 2009;11(6):697–700.
133. Yamada Y, Tani T, Homma M, Saito S. Two cases of torsades de pointes associated with Takotsubo cardiomyopathy as the second insult. J Electrocardiol. 2011;44(6):806–9.
134. Available from: http://www.innovationsincrm.com/cardiac-rhythm-management/2014/august/629-wearable-cardioverter-defibrillator-takotsubo-cardiomyopathy.
135. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet. 2001;38(11):769–75.
136. Weidemann F, Sanchez-Nino MD, Politei J, Oliveira JP, Wanner C, Warnock DG, et al. Fibrosis: a key feature of Fabry disease with potential therapeutic implications. Orphanet J Rare Dis. 2013;8:116.
137. Shah JS, Hughes DA, Sachdev B, Tome M, Ward D, Lee P, et al. Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. Am J Cardiol. 2005;96(6):842–6.
138. Patel MR, Cecchi F, Cizmarik M, Kantola I, Linhart A, Nicholls K, et al. Cardiovascular events in patients with fabry disease natural history data from the fabry registry. J Am Coll Cardiol. 2011;57(9):1093–9.
139. Moon JC, Sachdev B, Elkington AG, McKenna WJ, Mehta A, Pennell DJ, et al. Gadolinium enhanced cardiovascular magnetic resonance in Anderson-Fabry disease. Evidence for a disease specific abnormality of the myocardial interstitium. Eur Heart J. 2003;24(23):2151–5.
140. Franz WM, Muller OJ, Katus HA. Cardiomyopathies: from genetics to the prospect of treatment. Lancet. 2001;358(9293):1627–37.
141. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation. 1982;65(2):384–98.
142. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. J Am Coll Cardiol. 1997;30(6):1512–20.
143. Bai R, Di Biase L, Shivkumar K, Mohanty P, Tung R, Santangeli P, et al. Ablation of ventricular arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy: arrhythmia-free survival after endo-epicardial substrate based mapping and ablation. Circ Arrhythm Electrophysiol. 2011;4(4):478–85.
144. Fernandez-Armenta J, Andreu D, Penela D, Trucco E, Cipolletta L, Arbelo E, et al. Sinus rhythm detection of conducting channels and ventricular tachycardia isthmus in arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm. 2014;11(5):747–54.
145. Garcia FC, Bazan V, Zado ES, Ren JF, Marchlinski FE. Epicardial substrate and outcome with epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation. 2009;120(5):366–75.
146. Corrado D, Wichter T, Link MS, Hauer RN, Marchlinski FE, Anastasakis A, et al. Treatment of arrhythmogenic right

ventricular cardiomyopathy/dysplasia: an international task force consensus statement. Circulation. 2015;132(5):441–53.
147. Link MS, Laidlaw D, Polonsky B, Zareba W, McNitt S, Gear K, et al. Ventricular arrhythmias in the North American multidisciplinary study of ARVC: predictors, characteristics, and treatment. J Am Coll Cardiol. 2014;64(2):119–25.
148. Duffee DF, Shen WK, Smith HC. Suppression of frequent premature ventricular contractions and improvement of left ventricular function in patients with presumed idiopathic dilated cardiomyopathy. Mayo Clin Proc. 1998;73(5):430–3.
149. Spragg DD, Kass DA. Pathobiology of left ventricular dyssynchrony and resynchronization. Prog Cardiovasc Dis. 2006;49(1):26–41.
150. Baman TS, Lange DC, Ilg KJ, Gupta SK, Liu TY, Alguire C, et al. Relationship between burden of premature ventricular complexes and left ventricular function. Heart Rhythm. 2010;7(7):865–9.

Arrhythmias in Congenital Heart Disease

21

Edward P. Walsh

Abstract

Patients with congenital heart disease (CHD) must contend with a high arrhythmia burden. In some instances these disorders are intrinsic to the structural malformation itself and begin to cause difficulties early in life, as in the case of Wolff-Parkinson-White syndrome in patients with Ebstein's anomaly, or atrioventricular block in patients with "congenitally corrected" transposition of the great arteries. For most other patients with CHD, arrhythmias represent an acquired condition related to the fibrotic and hypertrophied myocardial substrate created by surgical scarring in conjunction with abnormal pressure/volume loads of long duration, which may not surface until a decade or two after repair. The abnormal anatomy encountered in CHD has a major impact on treatment, especially the technical aspects of interventions such as catheter ablation and placement of pacemakers or implantable cardioverter defibrillators. This chapter will attempt to review the major rhythm difficulties encountered in the CHD population, concentrating on those electrophysiologic features that distinguish this unique group from patients with more conventional forms of heart disease.

Keywords

Atrial tachycardia • Atrial flutter • Atrioventricular block • Catheter ablation • Congenital heart disease • Ebstein's anomaly • Fontan operation • Intraatrial reentrant tachycardia • Sinus node dysfunction • Sudden cardiac death • Tetralogy of Fallot • Transposition of the great arteries • Ventricular tachycardia

Abbreviations

AV	Atrioventricular
AVNRT	Atrioventricular node reentrant tachycardia
CHD	Congenital heart disease
IART	Intraatrial reentrant tachycardia
ICD	Implantable cardioverter defibrillator
L-TGA	Congenitally corrected transposition of the great arteries
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White

E.P. Walsh, M.D.
Cardiac Electrophysiology Division, Department of Cardiology, Boston Children's Hospital, 300 Longwood Ave., Boston, MA 02115, USA

Harvard Medical School, Boston, MA, USA
e-mail: ed.walsh@childrens.harvard.edu

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_21

Introduction

In years past, the management of patients with congenital heart disease (CHD) was viewed principally as a hemodynamic challenge focused on operative solutions to extend life beyond infancy and early childhood. Thanks to a long series of innovations in surgical and interventional catheter techniques, it is rare nowadays to encounter a CHD lesion that cannot be corrected, or at least palliated, to permit patient survival well into adulthood [1]. However, this improved longevity has exposed a number of late complications for the survivors, central among which are cardiac arrhythmias that contribute substantially to morbidity and mortality for this rapidly expanding population [2]. A list of specific arrhythmias and the commonly associated congenital defects is provided in Table 21.1 to serve as an outline for this chapter.

Table 21.1 Specific arrhythmias and associated congenital heart defects

Tachycardias	
Accessory pathways	– Ebstein's anomaly
	– Some congenitally corrected TGA
Twin AV nodes	– Heterotaxy syndrome
Intraatrial reentrant tachycardia	– Postoperative Mustard
	– Postoperative Senning
	– Postoperative Fontan
	– Others
Atrial fibrillation	– Mitral valve disease
	– Aortic stenosis
	– Unrepaired single ventricle
Ventricular tachycardia	– Tetralogy of fallot
	– Congenital aortic stenosis
	– Others
Bradycardias	
Congenital sinus node dysfunction	– Heterotaxy syndrome
Acquired sinus node dysfunction	– Postoperative Mustard
	– Postoperative Senning
	– Postoperative Fontan
	– Postoperative Glenn
	– Others
Congenital AV block	– Atrioventricular canal defects
	– Congenitally corrected TGA
	– ASD (Holt-Oram syndrome)
Acquired AV block	– VSD closure
	– Aortic valve surgery
	– AV valve replacement

ASD atrial septal defect, *AV* atrioventricular, *TGA* transposition of the great arteries, *VSD* ventricular septal defect

Tachycardias in CHD

Accessory Pathways

The embryologic accidents responsible for congenital heart defects can have a direct impact on the specialized atrioventricular (AV) conduction tissues. This may take the form of simple displacement of the compact node and His bundle away from the usual septal position in Koch's triangle [3], but occasionally, the malformation results in accessory or duplicated AV connections with the potential for reentrant tachyarrhythmias. The most important example involves Ebstein's anomaly of the tricuspid valve, which is complicated by Wolff-Parkinson-White (WPW) syndrome in 20% or more of cases [4]. The accessory pathways in this condition are typically located along the posterior and septal aspect of the tricuspid ring where the valve leaflets are most displaced into the body of right ventricle [5]. Tachycardia events for Ebstein's patients become especially problematic during adolescent and adult years when right atrial dilation increases the likelihood of recurrent atrial flutter or atrial fibrillation with potentially rapid anterograde conduction over an accessory pathway. Definitive therapy with catheter ablation is now viewed as the standard of care for Ebstein's patients with WPW syndrome. However, compared to ablation for accessory pathways in a structurally normal heart, the acute success rate appears lower, and the risk of recurrence higher, in Ebstein's anomaly [6, 7]. These difference likely results from distorted anatomic landmarks, difficulty identifying the true AV groove, extremely fractionated electrograms, and the high incidence of multiple pathways (Fig. 21.1).

Atrioventricular Nodal Reentrant Tachycardia, and Twin AV Nodes

Patients with CHD can also have more simple forms of AV reciprocating tachycardia, including conventional AV nodal reentry (AVNRT). The electrophysiology is similar in every way to AVNRT in normal hearts, but anatomic distortion can obscure the usual landmarks of Koch's triangle and make identification of safe and effective sites for slow pathway modification difficult. The experience with ablation for AVNRT in CHD is still somewhat limited, but there are a growing number of case reports and clinical series [8–11] that indicate the procedure can be accomplished safely if proper technical modifications and precautions are employed (Fig. 21.2). Most reported cases in CHD have employed radiofrequency energy, but cryothermal ablation can be used for its safety benefit whenever precise location of the compact node is difficult to ascertain [11, 12].

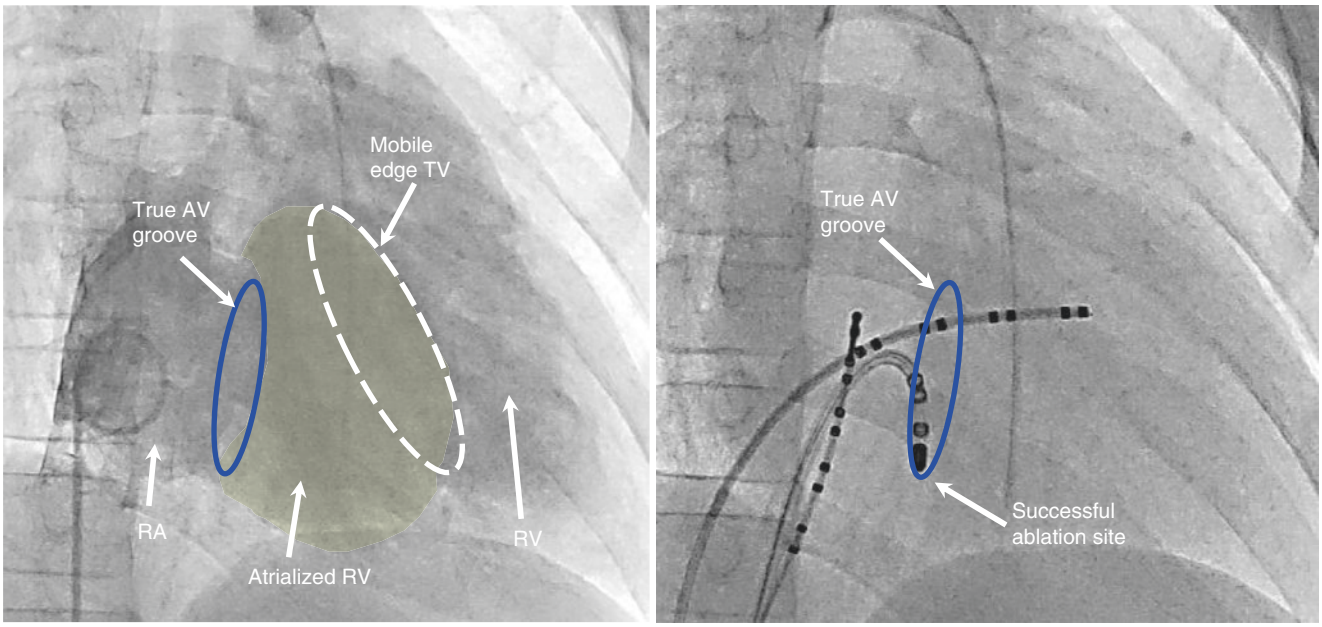


Fig. 21.1 Catheter ablation for an accessory pathway in a patient with Ebstein's anomaly. *Left Panel:* Right atrial angiogram (right anterior oblique projection) with transit of contrast into the right ventricle (RV), highlighting the contours of the right atrium (RA) and the atrialized RV (*yellow shading*), separated by the true atrioventricular (AV) groove. The mobile edge of the tricuspid valve (TV) is displaced into the body of the RV. *Right panel*: Catheter position for successful ablation is at the level of the true AV groove. The AV groove in Ebstein's can be identified using an angiogram such as this, by a right coronary angiogram, or by intracardiac echo

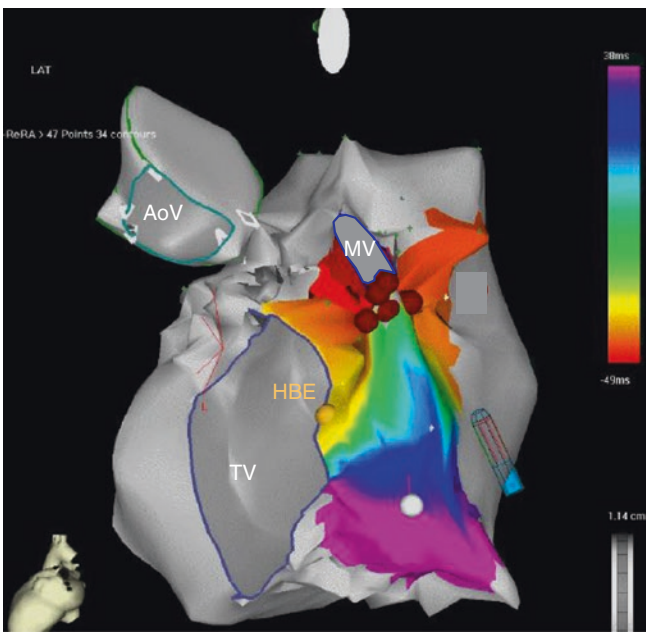


Fig. 21.2 Slow pathway modification for atrioventricular nodal reentrant tachycardia (AVNRT) in a patient with complex congenital heart disease involving hypoplastic mitral valve (MV) with a large tricuspid valve (TV) and a double outlet right ventricle. An electroanatomic shell of the common atrium is shown. Positions of the aortic valve (AoV) and the His bundle recording site (*orange dot*, HBE) are marked for orientation. It was fortuitous in this case that fast-slow AVNRT could be induced so that the retrograde slow pathway insertion site could be mapped. Earliest retrograde atrial activation over the slow pathway (*red zone*) allowed accurate targeting of the slow pathway for ablation (*red dots*)

More exotic disorders in AV conduction can occasionally be identified in patients with abnormalities of atrial situs and discordant relationships between the atria and ventricles, referred to as heterotaxy syndrome [13]. Heterotaxy can be broadly divided into two main categories. First is the polysplenia variety (so-called left atrial isomerism) where the sinus node and AV node can be underdeveloped such that pacemaker implant is often required to address bradyarrhythmias early in life. In contrast, the aspleenia variety of heterotaxy (so-called right atrial isomerism) can actually have two sinus nodes and a duplicated AV conduction system described as "twin AV nodes." This arrangement consists of two separate compact nodes with two discrete His bundles connected at the ventricular level with a bridge of conduction tissue known as a Mönckeberg sling. A wide assortment of reentrant tachycardias can arise within this complicated network, most of which can be eliminated by strategic ablation of the less-robust of the two compact nodes [14, 15]. Though twin AV nodes are very rare, the condition epitomizes the peculiar conduction arrangements that are possible in CHD.

Intraatrial Reentrant Tachycardia

The most common mechanism for symptomatic tachycardia in the CHD population is macroreentry within atrial muscle [16]. The location of these circuits varies according to the underlying heart defect and the method used for surgical

repair [17]. They are usually restricted to right atrial tissue, and are defined by regions of surgical scar which function in combination with natural conduction barriers to channel a wavefront along a macroreentrant path. If a tricuspid valve is present, the isthmus between the valve ring and the inferior vena cava is a common component of such circuits (similar to conventional atrial flutter), but the true isthmus may be difficult to reach (Fig. 21.3), and less predictable paths related to incisional lines and septal patches also occur (Fig. 21.4). Quite often, multiple circuits can be present in the same patient which may conduct in a figure-of-eight or dual-loop manner. The term "intraatrial reentrant tachycardia" (IART) has been adopted as a general term to describe all these circuits in CHD patients regardless of their precise location.

Most IART circuits are slower than typical atrial flutter seen in a normal heart [18], with atrial cycle lengths in the range of 250–320 ms (Fig. 21.5). This allows a relatively rapid ventricular response rate that can lead to hypotension, syncope, or possibly cardiac arrest in CHD patients with poor ventricular function [19]. Even when the ventricular response rate is safely controlled, IART may cause debilitating symptoms in CHD patients from loss of AV synchrony, and can contribute to thromboembolic complications if the duration is protracted. Usually, IART appears many years after operations that involved an atriotomy or other surgical manipulation of right atrial tissue. It can occasionally follow simple procedures such as closure of an atrial septal defect, but the incidence is highest among patients with advanced dilation, thickening, and scarring of their right atrium. Hence, IART is especially problematic for CHD patients who have undergone the Mustard or Senning operations for transposition of the great vessels, or the Fontan operation for single ventricle. Concomitant sinus node dysfunction is also common following these operations (tachy-brady syndrome) to further complicate matters.

The therapeutic options for IART include: (a) antiarrhythmic drugs, (b) catheter ablation, (c) pacemaker implantation to support rate in tachy-brady syndrome, and (d) surgical intervention with a modified atrial maze operation**.** The choice must be tailored to the hemodynamic and electrophysiologic status of the individual patient. Antiarrhythmic drugs are still prescribed occasionally, but the broad experience with pharmacologic therapy for this condition has been discouraging, even when using class I and class III agents [20]. Catheter ablation is now used at most centers as the preferred early intervention for IART [21]. The technique has evolved rapidly since the introduction of three-dimensional mapping for improved circuit localization, and irrigated-tip ablation catheters for more effective lesion creation [22]. When these technologies are combined with high-quality anatomic definition (MRI, CT, intracardiac echo, angiography) merged into an electroanatomic shell, acute success rates of nearly 90% can be achieved [16]. Unfortunately, later recurrence with a different circuit of IART is still disappointingly common. The recurrence risk is

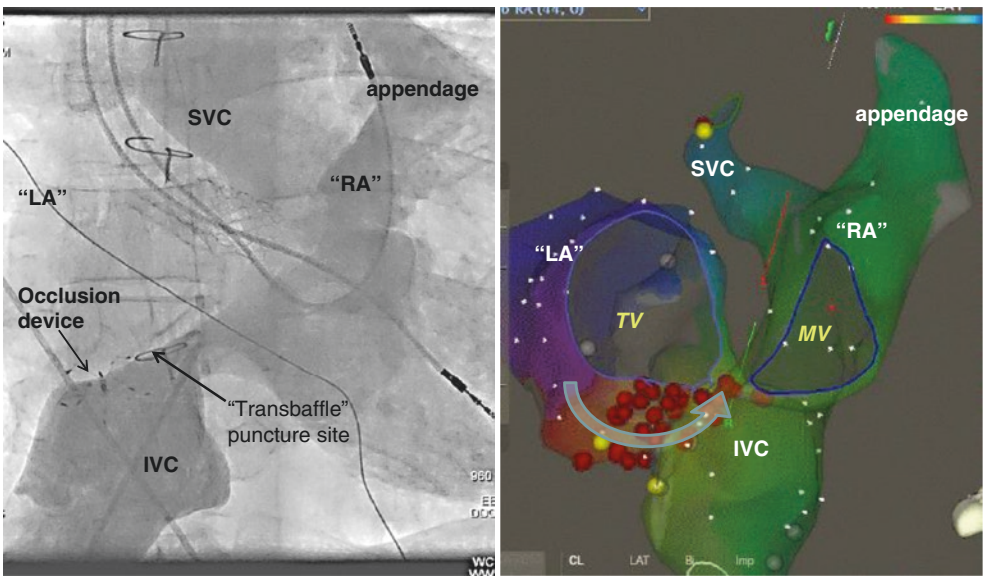


Fig. 21.3 Ablation for intraatrial reentrant tachycardia in a patient who has undergone a Mustard operation for transposition of the great arteries. *Left panel*: Angiogram in the "right atrium" ("RA") showing how the atrial baffle redirects blood return from the superior and inferior vena cavae (SVC and IVC) towards the mitral valve (*MV*). *Right panel:* The tachycardia involved a counterclockwise circuit around the tricuspid valve (*TV*). In order to reach the cavo-tricuspid isthmus region for ablation (*red dots*), a transbaffle puncture technique was used to enter the "left atrium" ("LA"). The successful puncture site was just medial (*arrow*) to an occlusion device that had been placed several years earlier to address a large baffle leak

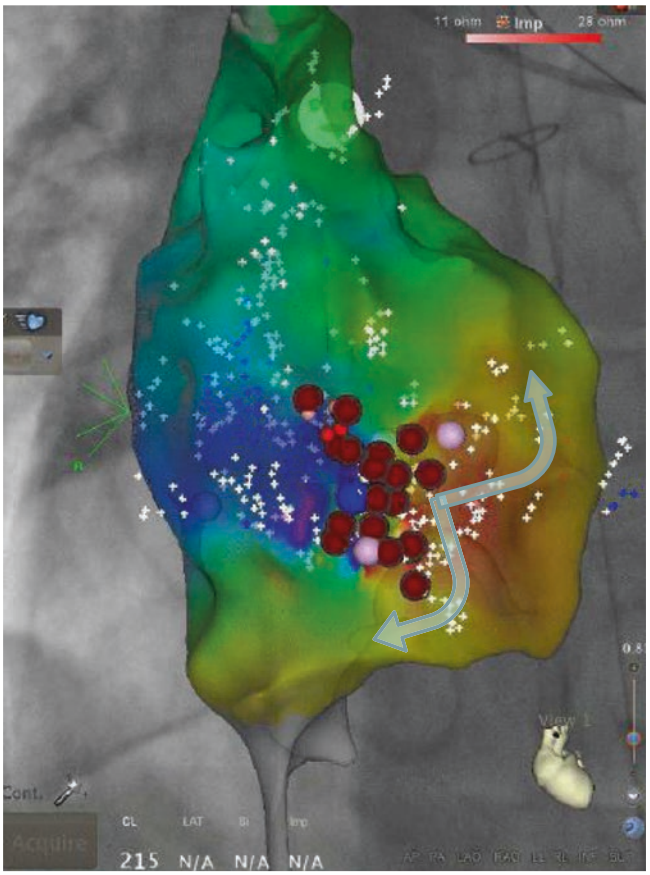


Fig. 21.4 Unusual circuit for intraatrial reentrant tachycardia in a patient who has undergone a Fontan operation for single ventricle. The electroanatomic shell is focused on the anterolateral aspect of the right atrium. Pink dots mark sites of split potentials that likely represented scarring from an atriotomy, but there was a narrow channel between the pink dots that allowed the circuit to propagate in a figure-of-eight pattern (*arrows*). Ablation at the blue dot site terminated tachycardia promptly, but multiple additional radiofrequency applications (red dots) were required before complete conduction block was established through this corridor

particularly high among Fontan patients, who tend to have the largest number of IART circuits and the thickest/largest atrial dimensions. Though still imperfect, outcomes for catheter ablation of IART continue to improve, and even now are far superior to the degree of control obtained with medications alone.

Pacemaker implantation may be reasonable to consider for patients with IART as part of the tachy-brady syndrome, since correcting slow atrial rates to a physiologic range often results in reduction of IART episodes. Pacemakers equipped with atrial antitachycardia pacing features can also be useful in select cases [19, 23]. If the above measures fail to prevent IART, and/or the patient is returning to the operating room for hemodynamic reasons, consideration can also be given to surgical ablation during a right atrial maze operation. This procedure is used most often for the Fontan population with the most refractory variety of IART, and is usually combined with revision of the Fontan connection from an older atriopulmonary anastomosis to a modern cavopulmonary connection in the same setting. Results are encouraging [24, 25], with relatively low rates of IART recurrence, but surgical risks must be weighed carefully against the electrophysiologic benefit.

Atrial Fibrillation

While IART remains by far the most common form of atrial tachycardia in CHD, atrial fibrillation is being encountered with increasing frequency as the CHD population survives to older ages. Most cases involve patients with hemodynamic derangements contributing to left atrial dilation and/or left ventricular diastolic dysfunction, such as congenital aortic stenosis, mitral regurgitation, or palliated single ventricle [26]. Medical management and techniques for acute conversion are in accordance with ACC/AHA/HRS guidelines [27], but like IART, pharmacologic therapy has been only marginally successful in preventing recurrences. There is now a small but growing literature describing transcatheter pulmonary vein isolation for atrial fibrillation in CHD patients [28]. Most cases reported to date have involved fairly simple lesions such as atrial septal defects, though the technique is being cautiously expanded to more complex anatomy (Fig. 21.6). A surgical maze operation incorporating a biatrial lesion set can also be considered, especially if a patient is returning to the operating room to address other hemodynamic issues [29].

Ventricular Tachycardia

Malignant ventricular arrhythmias are rare among CHD patients during their first decade or two of life, but once adulthood is reached [30, 31], the potential for ventricular tachycardia (VT) and sudden cardiac death begins to loom as a concern. Wolff et al. [32] were the first to sound the alarm in 1972 when they published observations on disrupted conduction patterns and VT associated with sudden unexpected death in postoperative tetralogy of Fallot patients. Since then, the topic of late postoperative sudden death and VT has occupied the attention of all cardiologists involved with the longitudinal care of CHD patients [33–39].

It is useful to consider two general categories of VT in CHD patients [40]. The first of these involves developmental and/or surgical abnormalities of ventricular geometry that can serve as a substrate for macroreentry, with central obstacles and narrow corridors of slow conduction capable of supporting one or more monomorphic VT circuits. Specific CHD lesions that best exemplify this anatomic

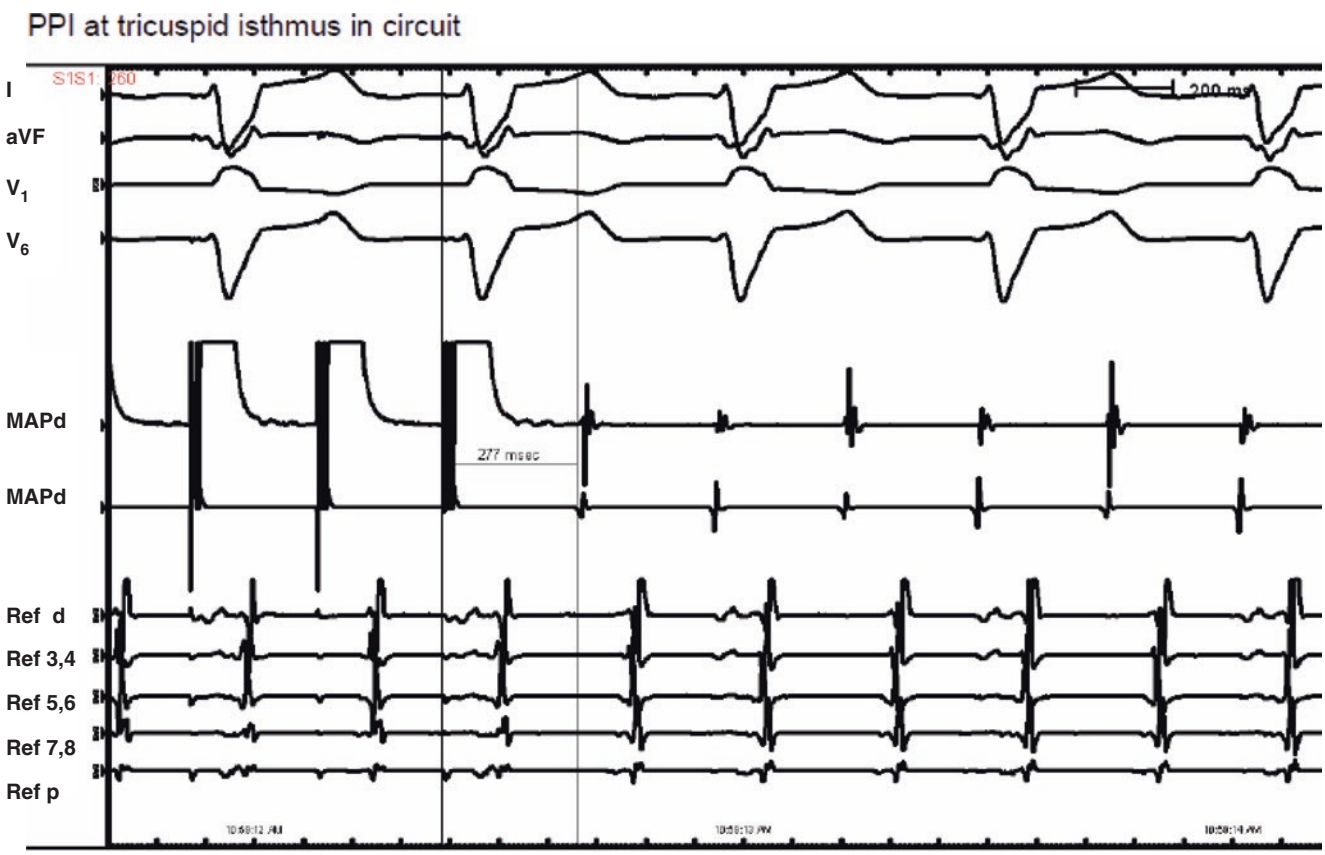


Fig. 21.5 Surface ECG (leads I, aVF, V1, V6) and intracardiac electrograms recorded from the mapping catheter (MAP) and an atrial reference catheter (Ref) during intraatrial reentrant tachycardia in a patient with repaired atrial and ventricular septal defects. The atrial cycle length is 277 ms, conducting in a 2:1 pattern. Entrainment pacing was performed from the distal MAP catheter at the cavo-tricuspid isthmus, and the postpacing interval (PPI) was identical to the tachycardia cycle length at this site. Ablation of the isthmus eliminated this circuit

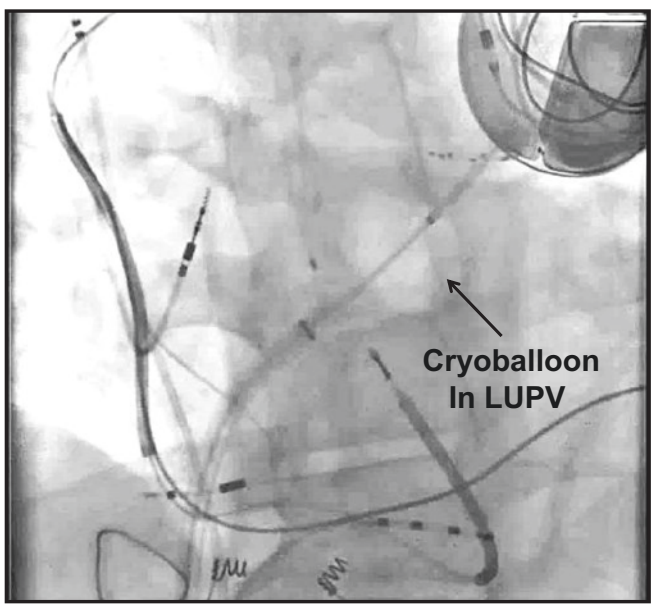


Fig. 21.6 Fluoroscopic view of catheter positions during a pulmonary vein isolation procedure for atrial fibrillation in a 44 year old who had undergone repair of tetralogy of Fallot as a child. This patient also had sinus node dysfunction and ventricular arrhythmias for which a transvenous dual chamber ICD had been placed. The inflated cryoballoon is positioned in the left upper pulmonary vein

predisposition to monomorphic VT include: (a) tetralogy of Fallot, (b) Ebstein's anomaly, and (c) other conditions repaired through a free-wall ventriculotomy incision. These are the patients most likely to benefit from catheter ablation therapy, and hence, are the source of most VT mapping data in the CHD population. A second category of VT seen in CHD involves less-organized polymorphic VT and ventricular fibrillation that occur as a nonspecific response to failing myocardium, similar to arrhythmias encountered in any other form of hypertrophic or dilated cardiomyopathy. This myopathic substrate can be generated by a number of factors, including chronic pressure and volume loads, longstanding cyanosis, injury from cardioplegia, and other myocardial insults. Examples of conditions associated with VT of this sort include: (a) chronic aortic valve or aortic arch obstruction, (b) transposition of the great arteries following Mustard or Senning operations where the right ventricle has been recruited as the systemic ventricle, (c) unrepaired septal defects with Eisenmenger's physiology, and (d) palliated single ventricle. The VT seen in these patients is less likely to respond to catheter ablation therapy, and usually must be managed with an implantable cardioverter defibrillator (ICD).

Table 21.2 Estimates of the sudden death incidence following tetralogy of fallot surgery

Study [reference]	Findings	Incidence
Murphy 1993 [33]	6% of 163 cases followed 30 years	2.0% per decade
Nollert 1997 [34]	3% of 490 cases followed 25 years	1.2% per decade
Silka 1998 [35]	~2 deaths per 1000 patient years	2.0% per decade
Norgaard 1999 [36]	5.6% of 125 cases followed 25 years	2.2% per decade
Gatzoulis 2000 [37]	6% of 793 cases followed 21 yrs	3.0% per decade

Most clinical experience with VT in CHD has centered on tetralogy of Fallot. The prevalence of VT after tetralogy repair has been estimated in the range of 3–14% in large clinical series [33–37], with most cases involving patients who are more than 20 years removed from their surgical repair [30, 31]. A few may present with slow VT capable of generating a perfusing rhythm, but VT tends to be rapid for the majority, causing syncope or cardiac arrest as the presenting symptom. Sustained VT appears to be the single biggest contributor to the sudden cardiac death risk in the tetralogy population (Table 21.2), and predicting such events has been a topic of intense investigation for over 4 decades [41]. To date, no perfect risk-stratification scheme has emerged, though several clinical variables with modest prognostic value have been identified, including: (a) older age of time of definitive surgery, (b) history of palliative shunts, (c) nonsustained VT on Holter monitor, (d) inducible VT at electrophysiologic study, (e) severe pulmonary regurgitation with right ventricular dilation, (f) prolonged QRS duration (>180 ms), and (g) depressed left ventricular function. When viewed in aggregate, this long list of variables helps to define a clinical profile for the tetralogy patient at risk, but no single item can be viewed as completely independent, and none provides perfect predictive accuracy. Programmed ventricular stimulation can be used to refine risk prediction when multiple noninvasive risk factors are detected [42, 43]. Inducible VT may prompt a recommendation for a primary prevention ICD [44], or if stable monomorphic VT can be induced, catheter ablation of the VT circuit might be considered. Correctable hemodynamic issues may also be identified at catheterization that could shift therapy towards a surgical solution, such as relief of pulmonary regurgitation combined with formal intraoperative VT mapping and ablation [45].

Catheter ablation has been applied to VT in select CHD patients since the early 1990s. The published experience is still somewhat limited [46–49], but the overall acute success rate is now approaching 90% with improved technology and a better appreciation for the common sites of the macroreentry circuits. In tetralogy (Fig. 21.7), mapping has verified that the right ventricular outflow region (including the conal septum between the ventricular septal defect and the pulmonary valve) is nearly always a productive ablation area, allowing empiric ablation to be performed there even when the full VT propagation pattern cannot be mapped due to rapid rates and hemodynamic instability [50, 51]. The recurrence rate after acutely successful ablation is still roughly 15%, which has prompted many centers to consider back-up ICD implant in these patients even if ablation is acutely successful.

Ebstein's anomaly is another condition capable of supporting monomorphic VT that may be amenable to ablation therapy. In this condition the common site for reentry is the thin and fibrotic right ventricular myocardium located above the displaced tricuspid valve (so-called "atrialized" ventricle….see Fig. 21.1). Conduction through this tissue tends to be slow and inhomogeneous, and can be fertile ground for macroreentry. There are several reports now of successful VT ablation in this abnormal tissue [5, 52]. If ablation for monomorphic VT is ever contemplated in a patient with Ebstein's anomaly, it is important that it be performed prior to any surgical reconstruction of the tricuspid valve since the target tissue may be very difficult to reach thereafter.

Recommendations for ICD placement in CHD patients largely reflect the established guidelines for adults with more conventional forms of heart disease. A recent joint consensus document from the Heart Rhythm Society and the Pediatric and Congenital Electrophysiology Society reviewed arrhythmia management and ICD guidelines in adults with CHD [44], and offered ICD recommendations which can be abstracted as follows:

1. *ICD therapy is indicated in adults with CHD who are survivors of cardiac arrest after reversible etiologies have been excluded (Class I).*
2. *ICD therapy is indicated in adults with CHD and spontaneous sustained VT after careful hemodynamic and electrophysiologic assessment, though catheter ablation or surgery may be a reasonable alternative or adjunct in selected patients (Class I).*
3. *ICD therapy is indicated in adults with CHD and a systemic ventricular ejection fraction less than or equal to 35%, biventricular physiology, and NYHA class II or III symptoms (Class I).*
4. *ICD therapy is reasonable in selected adults with tetralogy of Fallot and multiple risk factors such as LV dysfunction, nonsustained VT, QRS ≥ 180 msec, extensive RV scarring, or inducible sustained VT at EPS (Class IIa).*

It is important to emphasize that ICD implant in CHD patients with distorted anatomy can involve unique technical challenges related to vascular access and lead positioning [53]. Epicardial implant or a subcutaneous system (Fig. 21.8) needs to be considered in patients who lack conventional

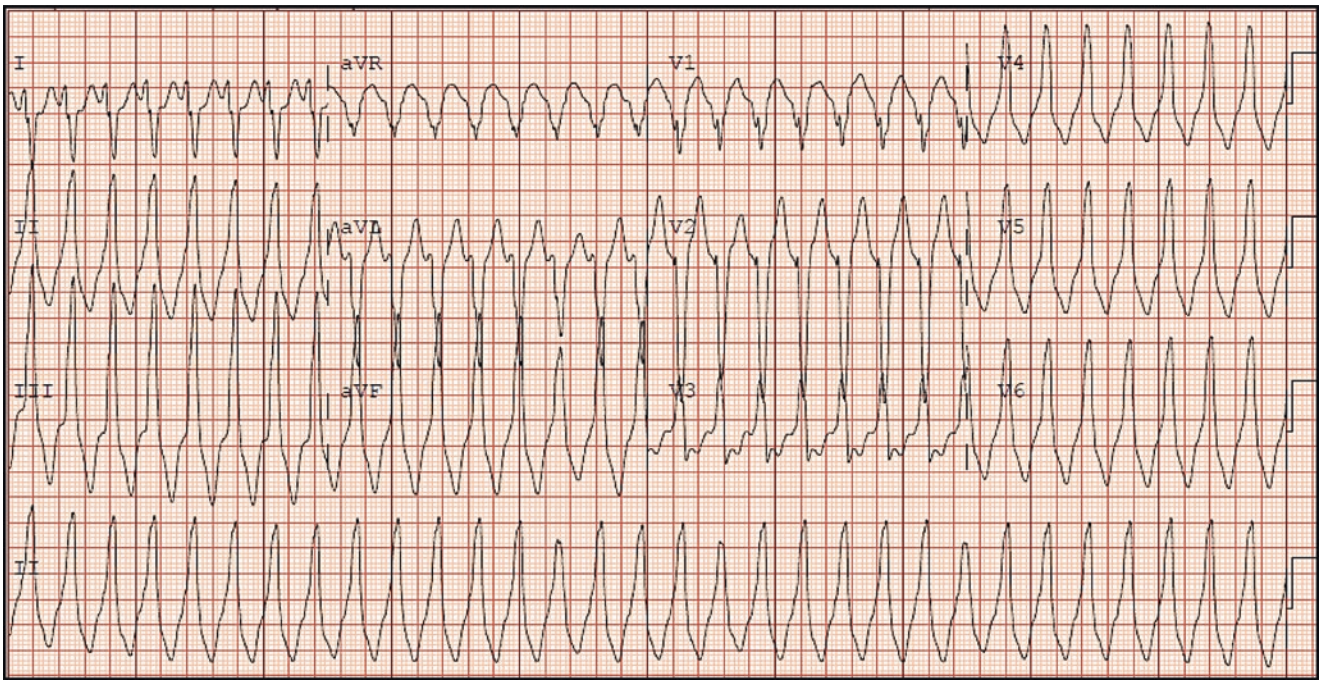


Fig. 21.7 Electrocardiogram from a woman with repaired tetralogy of Fallot during an episode of sustained ventricular tachycardia. The QRS has a pattern of left bundle branch block with an inferior axis, consistent with involvement of the right ventricular outflow region

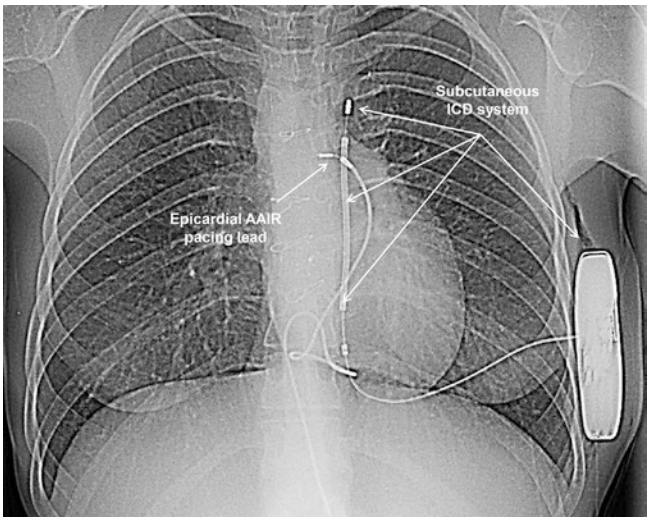


Fig. 21.8 Subcutaneous ICD system in a young woman who has undergone a Fontan operation for double outlet right ventricle with straddling tricuspid valve and a small left ventricle. The Fontan connection prevents transvenous access to the ventricle. She also had a previously placed epicardial atrial pacing system for sinus node dysfunction

venous access to the ventricle (e.g. following a Fontan operation for single ventricle) or who have residual intracardiac shunting that would put them at risk for thromboembolic complications if intravascular leads were used [54, 55]. It is reasonable to suggest that ICD procedures in patients with complex lesions only be attempted in experienced centers.

Bradycardia in CHD

Sinoatrial Node Dysfunction

Sinus node dysfunction in CHD patients can be either congenital or acquired. The congenital type is rare, but is seen occasionally in patients with the polysplenia type of heterotaxy syndrome (left atrial isomerism) who may lack a true sinus node [13], making atrial depolarization dependent upon slower atrial or junctional escape rhythms. Most patients with this unusual condition will ultimately require pacemaker implantation early in life.

A far more common cause of sinus node dysfunction in CHD is the acquired type that results from surgical trauma to the sinus node and/or its arterial supply. This is observed most often following the Mustard and Senning operations for patients with transposed great arteries, or following the Glenn and Fontan operations for patients with single ventricle [56]. The resulting chronotropic incompetence tends to be poorly tolerated in patients with such complex lesions. Furthermore, the likelihood of the patient developing IART or atrial fibrillation increases significantly in the setting of sinus node dysfunction [57].

The ACC/AHA/HRS guidelines for device-based therapy of cardiac rhythm abnormalities contained recommendations for pacemaker implantation in both children and adults with CHD and sinus node dysfunction [58]. The committee

offered recommendations which can be abstracted as follows:

1. *Pacemaker implant is indicated in CHD patients for sinus node dysfunction with correlation of symptoms during age-inappropriate bradycardia (Class I).*
2. *Pacemaker implant is reasonable for CHD patients with sinus bradycardia for the prevention of recurrent IART: the bradycardia may be intrinsic or secondary to antiarrhythmic drugs (Class IIa).*
3. *Pacemaker implant is reasonable for patients with complex CHD with a resting heart rate < 40 bpm or pauses in ventricular rate longer than 3 sec (Class IIa).*
4. *Pacemaker implant is reasonable for CHD patients and impaired hemodynamics due to sinus bradycardia or loss of AV synchrony (Class IIa).*
5. *Pacemaker implant may be considered for patients with simple CHD with a resting heart rate < 40 bpm or pauses in ventricular rate longer than 3 sec (Class IIb).*

Atrioventricular Block in CHD

The AV conduction tissues may be congenitally abnormal in terms of both their location and function in specific forms of CHD, most notably, "congenitally corrected" transposition of the great arteries (L-TGA), and atrioventricular canal defects [3]. In the former condition, the AV node and His bundle are displaced away from the usual position in Koch's triangle to an anterior location near the right-sided atrial appendage, while in the latter, the AV node and His bundle are displaced posterior to Koch's triangle to a site that is beneath the mouth of coronary sinus. The functional properties of these displaced conduction systems are often suboptimal. In L-TGA, for example, it is estimated that 3–5% of patients will have complete heart block at birth, and an additional 20% will spontaneously progress to complete AV block by adulthood [59, 60]. Patients with displaced conduction tissues also seem to be more susceptible to traumatic AV block during surgical or catheter procedures. Congenitally impaired AV conduction can also be observed in simple cases of atrial septal defect among patients with Holt-Oram syndrome [61], a hereditary disorder characterized by atrial defects and upper-limb deformities that involves a mutation on the *TBX5* gene.

Even when the conduction tissues are not congenitally abnormal, surgery can result in inadvertent trauma to the AV conduction tissues during closure of some ventricular septal defects, relief of left-heart outflow obstruction, and replacement or repair of an atrioventricular valve. Fortunately, in roughly two-thirds of such cases, this injury is a transient affair related to myocardial stretch or edema rather than physical severing of the conduction tissues, and AV conduction recovers within several days [62]. But, for any patient with postoperative AV block that persists after surgery, permanent pacemaker implant is considered an absolute requirement. The ACC/AHA/HRS guidelines [58] for pacemaker placement for AV conduction disorders in CHD can be abstracted as follows:

1. *Pacemaker implant is indicated in CHD patients for postoperative advanced second- or third-degree AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery (Class I).*
2. *Pacemaker implant may be considered for CHD patients with transient postoperative third-degree AV block that reverts to sinus rhythm with residual bifascicular block (Class IIb).*

Similar to the decisions involved with ICD implants, pacemaker implantation is never a casual exercise in CHD patients (Fig. 21.9). Epicardial implants may be required in those with distorted venous access and those with intracardiac shunting [63–65].

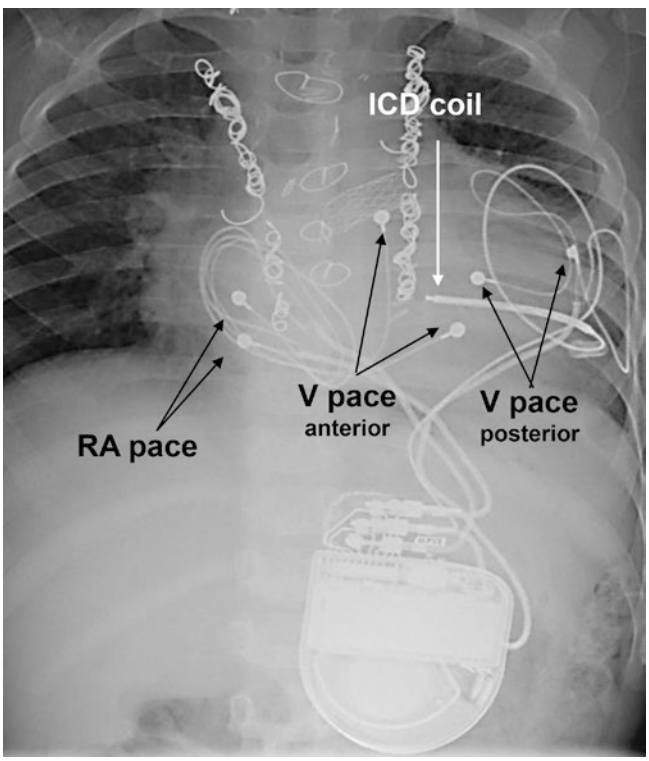


Fig. 21.9 Epicardial ICD system in a child with complex single ventricle, poor ventricular function, complete heart block, and ventricular arrhythmias. Hardware consists of an ICD shock coil positioned in the posterior pericardial space. Bipolar pacing leads are positioned on the right atrium (RA), with dual-site ventricular leads on the anterior and posterior aspects of the single ventricle (V) to provide resynchronization pacing

Table 21.3 Listing of specific CHD lesions and associated arrhythmias

LESION	IART	AFIB	WPW	VT/SCD	SAN DYSFXN	SPONT AV-BLK	SURG AV-BLK	TWIN AV NODES
ASD (late repair)	+	+			+			
ASD (Holt-Oram syndrome)	+					++		
VSD (transatrial repair)	+						+	
VSD (repair through ventriculotomy)				+			+	
Common AV canal defect	+					+	++	
Tetralogy of Fallot	++			++			+	
Congenital aortic stenosis		+		++			+	
Coarctation aorta (residual gradient or late repair)				++				
Congenital mitral valve disease	+	++					+	
Ebstein's Anomaly	++	+	+++	+				
D-TGA (Mustard or Senning)	+++			++	+++			
L-TGA	+	+	++	+		+++	++	
Single ventricle (Fontan)	+++	+		+	+++			
Single ventricle (palliated)		++						
Heterotaxy (right atrial isomerism)	+							++
Heterotaxy (left atrial isomerism)	+				+++	++		

+ = occasional, ++ = moderately frequent, +++ = very frequent
AFIB atrial fibrillation, *ASD* atrial septal defect, *AV* atrioventricular, *D-TGA* D-looped transposition of the great arteries, *IART* intraatrial reentrant tachycardia, *L-TGA* L-looped or "congenitally corrected" transposition of the great arteries, *SAN DYSFXN* sinoatrial node dysfunction, *SPONT AV-BLK* spontaneous atrioventricular block, *SURG AV-BLK* surgically-acquired atrioventricular block, *VSD* ventricular septal defect, *VT/SCD* ventricular tachycardia and sudden cardiac death

Summary

Patients with CHD have a unique myocardial substrate capable of generating unusual arrhythmias due to both developmental and acquired abnormalities (Table 21.3). Improved outcomes from childhood surgery have created a rapidly expanding population of adult survivors who require inventive solutions for these disorders. Successful navigation of the distorted anatomy during catheter ablation procedures and device implant requires clear unerstanding of the individual defect and the techniques used for surgical repair.

COI Declaration The author has no financial conflict of interest to declare regarding this work.

References

1. Shahian DM, Jacobs JP, Edwards FH, Brennan JM, Dokholyan RS, Prager RL, et al. The society of thoracic surgeons national database. Heart. 2013;99(20):1494–501.
2. Walsh EP. Interventional electrophysiology in patients with congenital heart disease. Circulation. 2007;115(25):3224–34.
3. Anderson RH, Ho SY. The disposition of the conduction tissues in congenitally malformed hearts with reference to their embryological development. J Perinat Med. 1991;19(Suppl 1):201–6.
4. Attenhofer Jost CH, Connolly HM, Edwards WD, Hayes D, Warnes CA, Danielson GK. Ebstein's anomaly—review of a multifaceted congenital cardiac condition. Swiss Med Wkly. 2005;135(19):269–81.
5. Shivapour JK, Sherwin ED, Alexander ME, Cecchin F, Mah DY, Triedman JK, et al. Utility of preoperative electrophysiologic studies in patients with Ebstein's anomaly undergoing the Cone procedure. Heart Rhythm. 2014;11(2):182–6.

6. Reich JD, Auld D, Hulse E, Sullivan K, Campbell R. The Pediatric Radiofrequency Ablation Registry's experience with Ebstein's anomaly. Pediatric Electrophysiology Society. J Cardiovasc Electrophysiol. 1998;9(12):1370–7.
7. Roten L, Lukac P, DE Groot N, Nielsen JC, Szili-Torok T, Jensen HK, et al. Catheter ablation of arrhythmias in Ebstein's anomaly: a multicenter study. J Cardiovasc Electrophysiol. 2011;22(12):1391–6.
8. Khairy P, Seslar SP, Triedman JK, F C. Ablation of atrioventricular nodal reentrant tachycardia in tricuspid atresia. J Cardiovasc Electrophysiol. 2004;15(6):719–22.
9. Ernst S, Ouyang F, Linder C, Hertting K, Stahl F, Chun J, et al. Modulation of the slow pathway in the presence of a persistent left superior caval vein using the novel magnetic navigation system Niobe. Europace. 2004;6(1):10–4.
10. Alberto Lopez J, Angelini P, Lufschanowski R. Successful ablation of atrioventricular node reentry tachycardia in a patient with crisscross heart and situs inversus levocardia. J Interv Card Electrophysiol. 2006;17(2):133–7.
11. Upadhyay S, Marie Valente A, Triedman JK, Walsh EP. Catheter ablation for atrioventricular nodal reentrant tachycardia in patients with congenital heart disease. Heart Rhythm. 2016;13(6):1228–37. doi:10.1016/j.hrthm.2016.01.020. pii: S1547–5271(16)00066–7
12. Collins KK, Schaffer MS. Use of cryoablation for treatment of tachyarrhythmias in 2010: survey of current practices of pediatric electrophysiologists. Pacing Clin Electrophysiol. 2011;34(3):304–8.
13. Anderson RH, Brown NA, Moorman AF. The sinus node, isomerism, and heterotaxy. Cardiovasc Pathol. 2013;22(3):243–4.
14. Epstein MR, Saul JP, Weindling SN, Triedman JK, Walsh EP. Atrioventricular reciprocating tachycardia involving twin atrioventricular nodes in patients with complex congenital heart disease. J Cardiovasc Electrophysiol. 2001;12(6):671–9.
15. MH W, Wang JK, Lin JL, Lai LP, Lue HC, Young ML, et al. Supraventricular tachycardia in patients with right atrial isomerism. J Am Coll Cardiol. 1998;32(3):773–9.
16. Sherwin ED, Triedman JK, Walsh EP. Update on interventional electrophysiology in congenital heart disease: evolving solutions for complex hearts. Circ Arrhythm Electrophysiol. 2013;6(5):1032–40.
17. Collins KK, Love BA, Walsh EP, Saul JP, Epstein MR, Triedman JK. Location of acutely successful radiofrequency catheter ablation of intraatrial reentrant tachycardia in patients with congenital heart disease. Am J Cardiol. 2000;86(9):969–74.
18. Triedman JK, Bergau DM, Saul JP, Epstein MR, Walsh EP. Efficacy of radiofrequency ablation for control of intraatrial reentrant tachycardia in patients with congenital heart disease. J Am Coll Cardiol. 1997;30(4):1032–8.
19. Rhodes LA, Walsh EP, Gamble WJ, Triedman JK, Saul JP. Benefits and potential risks of atrial antitachycardia pacing after repair of congenital heart disease. Pacing Clin Electrophysiol. 1995;18(5):1005–16.
20. Triedman JK. Atrial reentrant tachycardias. In: Walsh EP, Saul JP, Triedman JK, editors. Cardiac arrhythmias in children and young adults with congenital heart disease. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 137–60.
21. Delacretaz E, Ganz LI, Friedman PL, Walsh EP, Triedman JK, Sloss LJ, et al. Multiple atrial macroreentry circuits in adults with repaired congenital heart disease: entrainment mapping combined with three-dimensional electroanatomic mapping. J Am Coll Cardiol. 2001;37(6):1665–76.
22. Triedman JK, Alexander MA, Love BA, Collins KK, Berul CI, Bevilacqua LM, et al. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial tachycardia in patients with congenital heart disease. J Am Coll Cardiol. 2002;39(11):1827–35.
23. EA S, Casavant D, Tuzi J, Alexander ME, Law I, Serwer G, et al. Efficacy of atrial antitachycardia pacing using the Medtronic AT500 pacemaker in patients with congenital heart disease. Am J Cardiol. 2003;92(7):871–6.
24. Mavroudis C, Backer CL, Deal BJ, Johnsrude C, Strasburger J. Total cavopulmonary conversion and maze procedure for patients with failure of the Fontan operation. J Thorac Cardiovasc Surg. 2001;122(5):863–71.
25. Jang WS, Kim WH, Choi K, Nam J, Choi ES, Lee JR, et al. The mid-term surgical results of Fontan conversion with antiarrhythmia surgery. Eur J Cardiothorac Surg. 2014;45(5):922–7.
26. Kirsh JA, Walsh EP, Triedman JK. Prevalence of and risk factors for atrial fibrillation and intraatrial reentrant tachycardia among patients with congenital heart disease. Am J Cardiol. 2002;90(3):338–40.
27. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014;130(23):2071–104.
28. Lakkireddy D, Rangisetty U, Prasad S, Verma A, Biria M, Berenbom L, et al. Intracardiac echo-guided radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect or patent foramen ovale repair: A feasibility, safety, and efficacy study. J Cardiovasc Electrophysiol. 2008;19(11):1137–42.
29. Mavroudis C, Deal BJ, Backer CL, Tsao S. Arrhythmia surgery in patients with and without congenital heart disease. Ann Thorac Surg. 2008;86(3):857–68.
30. Walsh EP. Arrhythmias in patients with congenital heart disease. Card Electrophysiol Rev. 2002;6(4):422–30.
31. Kumar S, Tedrow UB, Triedman JK. Arrhythmias in Adult Congenital Heart Disease: Diagnosis and Management. Cardiol Clin. 2015;33(4):571–88.
32. Wolff GS, Rowland TW, Ellison RC. Surgically induced right bundle-branch block with left anterior hemiblock. An ominous sign in postoperative tetralogy of Fallot. Circulation. 1972;46(3):587–94.
33. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med. 1993;329(9):593–9.
34. Nollert G, Fischlein T, Bouterwek S, Bohmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. J Am Coll Cardiol. 1997;30(5):1374–83.
35. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol. 1998;32(1):245–51.
36. Norgaard MA, Lauridsen P, Helvind M, Pettersson G. Twenty-to-thirty-seven-year follow-up after repair for Tetralogy of Fallot. Eur J Cardiothorac Surg. 1999;16(2):125–30.
37. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet. 2000;356(9234):975–81.
38. Walsh EP, Rockenmacher S, Keane JF, Hougen TJ, Lock JE, Castaneda AR. Late results in patients with tetralogy of Fallot repaired during infancy. Circulation. 1988;77(5):1062–7.
39. Villafañe J, Feinstein JA, Jenkins KJ, Vincent RN, Walsh EP, Dubin AM, et al. Hot topics in tetralogy of Fallot. J Am Coll Cardiol. 2013;62(23):2155–66.
40. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation. 2007;115(4):534–45.

41. Walsh EP. Sudden death in adult congenital heart disease: risk stratification in 2014. Heart Rhythm. 2014;11(10):1735–42.
42. Alexander ME, Walsh EP, Saul JP, Epstein MR, Triedman JK. Value of programmed ventricular stimulation in patients with congenital heart disease. J Cardiovasc Electrophysiol. 1999;10(8):1033–44.
43. Khairy P, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marçon F, et al. Value of programmed ventricular stimulation after tetralogy of Fallot repair: a multicenter study. Circulation. 2004;109(16):1994–2000.
44. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation. 2008;117(3):363–70.
45. Therrien J, Siu SC, Harris L, Dore A, Niwa K, Janousek J, et al. Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. Circulation. 2001;103(20):2489–94.
46. Goldner BG, Cooper R, Blau W, Cohen TJ. Radiofrequency catheter ablation as a primary therapy for treatment of ventricular tachycardia in a patient after repair of tetralogy of Fallot. Pacing Clin Electrophysiol. 1994;17(8):1441–6.
47. Morwood JG, Triedman JK, Berul CI, Khairy P, Alexander ME, Cecchin F, et al. Radiofrequency catheter ablation of ventricular tachycardia in children and young adults with congenital heart disease. Heart Rhythm. 2004;1(3):301–8.
48. Burton ME, Leon AR. Radiofrequency catheter ablation of right ventricular outflow tract tachycardia late after complete repair of tetralogy of Fallot using the pace mapping technique. Pacing Clin Electrophysiol. 1993;16(12):2319–25.
49. Gonska BD, Cao K, Raab J, Eigster G, Kreuzer H. Radiofrequency catheter ablation of right ventricular tachycardia late after repair of congenital heart defects. Circulation. 1996;94(8):1902–8.
50. Zeppenfeld K, Schalij MJ, Bartelings MM, Tedrow UB, Koplan BA, Soejima K, et al. Catheter ablation of ventricular tachycardia after repair of congenital heart disease: electroanatomic identification of the critical right ventricular isthmus. Circulation. 2007;116(20):2241–52.
51. Kriebel T, Saul JP, Schneider H, Sigler M, Paul T. Noncontact mapping and radiofrequency catheter ablation of fast and hemodynamically unstable ventricular tachycardia after surgical repair of tetralogy of Fallot. J Am Coll Cardiol. 2007;50(22):2162–8.
52. Obioha-Ngwu O, Milliez P, Richardson A, Pittaro M, Josephson ME. Ventricular tachycardia in Ebstein's anomaly. Circulation. 2001;104(18):E92–4.
53. Walsh EP. Practical aspects of implantable defibrillator therapy in patients with congenital heart disease. Pacing Clin Electrophysiol. 2008;31(Suppl):S38–40.
54. Jarman JW, Lascelles K, Wong T, Markides V, Clague JR, Till J. Clinical experience of entirely subcutaneous implantable cardioverter-defibrillators in children and adults: cause for caution. Eur Heart J. 2012;33(11):1351–9.
55. Stephenson EA, Batra AS, Knilans TK, Gow RM, Gradaus R, Balaji S, et al. A multicenter experience with novel implantable cardioverter defibrillator configurations in the pediatric and congenital heart disease population. J Cardiovasc Electrophysiol. 2006;17(1):41–6.
56. Flinn CJ, Wolff GS, Dick M, Campbell RM, Borkat G, Casta A, et al. Cardiac rhythm after the Mustard operation for complete transposition of the great arteries. N Engl J Med. 1984;310(25):1635–8.
57. Drago F, Silvetti MS, Grutter G, De Santis A. Long term management of atrial arrhythmias in young patients with sick sinus syndrome undergoing early operation to correct congenital heart disease. Europace. 2006;8(7):488–94.
58. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. J Am Coll Cardiol. 2008;51(21):e1–62.
59. Huhta JC, Maloney JD, Ritter DG, Ilstrup DM, Feldt RH. Complete atrioventricular block in patients with atrioventricular discordance. Circulation. 1983;67(6):1374–7.
60. Connelly MS, Liu PP, Williams WG, Webb GD, Robertson P, McLaughlin PR. Congenitally corrected transposition of the great arteries in the adult: functional status and complications. J Am Coll Cardiol. 1996;27(5):1238–43.
61. Mori AD, Bruneau BG. TBX5 mutations and congenital heart disease: Holt-Oram syndrome revealed. Curr Opin Cardiol. 2004;19(3):211–5.
62. Weindling SN, Gamble WJ, Mayer JE, Walsh EP. Duration of complete atrioventricular block after congenital heart disease surgery. Am J Cardiol. 1998;82(4):525–7.
63. Walsh EP, Cecchin F. Recent advances in pacemaker and implantable defibrillator therapy for young patients. Curr Opin Cardiol. 2004;19(2):91–6.
64. Khairy P, Landzberg MJ, Gatzoulis MA, Mercier LA, Fernandes SM, Côté JM, et al. Transvenous pacing leads and systemic thromboemboli in patients with intracardiac shunts: a multicenter study. Circulation. 2006;113(20):2391–7.
65. Silvetti MS, Drago F, Grutter G, et al. Twenty years of paediatric cardiac pacing: 515 pacemakers and 480 leads implanted in 292 patients. Europace. 2006;8(7):530–6.

Arrhythmias in Special Populations

22

Paul J. Wang and Winston B. Joe

Abstract

The occurrence of cardiac arrhythmias is dependent on the cellular, structural, autonomic, and hormonal environment in which the heart functions. Stressors such as pregnancy, competitive athletics, and surgery serve to modulate this arrhythmogenic environment. The altered cardiac physiology that results from these stressors can lead to new and recurrent arrhythmias. When these occur, they may have significant implications with respect to patient management, morbidity, and mortality. Mitigation of these consequences depends on the understanding and treatment of pathological rhythms, and on an appreciation of issues particular to these unique populations. The following chapter discusses arrhythmias in the groups comprised of patients in competitive athletics, pregnancy, heart transplant, and after major surgery.

Keywords

Cardiac arrhythmias • Sudden death • Heart transplant • Cardiac surgery • Non-cardiac surgery • Perioperative care • Athlete's heart • Sports • Guidelines • Pregnancy • ICD • Catheter ablation • Pacemaker

Arrhythmias in Pregnancy

Though the impact of cardiac arrhythmias on pregnancy-related hospital admissions appears modest, arrhythmias in pregnancy are not rare and have important implications for mother and child when they occur [1]. Improved treatment strategies have had positive effects on long-term survival in women with congenital heart disease, a group of patients who carry their risk of arrhythmias into pregnancy. Rising maternal age permits progression of chronic arrhythmogenic disease processes, including congenital valvular and ischemic causes, and the increased cardiac output of pregnancy and delivery may disrupt homeostasis and precipitate arrhythmias. Often a dysrhythmia in a healthy woman is the first sign of peripartum cardiomyopathy. Finally, with the hypercoagulable state of pregnancy, pulmonary embolus may present as a rhythm change and/or hemodynamic deterioration. Equally important are the possibilities of amniotic fluid embolus and acute aortic or coronary dissection. Up to date drug safety information, FDA cautions, and teratogenicity guidelines should always be consulted given the risk-benefit ratios of all medications, including anti-arrhythmic agents, in pregnancy.

Mechanisms

Pregnancy is associated with a host of hemodynamic, hormonal, and autonomic changes which may have arrhythmogenic consequences. Blood volume increases between 30 and 50%, peaks at approximately 34 weeks, and remains high for the last month of gestation. Cardiac output increases

P.J. Wang, M.D. (✉) • W.B. Joe
School of Medicine, Stanford University, 300 Pasteur Dr MC 5233, Stanford, CA 94305-5233, USA
e-mail: pjwang@stanford.edu; wjoe@stanford.edu

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_22

by 6.7 L/min during the first trimester and by up to 8.7 L/min during the third trimester [2]. Expanded plasma and stroke volumes place tension on stretch-activated ion channels, predisposing the mother to new or recurrent arrhythmias [2, 3]. The increased oxygen consumption by 30% and physiologic anemia of pregnancy, may contribute to a mileu in which previously benign arrhythmias become symptomatic [4].

Increased progesterone and estradiol levels are proarrhythmic in animal models, and estrogen is thought to promote autonomic responsiveness through stimulation of adrenergic receptors [2, 5]. Additionally, arrhythmias often parallel resting sinus tachycardia seen in the third trimester [6].

Fortunately, most dysrhythmias during pregnancy can be managed medically and cardioversion can be used safely in most urgent situations [1, 7].

Supraventricular Tachycardia

Supraventricular tachycardia (SVT) is responsible for 24 out of 100,000 hospital admissions in pregnant women [1]. Pregnancy may precipitate recurrent SVT in up to 50% of previously diagnosed patients [8]. AV node reentrant tachycardia (AVNRT) is most frequent, followed by AV reentrant tachycardia (AVRT), which is maybe found in patients with Wolff-Parkinson-White syndrome (WPW) [9] or with concealed accessory pathways.

Adenosine is relatively safe and effective for the acute management of both AVNRT and AVRT [10]. Intravenous metoprolol or propranolol may be used if adenosine is ineffective [11]. Verapamil is considered a third-line drug for PSVT during pregnancy, although it should be avoided in patients with WPW due to the risk of rapid conduction during atrial fibrillation (AF) [2, 11]. Prophylaxis may be achieved using AV nodal blocking agents such as beta-blockers, calcium channel blockers and digoxin [11].

While medical therapy is the preferred form of therapy, SVT ablations can be performed successfully in pregnant women if required. Ablation is advised only after the first trimester and radiation exposure should be limited [12]. The theoretical safe limit for maternal exposure is 50 mGy, but always with radiation, the "as low as reasonably achievable" (ALARA) goal should be observed. When radiation was assessed in patients undergoing ablation for SVT, exposure to the fetus with shielding can reach as low as <1 mGy, much less than the minimum threshold for concern (50 mGy) [2, 13, 14].

Wolff-Parkinson-White and Preexcitation

Patients with WPW and concealed bypass tracts have increased risk of manifesting these during pregnancy [15]. As always, the management of preexcitation syndromes, particularly with atrial fibrillation, is aided by understanding the antegrade refractory period of the accessory pathway. DC cardioversion should be performed in setting of rapid conduction in atrial fibrillation. Orthodromic reciprocating tachycardias, which are the most commonly seen rhythms in pregnant women with pre-excitation, can usually be treated medically [2].

Atrial Fibrillation and Flutter

Like most dysrhythmias in pregnancy, studies of AF and flutter in this setting are limited, but the ACCF/AHA/HRS Guidelines do make Class I and Class IIb recommendations [16].

New-onset AF and atrial flutter are unusual in the absence of structural heart disease or hyperthyroidism and should prompt evaluation to include cardiomyopathy, valvular disease, and pulmonary embolus [2]. AF recurrence occurs in over half of women with previously diagnosed AF [17].

As mentioned above, electrical cardioversion is effective with hemodynamically unstable AF or flutter, and has been performed safely in all three trimesters [18]. Reduction in fetal blood flow is not seen [2]. Rate control with β-blockers, calcium channel blockers, or digoxin may be effective in both acute and long-term settings. Rhythm control with sotalol or flecainide is also an option for patients refractory to rate control drugs, but should be avoided during the first trimester [19].

The standard approach to reducing stroke risk is generally applied in pregnancy, particularly given the prothrombotic tendency in pregnancy. There is the risk of cerebral embolization with the relatively lowered left-sided intracardiac pressures in the setting of patent foramen ovale or atrial septal defect. Non Vitamin K dependent of novel agents for anticoagulation are generally not recommended in pregnancy. Low molecular weight heparin may be used for all but final weeks of pregnancy. Warfarin should generally be avoided in the first trimester due to its teratogenicity [20].

Ventricular Tachycardia

Clinically significant ventricular dysrhythmias are uncommon without other pathology. Quinidine and procainamide are quinidine levels in the fetus mimic maternal blood levels, but quinidine can be used with caution. Procainamide is generally used only after quinidine failure because of the common lupus-like syndrome and antibody formation [21]. In the absence of structural heart disease flecainide may be used.

Arrhythmias in Athletes

While athletes represent many of the most fit and healthiest individuals in our society, heart rhythms problems such as atrial, supraventricular, and ventricular arrhythmias can occur. A small proportion of athletes may be at risk for sudden cardiac death. In older athletes, the most common cause of ventricular tachycardia (VT) or ventricular fibrillation (VF) is known or occult CAD. On the other hand, in younger athletes, significant arrhythmias are more likely to be inherited, due to conditions such as channelopathies, arrhythmogenic right ventricular cardiomyopathy, and hypertrophic cardiomyopathy [22].

The Athletic Heart

Physiological changes in the athlete's heart vary by frequency, duration, and type of exercise (dynamic vs. isometric) [22]. Exercise may produce adaptive increases in chamber size and wall thickness, some of which may be reversible [23]. Hypertrophy may depend on chronically elevated cytosolic calcium, which has been shown to stimulate cardiac hypertrophy in animal models [24]. Marked wall thickening (>13 mm), however, occurs in only 2% of athletes. Physical training may result in LV enlargement (usually <60 mm but up to 70 mm) and increased stroke volume, with ejection fractions measuring as low as 45% [25]. Intense exertion may trigger troponin release and BNP elevation, though the significance of this phenomenon is unclear [26–28].

In this section we will discuss assessment of risk of arrhythmias and management of arrhythmias in athletes [29, 30].

Sinus Node Dysfunction

Resting sinus bradycardia (SB) is common in athletes, and results from increased vagal tone. Thus, SB with heart rates as low as 30 bpm is generally benign and does not significantly blunt chronotropic response, the ability to increase heart rate with exertion [31, 32]. On the other hand a small number of athletes may present with symptomatic SB, such as sinus pauses longer than 3 s, sinoatrial exit block, or sick sinus syndrome, which are not benign adaptations and should be evaluated [33], sometimes necessitating permanent pacemaker implantation.

Atrioventricular Node Dysfunction

While athletes can have increased vagal tone, athletes with first-degree AVB, Mobitz I with PR intervals greater than 300 ms [34], or AV nodal block during exercise, should be evaluated carefully [33]. Some patients may require electrophysiologic study (EPS) to rule out intra- or infra-Hisian block with exercise [30].

Evidence of A-V block should prompt an evaluation for underlying structural disease. In addition ECG, Holter, or loop monitoring may be valuable [34].

Congenital complete heart block is uncommon, but presents a number of management challenges, particularly in athletes. Most patients with congenital complete heart block have junctional QRS duration <120 ms and ventricular rates greater than 40 bpm with adequate chronotropic response and no history of ventricular arrhythmias**.** When the junctional rhythm during exercise is insufficient, pacemaker implantation may be needed. Patients with acquired CHB will receive permanent pacemaker implantation. Athletes with complete A-V block and permanent pacemakers will likely regain ability to create adequate heart rate response with exercise.

Supraventricular Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) due to AVNRT, AV tachycardia over accessory pathways, or ectopic atrial tachycardia occur in the general population and do not appear more frequent in athletes. Exercise may trigger PSVT and increase ventricular rates, potentially increasing the hemodynamic consequences [32, 33]. Exercise-induced SVT are frequently managed pharmacologically. Patients who develop SVT during exercise should stop exercise and seek treatment [34, 35].

Ventricular pre-excitation is seen in <0.5% of individuals [36]. Patients with ventricular pre-excitation may be asymptomatic or present with SVT, AF or rarely sudden cardiac arrest. A small percentage of patients, likely less than 1%, may have extremely rapid, anterograde conduction via the accessary pathway sometimes greater than 250 bpm. Extremely rapid conduction can result in deterioration of atrial fibrillation into ventricular fibrillation [37, 38].

Current guidelines for athletes with symptomatic WPW recommend that competitive athletes undergo electrophysiology testing to determine the ability to conduct rapidly and identify patients with short anterograde periods (< or = 250 ms) or short pre-excited intervals in AF [30].

Atrial Fibrillation/Flutter

AF is the most common arrhythmia in athletes and non-athletes. The incidence in athletes may vary based on age, years of exercise training, co-morbidities, and sport (endurance vs. non-endurance). Causation of AF in the athletic heart is probably multifactorial, including atrial and ventricular

remodeling [30]. Increased vagal tone may shorten the atrial refractory period, facilitating reentry and AF [39, 40]. An exertion-related inflammatory response with elevated markers (interleukin-6 and C-reactive protein) may increase AF risk [41, 42]. Inflammation may stimulate fibrosis at the cellular level, producing an AF substrate [43]. Evaluation should include thyroid studies and queries regarding alcohol and illicit drug use. Patients with low CHA2DS2-VASC score do not need anticoagulation [30]. Anticoagulation when indicated may add to the bleeding risk involved in sports due to impact. The sports that are lowest in risk for impact include golf, swimming, track, and weight lifting [44]. When rate and rhythm control are insufficient to prevent impaired exercise performance, AF ablation may be considered. In patients with paroxysmal AF, AF ablation is generally successful [45, 46]. Most athletes may resume sports 4–6 weeks after ablation [34, 35]. Antiarrhythmic agents such as flecainide and propafenone may be used for rhythm control when AF ablation is not performed. The experience with dronedarone in athletes is more limited [33].

Atrial flutter is often treated using catheter ablation and most patients remain free of arrhythmias [34].

Premature Ventricular Contractions

Premature ventricular contractions (PVCs) commonly originate in the right ventricular outflow tract (RVOT) and are frequent in healthy athletes. Athletes should be free to exercise unless they are found to have structural disease or become symptomatic [34].

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a primary disease of the myocardium. Responsible for 36% of all SCD, it is the most common cause of SCD in young athletes [47]. Echocardiogram, cardiac MRI and genetic testing are helpful [25]. Patients with a family history of SCD, prior syncope, nonsustained VT, sustained VT/VF, increased wall thickness > 3 cm, hypotension with exercise, should receive an ICD [23].

Current guidelines recommend that athletes with HCM should be excluded from most competitive sports, with the possible exception of low intensity (class IA) sports [25].

Current guidelines also state that it is reasonable to allow competitive sports in genetically positive patients without symptoms or morphologic abnormalities on echo and cardiac MRI, or dysrhythmia, especially without prior familial SCD.

Commotio Cordis

Commotio cordis consists of immediate VF resulting from impact to the chest, generally seen in young athletes (average age, 15 years) who still have chest wall elasticity [48]. Impact is usually from a projectile such as a baseball, lacrosse ball, or hockey puck, but may be seen with other localized fist or kick blows [49]. VF is triggered only if the impact occurs during the upstroke of the T wave. Impact results in activation of stretch-sensitive ion channels in the myocyte cell membrane at time of maximal dispersion of repolarization [22, 50]. Increased recognition has coincided with improved survival (now >50%), which is due in part to safety baseballs, education, and automatic external defibrillators (AEDs). Survivors of commotion cordis after a negative evaluation, may resume exercise [49] since they are not felt to be at increased risk of another event.

Anomalous Coronary Arteries

Abnormal origin of coronary arteries from the aortic trunk can lead to exertional hypoperfusion and SCD. Since ECG and echocardiography are usually normal, direct imaging such as by coronary CT angiography is required. Surgical reimplantation of abnormal coronaries is curative [23]. Guidelines prohibit competitve sports if an anomalous coronary passes between the great arteries [34]. Myocardial bridges, when they cause SCD, may be successfully treated by surgical unroofing.

Arrhythmogenic Right Ventricular Dysplasia

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVDC) is characterized by right ventricular (RV) dysfunction, enlargement and fibro-fatty infiltration [23]. Myocyte loss results in wall thinning, and there may be RV segmental wall motion abnormalities and LV involvement [25]. SCD is usually exertional, and prevalence in SCD patients is as high as 25% [51]. T-wave inversion in leads V1–3 is seen in >85% of cases, and the ECG changes persist during exercise [52]. Cardiac MRI and less frequently endomyocardial biopsy may be very important in diagnosis. Patients with borderline findings should be followed for development of the disease over time [53]. β-blockers, antiarrhythmic agents and catheter ablation are options, but recurrent arrhythmias are common [54]. ARVDC patients based on risk factors are usually considered for primary prevention ICDs [23]. However, competitive activity should be prohibited except for perhaps low-intensity sports [25, 34, 35].

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a disease caused by mutations in the gene for the Ryanodine receptor, resulting in calcium loading and VT/VF during physical stress [55]. Patients with CPVT have normal ECGs and echocardiograms. Diagnosis is made with cardiac stress (either by exercise or isoproterenol infusion), and can be confirmed with genetic testing. Patients with CPVT should be evaluated for ICD placement, and may be treated with β-blockers [23, 34]. Flecainide is often helpful [56]. European Society of Cardiology (ESC) guidelines exclude all genetically positive patients from competitive sports while Bethesda Conference (BC) guidelines permit them if the athlete does not show the CPVT phenotype [34, 35].

Idiopathic Ventricular Tachycardia

Idiopathic tachycardias such as right ventricular outflow tract tachycardia may occur in athletes [23]. Athletes may undergo VT ablation and return to competitive sports 2–4 weeks later, so long as VT is not inducible by EPS. Patients treated medically may compete after several months so long as VT is not inducible during exercise and does not recur [34].

Long QT Syndromes

With a prevalence of 0.4% in athletes, the long QT syndromes (LQTS) result from abnormalities of cardiac repolarization [57]. The genetic mutations causing many of these syndromes have been identified, and they have variable presentation depending on genotype and penetrance. There are three most common forms, each derived from a chromosomal mutation. LQTS-1 involves a slow outward delayed rectifier potassium current abnormality, and is associated with SCD upon exertion. LQTS-2 is a rapid component outward delayed rectifier potassium current abnormality with SCD associated with autonomic hyperactivity. LQTS-3 is a sodium channel abnormality with SCD associated with rest and bradycardia [23].

The diagnosis of LQTS is challenging as many cases show fairly normal ECGs since QT prolongation may be only intermittently observed. Identification of paradoxical prolongation of QT intervals upon challenge with epinephrine, isoproterenol, or adenosine may unmask LQTS. Genetic testing may be very helpful [23]. LQTS 1 and 2 are treated with β-blockers, whereas LQTS-3 may be treated with sodium channel blockers. Patients with recurrent syncope despite medical therapy or cardiac arrest are generally recommended to have ICD implantation [34]. ESC guidelines prohibit genotypically positive athletes from competitive sports, while BC guidelines allow athletics so long as they are phenotypically negative (except for patients with any form of LQTS-1, who are barred from watersports) [34, 35].

Short QT Syndrome

Short QT syndrome (QT intervals <300–320 ms), associated with potassium channel mutations, is a serious abnormality in athletes [58]. Genetic evaluation should follow any suggestive ECG findings. Although ICD implantation may be effective in these patients, guidelines prohibit competitive sports [23, 34].

Brugada Syndrome

Brugada syndrome (BS) results from various mutations yielding impaired sodium ion channel function. Diagnosis can be made by ECG, with coved ST segment elevation (>2 mm) in the right precordial leads followed by negative T-waves. Fever and sodium channel blockers, usually procainamide or flecainide, may unmask the ECG findings and trigger the dysrhythmia. Failure to respond to challenge with sodium channel blockers is suggestive of benign ST-elevation rather than BS [23]. Inducibility in EPS remains controversial [59]. BS patients should be prohibited from vigorous exercise [60].

Arrhythmias Following Heart Transplant

Orthotopic heart transplantation (OHT) is an indispensable therapeutic option for selected patients, with end-stage heart failure [61]. Advancements in surgical technique and care have enhanced survival rates, bringing the median duration of cardiac transplant survival to over 10 years [62].

Cardiac arrhythmias occur at a frequency of 23–79% and are important mediators of morbidity in this population [63, 64].

Sinus Bradycardia and Conduction System Disease

Relative bradycardia as a result of sinus node dysfunction (SND) occurs with a prevalence of 14–50% in OHT patients

[61, 65]. While not clearly associated with mortality [65], SB compromises cardiac output and may confer patient morbidity [66, 67]. Mechanisms of SND include surgical trauma to the sinus node, perinodal atrial tissue, or sinoatrial artery; pretransplant amiodarone use; and in some cases reactive processes such as transplant rejection [61]. The relationship between graft ischemia and SND remains controversial [67, 68].

SND associated bradycardia fails to spontaneously resolve in up to 21% of transplanted patients during the first three months [67], although pacemaker implantation is required occurs in only 7–16% of recipients [61, 66, 68]. Permanent pacemaker due to SND most commonly is performed in the early post-operative period [69]. A large analysis of the United Network for Organ Sharing/Organ Procurement and Transplantation Network database has demonstrated that cardiac transplant recipients with pacemaker-requiring bradyarrhythmias have an excellent long-term prognosis [66]. A general trend towards the bicaval surgical technique and the use of positive chronotropic drugs such as theophylline or terbutaline have helped mitigate the need for permanent pacemaker implantation in many patients [65, 66, 70].

Right bundle branch delay, which occurs in up to 70% of patients, is the most frequently observed conduction abnormality after OHT. Causal mechanisms include right ventricular hypertrophy from elevated pulmonary pressures, and damage to the right bundle from biopsy of the right ventricular septal wall [61]. Late onset complete AV block has also been reported following OHT with multiple possible causes including postoperative injury, progressive conduction system disease associated with CAD, LV dysfunction, chronic rejection, and tissue damage during biopsy [71]. High-grade or complete AV block observed in the setting of late transplant rejection is associated with particularly poor prognosis [72, 73].

Atrial Fibrillation

There is a lack of consensus concerning the frequency of AF in OHT patients [71]. With a fairly wide range in reported incidence, AF usually occurs during the early post-operative period. Possible causative factors include manipulation of the heart, pericardial inflammation, use of positive inotropic agents, and post-surgical autonomic changes [71]. Late-onset AF after OHT is rare, and its low incidence may be due to pulmonary vein isolation and denervation associated with surgery. However because it has been associated with transplant failure and increased mortality, patients experiencing episodes of late-onset AF should be evaluated for LV dysfunction, cardiac allograft vasculopathy, and acute rejection [74, 75].

Treatment with amiodarone for AF during the early post-operative period is effective, and the need for prolonged anti-arrhythmic therapy (>3 months) is uncommon. However, because of possible drug interactions between amiodarone and cyclosporine or tacrolimus, immunosuppressant levels should be monitored closely during and shortly after therapy. Adenosine for control of rapid atrial rhythms should generally be avoided, since supersensitivity associated with the transplanted heart greatly increases the risk of profound drug-induced bradycardia or asystole [71, 76].

Need for anticoagulation to reduce stroke risk in patients with AF presents a challenge, since these patients require frequent endomyocardial biopsies. Treatment with subcutaneous low-molecular-weight heparin is a good option for these patients, although costly and requiring injection. Large studies of direct thrombin inhibitors in these patients are needed; these drugs might become warfarin alternatives due to their relatively rapid mechanism of action permitting wash-out before endomyocardial biopsies [71].

Atrial Flutter

Atrial flutter has been described in 12–15% of OHT patients [64, 77]. This is both the most common late-onset atrial arrhythmia and the most common arrhythmia associated with rejection [71]. Suture lines are felt to serve as substrates for reentrant circuits, predisposing the transplanted heart to atrial flutter [74]. Case reports and small trials indicate that flutter ablation is highly effective in OHT patients [78–80]. In addition, overdrive pacing at the time of endomyocardial biopsy is also useful, with a short-term success rate greater than 90% [81].

Ventricular Arrhythmias

During the early post-operative period, nonsustained ventricular tachycardia (NSVT) and PVC's are not uncommon. Studies have suggested a link between early NSVT and poor prognosis, but current evidence is inconclusive [71]. Late-onset NSVT, although uncommon, is associated with severe allograft vasculopathy or rejection. Sustained VT is rare but may indicate hyperacute rejection [71].

Sudden Cardiac Death

SCD accounts for approximately 10% of all-cause mortality after heart transplantation [62]. Among SCD patients, terminal rhythms included asystole (34%), pulseless electrical activity (20%), and VF (10%) [74]. Acute ischemia resulting from allograft vasculopathy is the most common underlying

cause of SCD in these patients. Sympathetic denervation may explain why VF, the most common manifestation of ischemia-related SCD in the general population, occurs infrequently in OHT patients [71]. Data supporting the use of ICD therapy in OHT patients are limited, but these devices may be considered for select patients with elevated SCD risk due to graft vasculopathy [82]. Whether SCD reduction with ICD implantation translates to a reduction in total mortality has yet to be determined [62].

Post-operative Arrhythmias

Cardiac arrhythmias following surgery have been associated with increases in length of stay, stroke risk, healthcare costs, and mortality [83]. As such, understanding arrhythmias associated with surgery is an important aspect of post-operative care. New-onset arrhythmias occur in up to 36% of patients following cardiac surgery [84]. Major non-cardiac surgery is also associated with new-onset arrhythmias, although the incidence is significantly lower (7%) [85, 86]. Arrhythmias are associated with other post-operative complications such as myocardial infarction, pulmonary edema, and sepsis [85–87].

Risk factors vary slightly between patients undergoing cardiac versus non-cardiac surgery, particularly in the incidence of postoperative AF (POAF). These are summarized in Table 22.1 [83, 85–87].

Recognition of multifocal atrial tachycardia is important due to its diagnostic and therapeutic implications, namely, alleviation of causative factors first rather than treating the rhythm. Finally, the possibilities of drug interactions, perioperative myocardial infarction (MI), pulmonary embolus, intraoperative stroke, and suture failure with bleeding should be considered in any catastrophic setting.

Table 22.1 Risk factors for development of postoperative atrial fibrillation

Risk factors in cardiac surgery	Risk factors in non-cardiac surgery
Age	Age
Structural heart disease	Male gender
Obesity	Congestive heart failure
Surgical inflammation	Valvular heart disease
Ischemic injury during surgery	Asthma
Perioperative drugs	History of Supraventricular Arrhythmias
Electrolyte disorders	Preoperative PVCs
Preservation of anterior fat pads	ASA Class III or I
OHS for congenital heart disease	Hypertension
History of stroke or COPD	Low preoperative serum potassium

Bradycardias

Bradycardia in the post-operative period typically manifests as sick sinus syndrome and varying degrees of AV block [88]. These arrhythmias may occur as a result of spinal or epidural anesthesia, laryngoscopy, or the surgical intervention itself. Bradyarrhythmias, are typically transient and do not require treatment. Persistent post-operative bradycardia is treated the same as bradycardia in the non-surgical setting [88, 89]. High-degree AVB persisting for 1–2 weeks post-operatively is generally an indication for permanent pacing. Transient recurrence of AV block in the setting of valve surgeries or transcatheter aortic valve replacement (TAVR) is associated with a high risk of AV block [90, 91]. Permanent pacing may be needed to treat peri-operative atrial arrhythmias in the presence of underlying sinus node dysfunction [92, 93].

Supraventricular Arrhythmias

Supraventricular arrhythmias are common after surgery, and when associated with cardiac surgery, confer higher morbidity. Patients with post-operative atrial arrhythmias have been shown to require longer ICU stays, more ventricular arrhythmias, and more permanent pacing [94].

Atrial Fibrillation/Flutter

POAF is the most common atrial arrhythmia encountered in patients regardless of surgical category (cardiac vs. non-cardiac) [86, 88, 95, 96]. In cardiac surgery, it is seen in as many as 25–50% of patients. Age seems to be the strongest risk factor in this setting. A large series found that in cardiovascular surgery patients with persistent POAF, the risk of stroke was more than doubled, although underlying comorbidities may have also contributed [94]. An additional retrospective study identified substantially greater in-hospital and 4-year mortality in patients who developed AF after coronary artery bypass grafting (CABG) [97]. Generally, POAF occurs in the first few days after surgery, with peak incidence at 2–3 days post-op [95, 96]. POAF is typically self-limiting, with a spontaneous conversion rate of up to 80% in the early post-op period [86, 98].

Rate control therapy with β-blockers or calcium channel blockers is recommended. Pharmacologic or DC cardioversion are reasonable for persistent AF [99]. 2014 guidelines suggest that preoperative amiodarone may serve as a prophylactic agent in cardiac surgery patients at high risk for POAF, and preoperative sotolol may be useful as well. When surgically permissible, there is no difference in antithrombotic management of these patients from nonoperative cases [99].

To address the microvascular and inflammatory causes of postoperative atrial fibrillation, preoperative administration of a statin and also of magnesium sulfate has shown reductions in POAF [100, 101].

Ventricular Arrhythmias

Serious ventricular arrhythmias are rare following surgery [86]. Ventricular ectopy occurs more frequently than VT and VF [102]. Sustained VT/VF has a reported incidence of 1.2% following CABG [103]. Risk factors associated with ventricular arrhythmias after cardiac surgery include hemodynamic instability, electrolyte imbalances, hypoxia, hypovolemia, myocardial ischemia and infarction, acute graft closure, reperfusion rhythms after cardiopulmonary bypass, and the use of ionotropic or antiarrhythmic agents. No therapy is required for asymptomatic and hemodynamically stable ventricular ectopies. Management of sustained ventricular arrhythmias following surgery is not different from the non-acute setting [88].

References

1. Li JM, Nguyen C, Joglar JA, Hamdan MH, Page RL. Frequency and outcome of arrhythmias complicating admission during pregnancy: experience from a high-volume and ethnically-diverse obstetric service. Clin Cardiol. 2008;31(11):538–41.
2. Enriquez AD, Economy KE, Tedrow UB. Contemporary management of arrhythmias during pregnancy. Circ Arrhythm Electrophysiol. 2014;7(5):961–7.
3. Franz MR, Cima R, Wang D, Profitt D, Kurz R. Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. Circulation. 1992;86:968–78.
4. Connolly HM. Pregnancy and the heart. In: Murphy JG, Lloyd MA, editors. Mayo Clinic cardiology: concise textbook. New York: Oxford University Press; 2013.
5. Roberts JM, Insel PA, Goldfien A. Regulation of myometrial adrenoreceptors and adrenergic response by sex steroids. Mol Pharmacol. 1981;20:52–8.
6. Soliman EZ, Elsalam MA, Li Y. The relationship between high resting heart rate and ventricular arrhythmogenesis in patients referred to ambulatory 24 h electrocardiographic recording. Europace. 2010;12:261–5.
7. Rosemond R. Cardioversion during pregnancy. JAMA. 1993;269:3167.
8. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC. Recurrence rate of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal neonatal outcomes. Am J Cardiol. 2006;97:1206–12.
9. Lee SH, Chen SA, TJ W, Chiang CE, Cheng CC, Tai CT, et al. Effects of pregnancy on first onset and symptoms of paroxysmal supraventricular tachycardia. Am J Cardiol. 1995;76:675–8.
10. Elkayam U, Goodwin TM. Adenosine therapy for supraventricular tachycardia during pregnancy. Am J Cardiol. 1995;75:521–3.
11. Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). Circulation. 2003;108:1871–909.
12. Driver K, Chisholm CA, Darby AE, Malhotra R, Dimarco JP, Ferguson JD. Catheter ablation of arrhythmia during pregnancy. J Cardiovasc Electrophysiol. 2015;26(6):698–702.
13. Damilakis J, Theocharopoulos N, Perisinakis K, Manios E, Dmitriou P, Vardas P, et al. Conceptus radiation dose and risk from cardiac catheter ablation procedures. Circulation. 2001;104:893–7.
14. Best PJ, Skelding KA, Mehran R, Chieffo A, Kunadian V, Madan M, et al. SCAI consensus document on occupational radiation exposure to the pregnant cardiologist and technical personnel. Catheter Cardiovasc Interv. 2011;77:232–41.
15. Gleicher N, Meller J, Sandler RZ, Sullum S. Wolff-Parkinson-White syndrome in pregnancy. Obstet Gynecol. 1981;58:748–52.
16. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC Practice Guidelines: 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;123:e269–367.
17. Camm AJ, Lip G, DeCaterina R, Savelieva I, Atar D, Hohnloser S, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (esc). Europace. 2010;12:1360–420.
18. Dugal S. Electrical cardioversion. In: Griffin BP, editor. Manual of cardiovascular medicine. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2013.
19. Joglar JA, Page RL. Management of arrhythmia syndromes during pregnancy. Curr Opin Cardiol. 2014;29(1):36–44.
20. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. J Am Coll Cardiol. 2003;41:1633–52.
21. Braunwald E. Heart disease, A textbook of cardiovascular medicine. 3rd ed. Philadelphia: WB Saunders; 1988.
22. Stoebner R, Bellin DA, Haigney MC. Cardiac electrophysiology and the athlete: a primer for the sports clinician. Curr Sports Med Rep. 2012;11(2):70–7.
23. Walker J, Calkins H, Nazarian S. Evaluation of cardiac arrhythmia among athletes. Am J Med. 2010;123(12):1075–81.
24. Molkentin JD. Calcineurin and beyond: cardiac hypertrophic signaling. Circ Res. 2000;87:731–8.
25. Maron BJ, Udelson JE, Bonow RO, Nishimura R, Ackerman M, Estes NA III, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2015;66(21):2362–71.
26. Pelliccia A, Maron BJ, Di Paolo FM. Prevalence and clinical significance of left atrial remodeling in competitive athletes. J Am Coll Cardiol. 2005;46:690–6.
27. La Gerche A, Burns AT, Mooney DJ, Inder W, Taylor A, Bogaert J, et al. Exercise-induced right ventricular dysfunction and structural remodeling in endurance athletes. Eur Heart J. 2012;33:998–1006.
28. La Gerche A, Connelly KA, Mooney DJ, Maclsaac AI, Pior DL. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. Heart. 2008;94:860–6.
29. Lampert R, Olshansky B, Heidbuchel H, Lawless C, Saarel E, Ackerman M, et al. Safety of sports for athletes with implantable

cardioverter-defibrillators: results of a prospective, multinational registry. Circulation. 2013;127(20):2021–30.
30. Zipes DP, Link MS, Ackerman MJ, Kovacs R, Myerburg R, Estes NA III. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 9: arrhythmias and conduction defects: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2015;66(21):2412–23.
31. Link MS, Olshansky B, Estes NA III. Cardiac arrhythmias and the athlete. Curr Opin Cardiol. 1999;14:24–9.
32. Link MS, Estes NA. Athletes and arrhythmias. J Cardiovasc Electrophysiol. 2010;21:1184–9.
33. Fragakis N, Pagourelias ED, Koskinas KC, Vassilikos V. Arrhythmias in athletes: evidence-based strategies and challenges for diagnosis, management, and sports eligibility. Cardiol Rev. 2013;21(5):229–38.
34. Zipes DP, Ackerman MJ, Estes NA III, Grant AO, Myerburg RJ, Van Hare G. Task Force 7: arrhythmias. J Am Coll Cardiol. 2005;45:1354–63.
35. Pelliccia A, Fagard R, Bjørnstad HH, Anastassakis A, Arbustini E, Assanelli D, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur Heart J. 2005;26:1422–45.
36. Cohen MI, Triedman JK, Cannon BCPACES. HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Heart Rhythm. 2012;9:1006–24.
37. Obeyesekere MN, Leong-Sit P, Massel D, Manlucu J, Modi S, Krahn A, et al. Risk of arrhythmia and sudden death in patients with asymptomatic preexcitation: a meta-analysis. Circulation. 2012;125:2308–15.
38. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. Circulation. 2009;119:1085–92.
39. Turagam MK, Velagapudi P, Kocheril AG. Atrial fibrillation in athletes. Am J Cardiol. 2012;109(2):296–302.
40. Alexander AM. Atrial fibrillation in the athlete. Curr Sports Med Rep. 2013;12(2):86–92.
41. Sorokin AV, Araujo CGS, Zweibel S. Atrial fibrillation in endurance-trained athletes. Br J Sports Med. 2011;45:185–8.
42. Swanson R. Atrial fibrillation in athletes: implicit literature-based connections suggest that overtraining and subsequent inflammation may be a contributory mechanism. Med Hypotheses. 2006;66:1085–92.
43. Bisbal F, Mont L. Arrhythmias in the athlete. Herzschrittmacherther Elektrophysiol. 2012;23(2):76–81.
44. Levine BD, Baggish AL, Kovacs RJ, Link MS, Maron MS, Mitchell JH, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 1: classification of sports: dynamic, static, and impact: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2015;66(21):2350–5.
45. Calvo N, Mont L, Tamborero D, Berruezo A, Viola G, Guasch E, et al. Efficacy of circumferential pulmonary vein ablation of atrial fibrillation in endurance athletes. Europace. 2010;12:30–6.
46. Furlanello F, Lupo P, Pittalis M, Foresti S, Vitali-Serdoz L, Francia P, et al. Radiofrequency catheter ablation of atrial fibrillation in athletes referred for disabling symptoms preventing usual training schedule and sport competition. J Cardiovasc Electrophysiol. 2008;19:457–62.
47. Maron BJ. Historical perspectives on sudden deaths in young athletes with evolution over 35 years. Am J Cardiol. 2015;116(9):1461–8.
48. Maron BJ, Estes M. Commotio cordis. N Engl J Med. 2010;362:917–27.
49. Link MS, Estes N III, Maron BJ. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 13: commotio cordis: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2015;66(21):2439–43.
50. Madias C, Maron BJ, Supron S, Estes NA III, Link MS. Cell membrane stretch and chest blowinduced ventricular fibrillation: commotio cordis. J Cardiovasc Electrophysiol. 2008;19(12):1304–9.
51. Furlanello F, Bertoldi A, Dallago M. Cardiac arrest and sudden death in competitive athletes with arrhythmogenic right ventricular dysplasia. Pacing Clin Electrophysiol. 1998;21:331–5.
52. Nasir K, Bomma C, Tandri H, Roguin A, Dalal D, Prakasa K, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation. 2004;110(12):1527–34.
53. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force criteria. Circulation. 2010;121(13):1533–41.
54. Dalal D, Jain R, Tandri H, Dong J, Eid SM, Prakasa K, et al. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol. 2007;50(5):432–40.
55. Lahat H, Pras E, Olender T, Avidan N, Ben-Asher E, Mano O, et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine induced polymorphic ventricular tachycardia in Bedouin families from Israel. Am J Hum Genet. 2001;69:1378–84.
56. Liu N, Napolitano C, Venetucci LA, Priori SG. Flecainide and antiarrhythmic effects in a mouse model of catecholaminergic polymorphic ventricular tachycardia. Trends Cardiovasc Med. 2012;22:35–9.
57. Basavarajaiah S, Wilson M, Whyte G, Shah A, Behr E, Sharma S. Prevalence and significance of an isolated long QT interval in elite athletes. Eur Heart J. 2007;28(23):2944–9.
58. Napolitano C, Bloise R, Priori SG. Long QT syndrome and short QT syndrome: how to make correct diagnosis and what about eligibility for sports activity. J Cardiovasc Med. 2006;7(4):250–6.
59. Bos JM, Ackerman MJ. Heritable cardiomyopathies and channelopathies: clinical presentations, genetics, and implications of genetic testing. In: Murphy JG, Lloyd MA, editors. Mayo Clinic cardiology: concise textbook. New York: Oxford University Press; 2013. p. 257–65.
60. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. 2005;111(5):659–70.
61. Eisen HJ, Kusmirek LS, Arrhythmias following cardiac transplantation. In: Yeon SB, editor. Waltham, MA: Wolters Kluwer. Accessed 22 Oct 2015.
62. Vakil K, Taimeh Z, Sharma A, Abidi KS, Colvin M, Luepker R, et al. Incidence, predictors, and temporal trends of sudden cardiac death after heart transplantation. Heart Rhythm. 2014;11(10):1684–90.
63. Scott CD, Dark JH, McComb JM. Sinus node function after cardiac transplantation. J Am Coll Cardiol. 1994;24:1334–41.
64. Ahmari SA, Bunch TJ, Chandra A. Prevalence, pathophysiology, and clinical significance of post-heart transplant atrial fibrillation and atrial flutter. J Heart Lung Transplant. 2006;25:53–60.

65. Jones DG, Mortsell DH, Rajaruthnam D, Hamour I, Hussain W, Markides V, et al. Permanent pacemaker implantation early and late after heart transplantation: clinical indication, risk factors and prognostic implications. J Heart Lung Transplant. 2011;30(11):1257–65.
66. Cantillon DJ, Tarakji KG, Hu T, Hsu A, Smedira NG, Starling RC, et al. Long-term outcomes and clinical predictors for pacemaker-requiring bradyarrhythmias after cardiac transplantation: analysis of the UNOS/OPTN cardiac transplant database. Heart Rhythm. 2010;7(11):1567–71.
67. Heinz G, Ohner T, Laufer G, Gossinger H, Gasic S, Laczkovics A. Demographic and perioperative factors associated with initial and prolonged sinus node dysfunction after orthotopic heart transplantation. The impact of ischemic time. Transplantation. 1991;51:1217–32.
68. DiBiase A, Tse TM, Schnittger I, Wexler L, Stinson EB, Valantine HA. Frequency and mechanism of bradycardia in cardiac transplant recipients and need for pacemakers. Am J Cardiol. 1991;67:1385–9.
69. Luebbert JJ, Lee FA, Rosenfeld LE. Pacemaker therapy for early and late sinus node dysfunction in orthotopic heart transplant recipients: a single-center experience. Pacing Clin Electrophysiol. 2008;31(9):1108–12.
70. Costanzo MR, Dipchand A, Starling R, Anderson A, Chang M, Desai S, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2010;29(8):914–56.
71. Thajudeen A, Stecker EC, Shehata M, Patel J, Wang X, McAnulty JH, et al. Arrhythmias after heart transplantation: mechanisms and management. J Am Heart Assoc. 2012;1:e001461.
72. Blanche C, Czer LS, Trento A, Fishbein MC, Doan D, Jordan S, et al. Bradyarrhythmias requiring pacemaker implantation after orthotopic heart transplantation: association with rejection. J Heart Lung Transplant. 1992;11:446–52.
73. Collins KK, Thiagarajan RR, Chin C, Dubin AM, Van Hare GF, Robbins RC, et al. Atrial tachyarrhythmias and permanent pacing after pediatric heart transplantation. J Heart Lung Transplant. 2003;22:1126–33.
74. Vaseghi M, Boyle NG, Kedia R, Patel JK, Cesario DA, Wiener I, Kobashigawa JA, Shivkumar K. Supraventricular tachycardia after orthotopic cardiac transplantation. J Am Coll Cardiol. 2008;51:2241–9.
75. Dizon J, Chen K, Bacchetta M, Argenziano M, Mancini D, Bivano A, et al. A comparison of atrial arrhythmias after heart or double-lung transplantation at a single center. J Am Coll Cardiol. 2009;54:2043–8.
76. Ellenbogen KA, Thames MD, DiMarco JP, Sheehan H, Lerman BB. Electrophysiological effects of adenosine in the transplanted human heart. Circulation. 1990;81:821–8.
77. Cui G, Tung T, Kobashigawa J, Laks H, Sen L. Increased incidence of atrial flutter associated with the rejection of heart transplantation. Am J Cardiol. 2001;88:280–4.
78. Pinski SL, Bredikis AJ, Winkel E, Trohman RG. Radiofrequency catheter ablation of atrial flutter after orthotopic heart transplantation: insights into the redefined critical isthmus. J Heart Lung Transplant. 1999;18:292–6.
79. Marine JE, Schuger CD, Bogun F. Mechanism of atrial flutter occurring late after orthotopic heart transplantation with atrio-atrial anastomosis. Pacing Clin Electrophysiol. 2005;28:412–20.
80. Rodriguez-Entem F, Exposito V, Gonzalez-Enriquez S, Garcia-Camarero T, Olalla J. Atrial flutter after heart transplantation: mechanism and catheter ablation. Transplant Proc. 2010;42:2697–701.
81. MacDonald P, Hackworthy R, Keogh A, Sivathasan C, Chang V, Spratt P. Atrial overdrive pacing for reversion of atrial flutter after heat transplantation. J Heart Lung Transplant. 1991;10:731–7.
82. Tsai VW, Cooper J, Garan H, Natale A, Ptaszek LM, Ellinor PT, et al. The efficacy of implantable cardioverter-defibrillators in heart transplant recipients: results from a multicenter registry. Circ Heart Fail. 2009;2:197–201.
83. Yadava M, Hughey AB, Crawford TC. Postoperative atrial fibrillation: incidence, mechanisms, and clinical correlates. Cardiol Clin. 2014;32(4):627–36.
84. Creswell LL. Postoperative atrial arrhythmias: risk factors and associated adverse outcomes. Semin Thorac Cardiovasc Surg. 1999;11:303–7.
85. Walsh SR, Oates JE, Anderson JA, Blair SD, Makin CA, Walsh CJ. Postoperative arrhythmias in colorectal surgical patients: incidence and clinical correlates. Color Dis. 2006;8(3):212–6.
86. Walsh SR, Tang T, Wijewardena C, Yarham SI, Boyle JR, Gaunt ME. Postoperative arrhythmias in general surgical patients. Ann R Coll Surg Engl. 2007;89(2):91–5.
87. Polanczyk CA, Goldman L, Marcantonio ER. Supraventricular arrhythmia in patients having noncardiac surgery: clinical correlates and effect on length of stay. Ann Intern Med. 1998;129:279–85.
88. Peretto G, Durante A, Limite LR, Cianflone D. Postoperative arrhythmias after cardiac surgery: incidence, risk factors, and therapeutic management. Cardiol Res Pract. 2014;2014:615987.
89. Hollenberg SM, Dellinger RP. Noncardiac surgery: postoperative arrhythmias. Crit Care Med. 2000;28(10 Suppl):N145–50.
90. Gregoratos G, Cheitlin MD, Conill A, Epstein AE, Fellows C, Ferguson B Jr, et al. ACC/AHA Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: executive summary. Circulation. 1998;97:1325–35.
91. Epstein AE, Ellenbogen KA, Freedman RA, Gillinov AM, Hammill SC, Hlatky MA, et al. ACCF/AHA/HRS focused update incorporated into the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. Circulation. 2012;127:e283–352.
92. Jaeger FJ, Trohman RG, Brener S, Loop F. Permanent pacing following repeat cardiac valve surgery. Am J Cardiol. 1994;74(5):505–7.
93. Brodell GK, Cosgrove D, Schiavone W, Underwood DA, Loop FD. Cardiac rhythm and conduction disturbances in patients undergoing mitral valve surgery. Cleve Clin J Med. 1991;58(5):397–9.
94. Creswell LL, Schuessler RB, Rosenbloom M. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg. 1993;56:539–49.
95. Zaman AG, Archbold RA, Helft G, Paul EA, Curzen NP, Mills PG. Atrial fibrillation after coronary artery bypass surgery: a model for preoperative risk stratification. Circulation. 2000;101:1403–8.
96. Aranki SF, Shaw DP, Adams DH. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation. 1996;94:390–7.
97. Villareal RP, Hariharan R, Liu BC. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol. 2004;43:742–8.
98. Soucier RJ, Mirza S, Abordo MG. Predictors of conversion of atrial fibrillation after cardiac operation in the absence of class I or III antiarrhythmic medications. Ann Thorac Surg. 2001;72:694–8.
99. January CT, Wann L, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1–e76.

100. Liu T, Li L, Korantzopoulos P, Liu E, Li G. Statin use and development of atrial fibrillation: a systematic review and meta-analysis of randomized clinical trials and observational studies. Int J Cardiol. 2008;126:160–70.
101. Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A. Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation. Health Technol Assess. 2008;12:3–4.
102. Batra GS, Molyneux J, Scott NA. Colorectal patients and cardiac arrhythmias detected on the surgical high dependency unit. Ann R Coll Surg Engl. 2001;83:174–6.
103. Abedin Z, Soares J, Phillips DF, Sheldon WC. Ventricular tachyarrhythmias following surgery for myocardial revascularization: A follow-up study. Chest. 1977;72:426–8.

Index

P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5